National Institute for Health and Care Excellence

Final

Suspected cancer: recognition and referral

[A] Evidence reviews for diagnostic accuracy of prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer

NICE guideline NG12

Evidence reviews underpinning recommendation 1.6.3 and research recommendation 5

December 2021

Final

These evidence reviews were developed by Guideline Updates Team

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Prostate specific antigen (PSA) thresholds in people with suspected prostate cancer

1.1 Review question

In people with suspected prostate cancer (with any of the following symptoms - any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or erectile dysfunction or visible haematuria), what is the diagnostic accuracy of fixed PSA test threshold compared to age-adjusted PSA thresholds?

1.1.1 Introduction

The NICE guideline on suspected cancer (NICE guideline NG12) was reviewed in 2020 as part of NICE's surveillance programme. It was identified that the NICE guideline for suspected cancer was inconsistent with new guidance from Public Health England on the PSA threshold that should prompt referral to secondary care.

The aim of this review is to assess the diagnostic accuracy of age adjusted PSA thresholds and fixed PSA test thresholds to inform recommendations on PSA levels that should prompt referral to secondary care in people with symptoms of prostate cancer. See Appendix A for full details of the review protocol.

1.1.2 Summary of the protocol

Table 1: PICO table

Population	**Inclusion** People suspected of prostate cancer with any of the following symptoms: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency, or retention or • erectile dysfunction or • visible haematuria **Exclusion** • Screening for prostate cancer in those without symptoms. • People diagnosed with prostate cancer.
Index test	• Age-adjusted prostate-specific antigen test • PSA test (without age adjustment - fixed test threshold)
Reference standard	• Multiparametric MRI scan • Prostate biopsy
Outcome (s)	**Primary outcome:** • Positive predictive values (recalculated to prevalence in the UK population and not study population). **Secondary outcome:** • Sensitivity (detection rate) and specificity.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual and appendix L. Methods specific to this review question are described in the review protocol in appendix A and below:

1. The review protocol specified that only PSA thresholds that were clinically plausible as thresholds for prompting referral to secondary care would be included in the evidence review. Following discussion with the committee, the review was restricted to thresholds below 10 ng/ml.
2. The primary outcome specified in the review protocol was positive predictive value (PPV). This is consistent with the other reviews in the NICE guideline on suspected cancer. An upper clinical decision threshold of 3% PPV was specified in the NICE guideline on suspected cancer for assessing evidence for referral to secondary care. This decision threshold was also adopted in this review. A lower clinical decision threshold of 0.5% was chosen as the threshold below which the test would be of no clinical use. This was intially proposed by the reviewing team and confirmed by the committee.
3. PPVs vary dramatically according to the prevalence of a condition in a study sample. This contrasts with sensitivity and specificity which are relatively invariant across a range of prevalence. Consequently, for this review sensitivity and specificity were calculated from the study data, and PPVs were calculated by combining sensitivity and specificity estimates with a range of plausible prevalence estimates using the following formula:

   PPV= (sensitivity x prevalence)/(sensitivity x prevalence +(1-specificity) x (1-prevalence))

4. The NICE guideline on suspected cancer recommends that a PSA test should be considered for people with lower urinary tract symptoms (such as nocturia, urinary frequency, hesitancy, urgency or retention), erectile dysfunction or visible haematuria. This recommendation was not updated as part of this review. To calculate the PPV as described in point 3 above, a range of plausible prevalence values was estimated for this population using the QCancer risk calculator (Hippisley-Cox, 2013). This calculator is based on a large dataset of UK general practice records and can be used to estimate the prevalence of as-yet undetected prostate cancer according to whether a range of symptoms are present, including those mentioned in the existing NICE guideline as prompting consideration of a PSA test. Risk of having undiagnosed prostate cancer was calculated for 3 example patients (detailed in table 2), chosen to represent a range of prevalence values of undiagnosed prostate cancer for people presenting to primary care with symptoms suggestive of prostate cancer. For the purpose of these estimates the example patients were assumed to be non-smokers and to not drink alcohol. However, as smoking and alcohol use are not significant predictors of prostate cancer, this did not substantially impact the prevalence estimates. One limitation of this approach was the prevalence estimates would include people with undiagnosed cancer with a positive digital rectal examination. The NICE guideline recommends that such patients should be referred to secondary care irrespective of their PSA levels, and so these people are not relevant to this review. However, the QCancer dataset is large and UK based and so was considered to be the best source of prevalence data despite this limitation.

Table 2: Prostate cancer prevalence estimates for people with symptoms of prostate cancer

	Prevalence 1	Prevalence 2	Prevalence 3
Age	50	65	75

	Prevalence 1	Prevalence 2	Prevalence 3
Symptoms	Urinary frequency	Urinary frequency	Urinary retention and frequency
Estimated prevalence	0.1%	1.6%	6.1%

5. The review protocol specified that the population for the review is people with symptoms that might suggest prostate cancer. This population was the focus of the review. The protocol specified that if evidence could not be found for this population, then indirect evidence from people without symptoms of prostate cancer should be considered. As limited evidence was found for the diagnostic accuracy of age-adjusted PSA thresholds and no evidence was found that was stratified by age or ethnicity, evidence from a broader population was searched for these data. When evidence from a broader population was included, data from studies that included people without symptoms suggestive of prostate cancer were downgraded for indirectness.
6. The NICE guideline on suspected cancer recommends that people with a positive digital rectal examination are referred to secondary care irrespective of their PSA level. This population is therefore not relevant to this review. Some studies did include people with a positive digital rectal examination as part of their population. Studies for which people with a positive digital rectal examination comprised more than 30% of the population were downgraded for indirectness.

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

1.1.4 Diagnostic accuracy evidence

1.1.4.1 Included studies

A systematic search was carried out to identify cross sectional diagnostic accuracy studies and systematic reviews of these studies, which found 5402 references (see Appendix B) for the literature search strategy). From the first 2707 references screened, 2514 were excluded based on their titles and abstracts and 193 references were ordered for screening based on their full texts. Based on the rules for using priority screening software (see Appendix L), the screening was terminated at this point, and the remaining 2695 references were not screened on title and abstract.

Of the 193 references screened as full texts, 25 references were included based on their relevance to the review protocol (Appendix A). A further study was identified at consultation and subsequently included.The clinical evidence study selection is presented as a diagram in Appendix C.

See section 1.1.14 References – included studies for a list of included references.

1.1.4.2 Excluded studies

See Appendix J for a list of excluded studies with reasons for exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

Table 3: Summary of studies

Study	Study design	Population (n=) [2]	PSA thresholds	Population PSA range [1]	% Positive DRE (digital rectal exam)	Age	Country	Prostate cancer symptoms
Studies including a population with symptoms or prostate cancer:								
Abdrabo 2011	Cross-sectional	118	4.1ng/ml	2.5-10ng/ml	41.5%	Mean: 70 Range: 56-83	Sudan	LUTS (lower urinary tract symptoms)
Agnihotri 2014	Cross-sectional	875	4.1ng/ml	4 - >20ng/ml	51.2%	Mean 65.72 SD: 7.4	India	LUTS
Clark 1997	Cross-sectional	1330	Age adjusted	Not stated	59.25%	Mean: 66 SD: 8.4	Canada	Voiding symptoms
Dalva 1999	Cross-sectional	76	4.1ng/ml	4 - >10ng/ml	Not stated	Mean: 69.11 SD: 1.48	Turkey	Prostatism symptoms
Djavan 2002	Cross-sectional	1246	4ng/ml	2.5-10ng/ml	Not stated	Mean: (67.25) SD: 8.13	Europe (multiple sites)	LUTS
Filella 1996	Cross-sectional	587	3.1ng/ml 4.1ng/ml 10ng/ml	<3.1 - >10ng/ml	30.83%	Mean 66.6	Spain	LUTS
Kikuchi 2000	Cross-sectional	281	5.3ng/ml 6.9ng/ml	4.1-10ng/ml	55.2%	Mean: 68.4 SD: 0.5	Japan	LUTS
Kuppasamy/ Rajandram 2018	Cross-sectional	286	6 ng/ml 7 ng/ml 8 ng/ml 9 ng/ml	4.01-30ng/ml	22.38%	Mean: 69.01 SD: 7.5	Malaysia	LUTS

Study	Study design	Population (n=) [2]	PSA thresholds	Population PSA range [1]	% Positive DRE (digital rectal exam)	Age	Country	Prostate cancer symptoms
Kobayashi 2005	Cross-sectional	315	2.3ng/ml 2.4ng/ml 2.5ng/ml 4.2ng/ml 4.5ng/ml 4.7ng/ml	1.5->10ng/ml	43%	Mean: 67.1 SD: 8 Range 46-79	Japan	LUTS
Martinez-Pineiro 2000	Cross-sectional	180	5-9ng/ml	4-10ng/ml	0%	Mean: 67.29 SD: 7.43	Spain	Prostatism symptoms
Lopez-Saez (Senra-Varela 2004)	Cross-sectional	556	4.1ng/ml 10ng/ml	0.01-4ng/ml	34.2%	Mean: 68.53 SD: 0.96)	Spain	Prostatism symptoms
McArdle 2004	Cross-sectional	171	4ng/ml	4-10ng/ml	Not stated	Median: Benign group 66 (45-79) Cancer group: 69 (46-88)	UK	Symptoms (not specified)
Mitchell 2001	Cross-sectional	160	3.12ng/ml 3.97ng/ml 5.09ng/ml 5.67ng/ml 6.2ng/ml	2.6-20ng/ml	51%	Mean: 68.9	UK	LUTS
Mutlu 2009	Cross-sectional	177	2.13ng/ml 2.83ng/ml 3ng/ml 4.69ng/ml	0.1-348ng/ml	Not stated	Mean: Benign group: 64.3 (SD 9.1) Cancer group: 65 (SD 7.2)	Turkey	LUTS

Study	Study design	Population (n=) [2]	PSA thresholds	Population PSA range [1]	% Positive DRE (digital rectal exam)	Age	Country	Prostate cancer symptoms
Putra 2019	Cross-sectional	1232	4ng/ml 10ng/ml	<4 - >20ng/ml	Not stated	Median: Benign group 66 (40-83) Cancer group: 68 (35-89)	Indonesia	LUTS
Rahardjo 2000	Cross-sectional	118	4ng/ml 8ng/ml 10ng/ml	4.1 -10ng/ml	Not stated	Mean: Benign group: 64.37 (SD 8.22) Cancer group: 73 (SD 6.08)	Indonesia	Prostate symptoms without acute urinary retention
Rashid 2012	Cross-sectional	206	3ng/ml 3.5ng/ml 4ng/ml	>2.5ng/ml	Not stated	>50 (mean/median not reported)	Bangladesh	LUTS
Shim 2007	Cross-sectional	344	4ng/ml 10ng/ml	2.8 - 57ng/ml	29%	Median: Benign group 73 Cancer group: 73	Korea	Voiding symptoms
Sozen 2005	Cross-sectional	351	4ng/ml	2.5- 20 ng/ml	0%	Mean: Benign group: 62.3 (SD 7.9) Cancer group: 65 (SD 7.8)	Turkey	LUTS
Tan 1995	Cross-sectional	579	Age adjusted	0-100ng/ml	30.4%	Mean: 71	Singapore	Symptoms (not specified)
Vukotic 2005	Cross-sectional	579	4ng/ml 10ng/ml	<2.5-50ng/ml	60.8%	Mean: 67.5	Serbia	Urinary disturbance
Studies including a population with no symptoms of prostate cancer:								

Study	Study design	Population (n=) [2]	PSA thresholds	Population PSA range [1]	% Positive DRE (digital rectal exam)	Age	Country	Prostate cancer symptoms
Catalona 1994	Cross-sectional	1167	3 – 10ng/ml	>4ng/ml	Not stated (for those biopsied)	Median: 63	USA	No symptoms reported
Crawford 1999	Cross-sectional	3029	Age adjusted	Not stated	69.8%	Range: 40-79	USA	No symptoms reported
Gilbert 2018	Cross-sectional	8016	Age adjusted	3-10ng/ml	Not stated	Mean PC group: 62.4 Mean No/low risk: 59.3 Range: 50-69	UK	No symptoms reported
Reljic 2004	Cross-sectional	80	Age adjusted	4 - 9.9ng/ml	0%	Range: 46-87	Croatia	No symptoms stated
Veltri 2002	Cross-sectional	3597	3.3-5.5ng/ml	2-20ng/ml	Not stated	Mean: 66.9 SD: 8.4	USA	No symptoms reported

1. PSA range in population as reported. Majority of studies used 2.5ng/ml or 4ng/ml as a criterion for biopsy. Most participants included with a PSA under these thresholds were referred for biopsy due to an abnormal/positive digital rectal exam

2. Population included in this analysis

See Appendix C for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Table 4: Fixed thresholds in population with symptoms of prostate cancer:

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
1	177	2.13 ng/ml	0.95 (0.84-0.99)	0.46(0.38-0.54)	0.1%	0.18% (0.14-0.21)	Low[1]
					1.6%	2.28% (2.16-3.38)	Very Low[2]

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
					6.1%	10.3% (8.1-12.27)	Low[1]
1	315	2.5 ng/ml	0.8 (0.71-0.87)	0.28 (0.22-0.35)	0.1%	0.11% (0.09-0.13)	Low[1]
					1.6%	1.78% (1.47-2.11)	Low[1]
					6.10%	6.74% (5.63-7.92)	Low[1]
1	177	2.83 ng/ml	0.91 (0.78 - 0.97	0.55 (0.46 - 0.63)	0.1%	0.2% (0.15-0.26)	Low[1]
					1.6%	3.17% (2.32-4.08)	Very low[2]
					6.1%	11.58% (8.66-14.52)	Low[1]
4	1068	3-3.12 ng/ml	0.92 (0.84-0.96)	0.16 (0.05-0.42)	0.1%	0.11% (0.09-0.17)	Very Low[3]
					1.6%	1.75% (1.42-2.62)	Very Low[3]
					6.1%	6.64% (5.4-9.71)	Very Low[3]
14	6387	3.97-4.1ng/ml	0.93 (0.87-0.96)	0.16 (0.1-0.25)	0.1%	0.11% (0.1-0.13)	Very Low[4]
					1.6%	1.7% (1.5-2.04)	Very Low[4]
					6.1%	6.7% (5.9-7.7)	Very Low[4]
1	315	4.5 ng/ml	0.91 (0.83-0.948)	0.13 (0.05-0.27)	0.1%	0.11% (0.10-0.13)	Low[1]
					1.6%	1.78% (1.55-2)	Low[1]
					6.1%	6.74% (5.94-7.53)	Low[1]
2	492	4.69-4.7 ng/ml	0.78 (0.68-0.85)	0.47 (0.09-0.88)	0.1%	0.15% (0.07-0.7)	Very Low[5]
					1.6%	2.34% (1.2-10.33)	Very Low[5]
					6.1%	8.73% (4.63-31.51)	Very Low[3]
3	487	5-5.3 ng/ml	0.86 (0.76-0.93)	0.25 (0.17-0.33)	0.1%	0.11% (0.09-0.14)	Very Low[6]
					1.6%	1.8% (1.47-2.21)	Very Low[6]
					6.1%	6.9% (5.6-8.27)	Very Low[6]
1	160	5.67 ng/ml	0.84 (0.716-0.92)	0.34 (0.257-0.433)	0.1%	0.13% (0.1-0.16%	Low[1]
					1.6%	2% (1.54-2.57)	Low[1]
					6.1%	7.65% (5.9-9.54)	Low[1]
3	626	6-6.2 ng/ml	0.76 (0.68-0.83)	0.39 (0.28-0.50)	0.1%	0.12% (0.09-0.17)	Very Low[4]
					1.6%	2% (1.51-2.63)	Very Low[4]

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
					6.1%	7.49% (5.8-9.73)	Very Low[4]
3	613	6.9-7 ng/ml	0.58 (0.46-0.68)	0.55 (0.45-0.64)	0.1%	0.13% (0.08-0.19)	Very Low[4]
					1.6%	2.1% (1.34-2.98)	Very Low[4]
					6.1%	7.73% (5.2-10.93)	Very Low[4]
3	586	8 ng/ml	0.5 (0.38-0.61)	0.73 (0.52-0.87)	0.1%	0.2% (0.08-0.5)	Very Low[7]
					1.6%	2.9% (1.27-7.09)	Very Low[7]
					6.1%	10.74% (4.9-23.36)	Very Low[4]
2	466	9 ng/ml	0.37 (0.15-0.67)	0.78 (0.45-0.94)	0.1%	0.19% (0.03-1.1)	Very Low[7]
					1.6%	2.7% (0.44-15.37)	Very Low[8]
					6.1%	9.85% (1.7-42.04)	Very Low[7]
6	3225	10ng/ml	0.70 (0.58-0.79)	0.63 (0.35-0.84)	0.1%	0.19% (0.09-0.49)	Very Low[9]
					1.6%	2.98% (1.4-7.4)	Very Low[7]
					6.1%	10.95 (5.48-24.3)	Very Low[9]

1. Downgraded due to serious risk of bias and serious indirectness
2. Downgraded due to serious risk of bias, serious indirectness, and serious imprecision
3. Downgraded due to serious risk of bias, serious indirectness, and very serious inconsistency
4. Downgraded due to very serious risk of bias, very serious inconsistency, and serious indirectness
5. Downgraded due to serious risk of bias, serious indirectness, very serious inconsistency, and serious imprecision
6. Downgraded due to very serious risk of bias, serious indirectness
7. Downgraded due to very serious risk of bias, serious indirectness, very serious inconsistency, and serious imprecision
8. Downgraded due to very serious risk of bias, serious indirectness, very serious inconsistency, and very serious imprecision
9. Downgraded due to very serious risk of bias, serious indirectness, and very serious inconsistency

Table 5: Age Adjusted thresholds: Population without symptoms of prostate cancer

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
1	3029	Age Adjusted[1]	0.4 (0.36-0.43)	0.73 (0.71-0.75)	0.1%	0.15% (0.13-0.17)	Very low[3]
					1.6%	2.32% (2-2.7)	Very low[3]
					6.1%	8.68% (7.52-10)	Very low[3]
1	80	Age Adjusted[2]	0.92 (0.61-0.99)	0.16 (0.09-0.27)	0.1%	0.1% (0.07-0.14)	Very low[3]
					1.6%	1.76% (1.08-2.16)	Very low[3]
					6.1%	6.7% (4.18-8.12)	Very low[3]
1	8016	Age Adjusted[4]	0.35 (0.32-0.39)	0.78 (0.77-0.784)	0.1%	0.16% (0.14-0.18)	Very low[3]
					1.6%	2.48% (2.17-2.82)	Very low[3]
					6.1%	9.23% (8.13-10.40)	Very low[3]
1	8016	Age Adjusted[5]	0.81 (0.78-0.84)	0.31 (0.3-0.32)	0.1%	0.12% (0.11-0.12)	Very low[3]
					1.6%	1.87% (1.78-1.97)	Very low[3]
					6.1%	7.09% (6.75-7.43)	Very low[3]

1. Age adjusted cut offs: 40-49: 2.4ng/ml, 50-59: 3.8ng/ml, 60-69: 5.6ng/ml, 70-79 – 6.9ng/ml
2. Age adjusted cut offs: 40-49: 2.5ng/ml, 50-59: 3.5ng/ml, 60-69: 4.5ng/ml, 70-79: 6.5ng/ml
3. Downgraded due to very serious risk of bias and serious indirectness
4. Age adjusted cut offs: age (years):PSA (ng/mL): 50: 2.8ng/ml, 51:3.0 ng/ml, 52:3.2 ng/ml, 53:3.4 ng/ml, 54:3.6 ng/ml, 55:3.8 ng/ml, 56:4 ng/ml, 57:4.2 ng/ml, 58:4.6 ng/ml, 59:4.9 ng/ml, 60:5.2 ng/ml, 61:5.6 ng/ml, 62:6.1 ng/ml, 63:6.5 ng/ml, 64:7 ng/ml, 65:7.6 ng/ml, 66:8.3 ng/ml, 67:9 ng/ml, 68:9.8 ng/ml, 69:10.4 ng/ml, 70:11.3 ng/ml
5. Age adjusted cut offs: 50–59: PSA = 3 ng/mL; 60–70: PSA = 4 ng/mL; ≥ 70: PSA = 5 ng/mL

Table 6: Age Adjusted threshold: Population with symptoms of prostate cancer

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
2	1857	Age Adjusted[1]	0.87 (0.68-0.96)	0.35 (0.30-0.40)	0.1%	0.13% (0.1-0.16)	Very low[2]
					1.6%	2.13% (1.55-2.54)	Very low[2]
					6.1%	8% (5.94-9.42)	Very low[2]

1. Age adjusted cut offs: 40-49: 2.5ng/ml, 50-59: 3.5ng/ml, 60-69: 4.5ng/ml, 70-79: 6.5ng/ml
2. Downgraded due to serious risk of bias, serious indirectness, and very serious inconsistency

Table 7: Age stratified fixed thresholds: population without symptoms of prostate cancer

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
2	1004	Age 45-59: 3-3.3ng/ml	0.89 (0.63-0.98)	0.25 (0.02-0.83)	0.1%	0.1% (0.06-0.6)	Very low[1]
					1.6%	1.9% (1.03-8.57)	Very low[1]
					6.1%	7.16% (4-27.25)	Very low[2]
2	1997	Age 60-69: 3-3.4ng/ml	0.91 (0.74-0.97)	0.16 (0.01-0.71)	0.1%	0.1% (0.07-0.3)	Very low[2]
					1.6%	1.7% (1.2-5.16)	Very low[1]
					6.1%	6.58% (4.6-17.85)	Very low[2]
1	342	Age 70-96: 3ng/ml	0.93 (0.85-0.96	0.33 (0.27-0.39)	0.1%	0.14% (0.12 - 0.2)	Very low[3]
					1.6%	2.2% (1.86-2.5)	Very low[3]
					6.1%	8.27% (7-9.28)	Very low[3]
2	1004	Age 45-59: 4 ng/ml	0.81 (0.7-0.9)	0.36 (0.06-0.83)	0.1%	0.13% (0.07-0.52)	Very low[2]
					1.6%	2.03% (1.2-7.85)	Very low[2]

No. of studies	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
					6.1%	7.65% (4.64-25.4)	Very low[2]
2	1997	Age 60-69: 4ng/ml	0.86 (0.74-0.93)	0.22 (0.03-0.73)	0.1%	0.1% (0.08-0.3)	Very low[2]
					1.6%	1.8% (1.2-5.3)	Very low[1]
					6.1%	6.68% (4.7-18.3)	Very low[2]
2	1763	Age 70-96: 3.8-4 ng/ml	0.92 (0.81-0.97)	0.19 (0.03-0.6)	0.1%	0.1% (0.08-0.2)	Very low[2]
					1.6%	1.8% (1.3-3.8)	Very low[1]
					6.1%	6.9% (5.1-13.6)	Very low[2]
2	1997	Age 60-69: 4.8 - 5ng/ml	0.76 (0.66-0.84)	0.40 (0.09-0.81)	0.1%	0.1% (0.07-0.4)	Very low[2]
					1.6%	2% (1.12-6.7)	Very low[1]
					6.1%	7.6% (4.5-22.3)	Very low[2]
2	1763	Age 70-96: 5 - 5.2ng/ml	0.8 (0.76-0.84)	0.31 (0.13-0.57)	0.1%	0.12% (0.09-0.2)	Very low[2]
					1.6%	1.86% (1.39-3.14)	Very low[2]
					6.1%	7.03% (5.33-11.46)	Very low[2]

1. Downgraded due to very serious risk of bias, very serious indirectness, very serious inconsistency, and serious imprecision
2. Downgraded due to very serious risk of bias, very serious inconsistency, and very serious indirectness
3. Downgraded due to very serious risk of bias and very serious indirectness

Table 8: Age adjusted split into age categories: population without symptoms of prostate cancer

No. of studies	Sample size	Age and PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
1	857	Age 50-54[1]	0.87 (0.78 – 0.93)	0.26 (0.23-0.29)	0.10%	0.12% (0.1-0.13	Very low[3]
					1.60%	1.87% (1.62-2.08)	Very low[3]

No. of studies	Sample size	Age and PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
					6.10%	7.09% (6.17-7.81)	Very low[3]
1	1,878	Age 55-59[1]	0.63 (0.55-0.695)	0.63(0.6-0.65)	0.10%	0.17%(0.14-0.2)	Very low[3]
					1.60%	2.67% (2.23-3.14)	Very low[4]
					6.10%	9.87% (8.35-11.45)	Very low[3]
1	2618	Age 60-64[1]	0.33 (0.27-0.39)	0.85 (0.831-0.86)	0.10%	0.21% (0.16-0.28)	Very low[3]
					1.60%	3.38% (2.59-4.3)	Very low[4]
					6.10%	12.25% (9.59-15.32)	Very low[3]
1	2618	Age 60-64[2]	0.7 (0.64-0.75)	0.47 (0.45-0.49)	0.10%	0.13% (0.12-0.15)	Very low[3]
					1.60%	2.1% (1.86-2.34)	Very low[3]
					6.10%	7.89% (7.03-8.74)	Very low[3]
1	2663	Age > 65[1]	0.07 (0.043-0.1)	0.98 (0.97-0.983)	0.10%	0.3% (0.15-0.59)	Very low[3]
					1.60%	4.65% (2.35-8.73)	Very low[3]
					6.10%	16.31% (8.79-27.65)	Very low[3]
1	2663	Age > 65[2]	0.75 (0.696-0.794)	0.48 (0.45-0.495)	0.10%	0.14% (0.13-0.16)	Very low[3]
					1.60%	2.26% (2.03-2.49)	Very low[3]
					6.10%	8.47% (7.66-9.27)	Very low[3]

1. Age adjusted cut offs: age (years):PSA (ng/mL): 50: 2.8ng/ml, 51:3.0 ng/ml, 52:3.2 ng/ml, 53:3.4 ng/ml, 54:3.6 ng/ml, 55:3.8 ng/ml, 56:4 ng/ml, 57:4.2 ng/ml, 58:4.6 ng/ml, 59:4.9 ng/ml, 60:5.2 ng/ml, 61:5.6 ng/ml, 62:6.1 ng/ml, 63:6.5 ng/ml, 64:7 ng/ml, 65:7.6 ng/ml, 66:8.3 ng/ml, 67:9 ng/ml, 68:9.8 ng/ml, 69:10.4 ng/ml, 70:11.3 ng/ml

No. of studies	Sample size	Age and PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Quality
2. Age adjusted cut offs: 50–59: PSA = 3 ng/mL; 60–70: PSA = 4 ng/mL; ≥ 70: PSA = 5 ng/mL 3. Downgraded due to very serious risk of bias and serious indirectness 4. Downgraded due to very serious risk of bias, serious indirectness and serious imprecision							

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to any of the questions in this guideline update (see Appendix B) **Error! Reference source not found.**). This search retrieved 234 studies. Based on title and abstract screening, 234 of the studies could confidently be excluded for this question. Thus, there are no existing economic studies for this review question.

1.1.7.2 Excluded studies

All studies were excluded at title and abstract screening.

1.1.8 Summary of included economic evidence

There are no existing studies for this review question

1.1.9 Economic model

No original economic modelling was completed for this review question.

1.1.10 Unit costs

Table 9: Unit costs

Description	Cost	Source
Transrectal Ultrasound Guided Biopsy of Prostate	£606.50	NHS Cost collection 2019/2020
Trans perineal Template Biopsy of Prostate	£878.34	NHS Cost collection 2019/2020
Magnetic Resonance Imaging (MRI)	£159.66	NHS Cost collection 2019/2020
Nurse time (GP, per 5 mins)	£2.50	PSSRU 2020
GP appointment	£28.00	PSSRU 2020
Phlebotomy (Secondary care)	£4.00	NHS Cost collection 2019/2020

There was no existing evidence on the cost effectiveness of using a fixed threshold versus an age specific threshold for PSA testing. However, changing the threshold from an age-specific to a fixed value for all age could potentially have a large resource impact, as there is a considerable number of men who would be referred for further investigation on a fixed value threshold that would not be on an age-specific threshold. Therefore, a costing analysis was done.

It was not possible to find the cost of a false negative as it is unknown at what point a patient who received a false negative would be correctly diagnosed and the effect of a delayed diagnosis on false reassurance, delayed diagnosis and treatment. There are likely to be more false negatives with the age-specific threshold as if a patient is older then there is a

higher threshold for referral, therefore a person with prostate cancer would require a higher PSA value to be referred and the cancer discovered. From an economic perspective this is important because people with prostate cancer that is discovered later could have disease progression and require higher levels of care which would incur higher costs.

A cost analysis was completed to examine the range of costs of a false positive. Recommendations from NG131 were used to predict what would happen to a patient who was getting positive or indetermined results but did not have prostate cancer. Figure 1 shows the investigations undertaken after a referral to secondary care; if at any point patients have a confirmed diagnosis of prostate cancer, they leave the diagnostic pathway and are excluded from this diagram. The first investigation patients get is multiparametric magnetic resonance imaging (MRI). Depending on the results of the MRI the patient will receive a biopsy and potentially a further PSA test or further PSA test in 3 to 6 months. The patient will then either be sent back to primary care or they may receive another biopsy. Each item was then costed with the unit prices in table 9. If there were multiple costs of a procedure, e.g. A biopsy, then a weighted average was used, this used the number of procedures were conducted during the same costing period (2019/2020). No value of a PSA cost could be found therefore, the cost of phlebotomy was used. Figure 1 shows the cost of each branch of the decision tree. The range of intervention costs is £34.50 to £1,753.69 with an annual follow up of £32 assuming an annual PSA test. If a person is referred for further investigations in secondary care, recommendations from NG131 suggest that if no cancer is found and the person is referred back to primary care then they should continue to have PSA tests either annually or every two years.

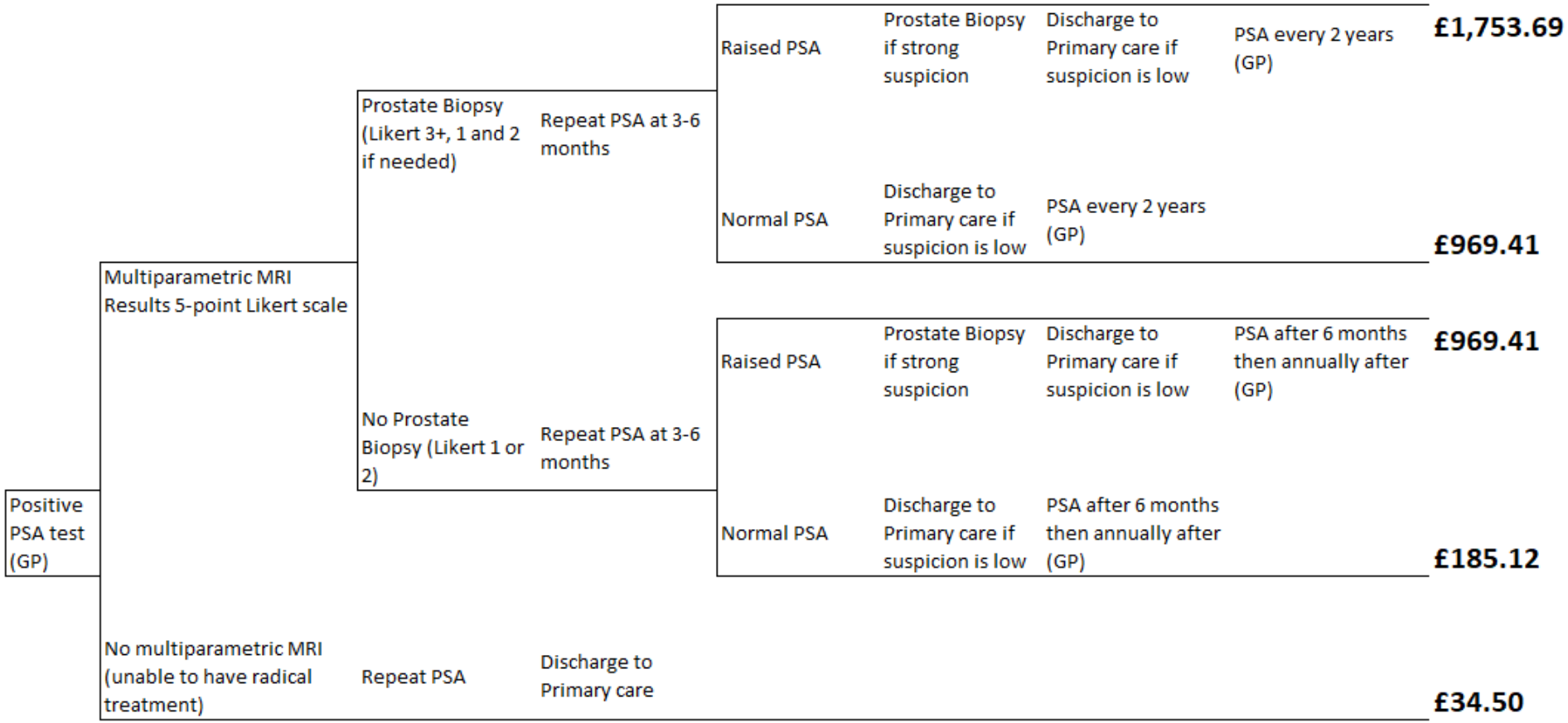

Figure 1: Costs of investigations after referral

*If at any point patients have a confirmed diagnosis of prostate cancer, they leave the diagnostic pathway and are excluded from this diagram
*Costs in the decision tree do not include the annual costs of PSA tests after referred back to primary care.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

While the committee agreed a timely referral and diagnosis of prostate cancer was important, they also thought resource impact and the burden of overtreatment should be considered when deciding to adopt a fixed or age adjusted PSA threshold. The committee agreed that positive predictive values calculated to a UK prevalence were important to give GPs confidence in using PSA thresholds as a clinically important tool for referral. The committee agreed that the range of prevalence estimates used to calculate PPV were plausible in a symptomatic population in the UK. The committee took into account the decision threshold of 3% PPV that was set by the committee who developed the 2015 version of the NICE guideline on suspected cancer when making recommendations.

The committee also considered the consequences of PSA testing outcomes as per the categories of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) in the 2x2 diagnostic table:

- A true positive result could lead to a timely diagnosis and earlier treatment, but in some cases, there would be a risk of overtreatment for non-aggressive forms of prostate cancer. This could lead to other negative health outcomes and create health anxiety.
- A false positive result could create unnecessary health anxiety and lead to iatrogenic complications associated with unnecessary biopsy.
- A true negative result could rule out further investigations in those without prostate cancer and provide appropriate reassurance.
- A false negative could lead to false reassurance, delayed diagnosis and treatment.

The committee agreed that the purpose of the PSA test was to rule out prostate cancer rather than diagnose it, so it was more important that the test was highly sensitive than highly specific but that both sensitivity and specificity were important for decision making.

1.1.12.2 The quality of the evidence

The committee noted that the quality of the evidence was low to very low based on:

- High risk of bias due to an inclusion criterion in most studies of PSA 2.5 or 4mg/ml and above. This excludes people who might have a positive diagnosis of prostate cancer with a lower PSA and falsely inflates the sensitivity of the test.
- Most studies contained a significant population of people with a positive/abnormal digital rectal examination. According to current guidance, this population would have been referred to secondary care anyway irrespective of PSA levels, so this evidence was rated down for indirectness.
- The committee cautioned that no studies sampled a population from primary care, also making it less applicable to primary care physicians.
- The committee reflected on the heterogenous population sampled which would explain some of the inconsistency between studies as demonstrated by the I^2 statistic.
- All studies used biopsy as the reference standard without combination with MRI scanning. Current practice is to use MRI-guided biopsy to diagnose prostate cancer as this identifies a greater proportion of prostate cancers. The committee agreed that the biopsies used in the studies were an imperfect test which was likely to miss some prostate cancer cases.
- The committee noted that most of the evidence didn't differentiate between clinically significant and insignificant cancer. One further study highlighted at consultation did differentiate between high risk and low risk cancers, but the committee disagreed with

the author's definition of high risk which included Gleason score 7, which the committee did not think constituted high risk cancer.
- The committee noted that some studies were quite old, meaning the methods used for measuring PSA may be outdated. However, the committee agreed that this would not significantly impact on the data.
- No study had evidence of blinded cross-verification between index test and reference standard.
- Most studies did not specify the time interval between PSA test and biopsy.

1.1.12.3 Benefits and harms

The 2015 version of the guideline recommended that people should be referred to secondary care if they have symptoms of possible prostate cancer and a PSA above the age-specific reference range. The committee made a weaker 'consider' recommendation based on uncertainties in the evidence that they reviewed, the low positive predictive value of the PSA test for prevalence estimates based on UK population data, and the fact that some people may choose not to be referred to secondary care because they might be not suitable for radical treatment or because prostate cancer might not be expected to have an impact on their life expectancy. Each of these points is expanded below.

The primary outcome specified in the protocol was positive predictive values (PPV); a measure of probability that someone with a PSA above a fixed or age adjusted threshold will have prostate cancer. The committee noted that PPVs increased as prostate cancer prevalence increases. The PPVs for both age-adjusted and all fixed test thresholds fell below the 3% decision threshold set by the committee for the 2015 version of this guideline for both lower prevalence estimates (0.1% or 1.6%) for the UK. At a prevalence estimate of 6.1%, the PPV was higher than 3% in all cases, illustrating the strong effect of prevalence on the PPV for PSA testing. The PPV was slightly higher using an age adjusted threshold (table 6) compared to the fixed thresholds of 3 or 4mg/ml (table 4), however, the committee noted the uncertainly in these effect estimates given the very low quality of the evidence. The prevalence of prostate cancer is strongly affected by age. The committee noted that many prostate cancers are slow growing and may not impact on a person's life expectancy in some cases. The committee highlighted that referral should be made in discussion with the patient, and that some patients may decide not to be referred to secondary care to avoid invasive tests and treatments that might not benefit them. They noted that some patients might not be suitable for treatment, particularly those with co-morbidities and that this, along with their preferences, should be taken into consideration and reflected in the recommendation.

The committee agreed that PSA was heavily influenced by age. While a lower PSA threshold would pick up more cases of prostate cancer, it could lead to unnecessary biopsies and the potential overtreatment of less clinically significant cancer in some older age groups. This could also lead to a significant resource impact on secondary care. A higher threshold would lead to less false positives but could miss a significant proportion of people with prostate cancer and a lower PSA. The committee noted that while sensitivity and specificity were inconsistent due to high risk of bias and differences between study populations, overall it did show a general pattern of sensitivity decreasing as thresholds went up.

Overall, the committee didn't feel the evidence was strong enough to move practice away from age-adjusted thresholds, but also that the evidence supporting age-adjusted thresholds was not strong and that a weaker 'consider' recommendation should be made to reflect this. As there was variation in practice around the country, the committee also felt it would be helpful to define the age adjusted thresholds in the recommendation. In the absence of other evidence to suggest different thresholds in a population with symptoms, the age adjusted thresholds used in the evidence reviewed (table 6) were considered appropriate by the committee based on their knowledge of current practice and the marginally higher PPV found for these compared to fixed thresholds of 3 or 4mg/ml. No evidence was found for thresholds

below the age of 40 or above the age of 79, and so the committee recommended that clinical judgment was used in these groups.

One further study (table 5 and 8) highlighted at consultation by stakeholders provided new evidence on different age-adjusted thresholds in an asymptomatic population. The committee noted that this evidence was for a population without symptoms so was indirectly applicable to the review question. The positive predictive values for age-specific thresholds were similar to those for the age-specific thresholds recommended in the pre consulation version of the guideline. The committee therefore did not make any changes to the recommendations as a result of this study.

The committee agreed that due to the lack of good quality evidence on the diagnostic accuracy of fixed and age adjusted PSA thresholds, a research recommendation would help address this question for future guideline updates (see appendix K for more details).

1.1.12.4 Cost effectiveness and resource use

There was not any existing health economic evidence for this review question. However, the committee was shown a range of costs of a false positive PSA test.

The committee felt that the transperineal template biopsy of prostate was not commonly used however, the NHS Cost Collection showed that it was used about half the time a biopsy was done therefore the average cost of both biopsies was used. If the lower cost biopsy was the only one used then the most expensive line of the decision tree (two biopsies, a MRI and two PSA tests) would be £1,398.13.

The committee noted that while it was assumed that patients would receive a maximum of two biopsies and then be discharged back to primary care, it is possible that the patient could still receive investigations in secondary care and therefore the cost of a false positive could be more than the £1,753.69 estimated.

The committee noted that there is large variation in practice around the country. Most areas currently use an age-specific PSA level but there are differing values for all the age ranges depending on location. Therefore, the committee felt that it was important to introduce standardised thresholds to reduce this variation. The committee noted that the population of people with symptoms undergoing a PSA test is large and therefore a change in referral threshold could have a large resource impact. This would especially be true if it increased the number of false positives being referred. The committee felt that current practice uses a referral value of about 3 ng/ml for the age range 50-59 with younger ages using a lower value and older ages using a higher value. Therefore, the committee felt that there would not be a significant resource impact from the new recommendation.

1.1.12.5 Other factors the committee took into account

The committee reflected that risk of prostate cancer and experiencing poor outcomes is heavily influenced by both family history and ethnicity. The committee discussed whether these factors should be taken into account when deciding what PSA threshold should prompt referral to secondary care. However, no evidence was found for these populations, and the committee noted that recommending different thresholds for referral in the absence of evidence could do more harm than good, because the risks of under and overtreatment are both important. Instead, the committee made a research recommendation that included stratification of data for people at high risk of prostate cancer (include people with a family history of prostate cancer and a black African family origin) to determine whether the PSA threshold that should prompt referral to secondary should differ for these groups. The committee noted that a key decision for the original committee that developed NG12 was whether their recommendations, across all types of cancer, were to be the same for patients irrespective of whether a specific risk factor, such as family history, was also present. Of the possible risk factors that were reported in the literature identified by the original searches for

NG12, only age and smoking (in lung cancer) were found to significantly influence the chance of symptoms being predictive of cancer and this was reflected in the NG12 recommendations. The current committee questioned whether a person's ethnicity or family history of prostate cancer might alter the predictive value of symptoms for prostate cancer, and therefore might need to be taken into account when deciding whether to conduct a PSA test, but noted that this question was beyond the scope of this update.'

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendation 1.6.3 and the research recommendation on prostate specific antigen testing.

1.1.14 References – included studies

1.1.14.1 Diagnostic evidence

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1.1.14.2 Economic

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1.1.14.3 Other

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Appendices

Appendix A – Review protocols

Table 10: Review protocol for prostate specific antigen (PSA) thresholds for referring people with suspected prostate cancer

ID	Field	Content
0.	PROSPERO registration number	CRD42021270545
1.	Review title	Suspected prostate cancer referral – PSA levels
2.	Review question	In people with suspected prostate cancer (with any of the following symptoms - any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or) erectile dysfunction or visible haematuria), what is the diagnostic accuracy of fixed PSA test threshold compared to age-adjusted PSA thresholds?
3.	Objective	To determine the most accurate PSA level and whether age-adjustment threshold is appropriate for referring people using the suspected cancer pathway referral for prostate cancer.
4.	Searches	The following databases will be searched: • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

		Searches will be restricted by: • No date limit. • English language • Human studies Other searches: • Reference lists The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Prostate specific antigen levels in those people suspected of prostate cancer.
6.	Population	Initially the inclusion will be for the population in this question (symptomatic). But if there is insufficient evidence available then other populations as listed below will be considered that may provide indirect evidence.

		Inclusion: People suspected of prostate cancer with any of the following symptoms: • any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or • erectile dysfunction or • visible haematuria Exclusion: • Screening for prostate cancer in those without symptoms. • People diagnosed with prostate cancer. **Other populations from which indirect evidence may be extracted:** Inclusion: • Asymptomatic people • People with any other prostate cancer symptoms not listed above.

7.	Test/Intervention	• Age-adjusted prostate-specific antigen test • PSA test (without age adjustment - fixed test threshold) Please note we will only look at data using clinically plausible thresholds as discussed with the committee.
8.	Reference standard/Comparator	• Multiparametric MRI scan • Prostate biopsy
9.	Types of study to be included	• Cross-sectional diagnostic test accuracy studies. Systematic reviews of the diagnostic test accuracy studies.
10.	Other exclusion criteria	• All other study types. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals.
11.	Context	Prostate-specific antigen (PSA) test aims to detect localized prostate cancer. Current NICE recommendations refer to age-specific cut-offs as part of the suspected prostate cancer referral pathway. However, recent evidence shows that around 15% of men with a normal PSA do have cancer and age-specific cut-offs may not be appropriate for referring people for specialist services.

		The Prostate Cancer Risk Management Programme realigned the PSA referral values to the evidence and PHE issued guidance stating that men with PSA over 3ng/ml should be referred to a specialist, regardless of age. This review aims to consider the new evidence and potentially change current NICE suspected prostate cancer referral recommendations.
12.	Primary outcomes (critical outcomes)	• Positive predictive values (recalculated to prevalence in the UK population and not study population). Note: in NG12 the PPV of >3% is used.
13.	Secondary outcomes (important outcomes)	• Sensitivity (detection rate) and specificity.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.

		This review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the QUADAS-2 checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis** Meta-analysis of diagnostic accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). Where five or more studies were available for all included strata, a bivariate model will be 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 is not available (2-4 studies), separate independent pooling will be 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) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). **Approach to GRADE**

		Evidence from diagnostic accuracy studies will initially be rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness). Positive predictive values will be used as the primary outcome for decision making to define clinical decision thresholds in GRADE. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes will be considered. This will be done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences will be incorporated here in addition.	
17.	Analysis of sub-groups	• Age cut-offs as defined in the studies. • Ethnicity • Family history of prostate cancer.	
		□	Intervention

18.	Type and method of review	☒	Diagnostic	
		☐	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	12 May 2021		
22.	Anticipated completion date	To be determined		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**

		Preliminary searches	☐ ☐	☐ ☐
		Piloting of the study selection process	☐ ☐	☐ ☐
		Formal screening of search results against eligibility criteria	☐ ☐	☐ ☐
		Data extraction	☐ ☐	☐ ☐

		Risk of bias (quality) assessment	☐ ☐	☐ ☐
		Data analysis	☐ ☐	☐ ☐
24.	Named contact	**5a. Named contact** NICE Guideline Updates Team **5b Named contact e-mail** gutprospero@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and Guideline Updates Team / NICE		
25.	Review team members	From the Guideline Updates Team • Kathryn Hopkins – Technical Adviser • Anthony Gildea- Technical Analyst • Lucy Beggs – Technical Adviser – Health Economics • Stephanie Armstrong – Technical Analyst – Health Economics • Hannah Lomax – Technical Analyst – Health Economics		

		• Vonda Murray – Project Manager • Wes Hubbard – Information Specialist
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Updates Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10194/documents
29.	Other registration details	Registration no: CRD42021270545
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021270545
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts

		• issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	prostate-specific antigen, PSA levels, suspected prostate cancer
33.	Details of existing review of same topic by same authors	This is a new review question that will update prostate cancer section in the NICE Guideline: Suspected cancer: recognition and referral (2021) NICE guideline NG12.
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	This review will be used the referral section for prostate cancer in the current NICE guideline NG12 Suspected Cancer: recognition and referral.
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were originally run in July 2021. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review Management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The terms for 'prostate cancer' are based on those used for the previous NICE guideline, NG131 Prostate cancer: diagnosis and management (2019). However, amendments were made to the search strategy as appropriate for this specific evidence review topic.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude, comment or letter or editorial or historical articles or conference abstract or conference paper or "conference review" or letter or case report were applied in adherence to standard NICE practice and the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters

Diagnosis

The following search filter was applied to the clinical searches in MEDLINE and Embase to identify diagnostic studies: McMaster Diagnosis - (best balance of sensitivity and specificity)

Cost effectiveness searches

The NICE cost utility filter was applied to the search strategies in MEDLINE and Embase to identify cost-utility studies. *(Hubbard W, et al. Development of a validated search filer to identify cost utility studies for NICE economic evidence reviews. NICE Information Services.)*

Clinical searches

Databases	Date searched	Version/files	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley	12/07/2021	Issue 7 of 12, July 2021	402
Cochrane Database of Systematic Reviews (CDSR) via Wiley	12/07/2021	Issue 7 of 12, July 2021	11
Database of Abstracts of Reviews of Effect (DARE) via CRD	12/07/2021	n/a	77
Embase (Ovid)	12/07/2021	1974 to 2021 July 09	3824
Health Technology Assessment (HTA) via CRD	12/07/2021	n/a	59
International Network of Agencies for Health Technology Assessment (INAHTA)	12/07/2021	n/a	62
MEDLINE (Ovid)	12/07/2021	1946 to June Week 5 2021	3963
MEDLINE In-Process (Ovid)	12/07/2021	1946 to July 09, 2021	55
MEDLINE Epub Ahead of Print (Ovid)	12/07/2021	July 09, 2021	50
Total			**8503**

Database: Ovid MEDLINE(R) <1946 to June Week 5 2021>
1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 52971

2 Prostatic Intraepithelial Neoplasia/ 1375
3 (PCa or PrCa).tw. 38439
4 *Early Detection of Cancer/ and Prostat*.tw. 1512
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 15215
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 9003
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 7640
8 or/1-7 91741
9 *Prostate-Specific Antigen/ 11939
10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 9754
11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 13606
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 10036
13 or/9-12 32948
14 8 and 13 14096
15 (sensitiv: or predictive value:).mp. or accurac:.tw. 1989766
16 14 and 15 4490
17 Animals/ not Humans/ 4821499
18 16 not 17 4480
19 limit 18 to english language 4055
20 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2152440
21 19 not 20 3963

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to July 09, 2021>

1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 0
2 Prostatic Intraepithelial Neoplasia/ 0
3 (PCa or PrCa).tw. 1253
4 *Early Detection of Cancer/ and Prostat*.tw. 0

5	((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw.	412
6	((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw.	192
7	((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw.	216
8	or/1-7	1743
9	*Prostate-Specific Antigen/	0
10	(Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw.	204
11	(PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw.	307
12	(Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw.	84
13	or/9-12	475
14	8 and 13	197
15	(sensitiv: or predictive value:).mp. or accurac:.tw.	34154
16	14 and 15	55
17	Animals/ not Humans/	0
18	16 not 17	55
19	limit 18 to english language	55

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 09, 2021>

1	exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw.	0
2	Prostatic Intraepithelial Neoplasia/	0
3	(PCa or PrCa).tw.	983
4	*Early Detection of Cancer/ and Prostat*.tw.	0
5	((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw.	307
6	((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw.	188

7	((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 164
8	or/1-7 1371
9	*Prostate-Specific Antigen/ 0
10	(Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 159
11	(PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 262
12	(Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 57
13	or/9-12 376
14	8 and 13 151
15	(sensitiv: or predictive value:).mp. or accurac:.tw. 27178
16	14 and 15 51
17	Animals/ not Humans/ 0
18	16 not 17 51
19	limit 18 to english language 50

Database: Embase <1974 to 2021 July 09>

1	exp prostate tumor/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 111203
2	prostatic intraepithelial neoplasia/ 2927
3	(PCa or PrCa).tw. 70789
4	*early cancer diagnosis/ and Prostat*.tw.206
5	((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 27964
6	((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 14758
7	((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 14006
8	or/1-7 176619
9	*prostate specific antigen/ 15111
10	(Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 13865

11	(PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw.	27668
12	(Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw.	12269
13	or/9-12	51765
14	8 and 13	24913
15	(sensitiv: or predictive value:).mp. or accurac:.tw.	2756602
16	14 and 15	6401
17	Nonhuman/ not Human/	4818551
18	16 not 17	6360
19	limit 18 to english language	5909
20	Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt.	6810422
21	19 not 20	3824

Database: Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL)

#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees	5746
#2	(suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*):ti,ab,kw	492308
#3	#1 and #2	2850
#4	MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only	47
#5	(PCa or PrCa):ti,ab,kw	5247
#6	MeSH descriptor: [Early Detection of Cancer] this term only	1267
#7	Prostat*:ti,ab,kw	22725
#8	#6 and #7	194
#9	((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) near/2 prostat* near/2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)):ti,ab,kw	2374
#10	((Assess* or investigat* or test* or screen* or detect*) near/2 prostat* near/2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)):ti,ab,kw	1309
#11	((Confirm* or diagnos*) near/2 prostat* near/2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)):ti,ab,kw	1862
#12	#3 or #4 or #5 or #8 or #9 or #10 or #11	10343
#13	MeSH descriptor: [Prostate-Specific Antigen] this term only	1321
#14	(Prostate* specific antigen near/2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)):ti,ab,kw	1124

#15 (PSA near/2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)):ti,ab,kw 2316
#16 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3):ti,ab,kw 624
#17 #13 or #14 or #15 or #16 3911
#18 #12 and #17 1829
#19 (sensitiv* or predictive value* or accurac*) 111223
#20 #18 and #19 413

Database: Database of Abstracts of Reviews of Effect (DARE) and Health Technology Assessment (HTA)

1 MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES 709
2 ((suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect)) 32541
3 #1 AND #2 297
4 MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia EXPLODE ALL TREES 2
5 ((PCa or PrCa)) 44
6 MeSH DESCRIPTOR Early Detection of Cancer EXPLODE ALL TREES 277
7 (Prostat*) 1302
8 #6 AND #7 11
9 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 507
10 ((Assess* or investigat* or test* or screen* or detect*)) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 715
11 ((Confirm* or diagnos*)) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 331
12 #3 OR #4 OR #5 OR #8 OR #9 OR #10 OR #11 850
13 MeSH DESCRIPTOR Prostate-Specific Antigen EXPLODE ALL TREES 115
14 (Prostate* specific antigen) AND ((level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)) 184
15 (PSA) AND ((level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)) 157
16 ((Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3)) 18

17	#13 OR #14 OR #15 OR #16	264
18	#12 AND #17	192
19	* IN DARE	45418
20	#18 AND #19	77
21	* IN HTA	17351
22	#18 AND #21	59

Database: International Network of Agencies for Health Technology Assessment

16	#15 AND #10	62
15	#14 OR #13 OR #12 OR #11	77
14	((Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3))	2
13	(PSA) AND (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)	61
12	(Prostate* specific antigen) AND (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)	40
11	"Prostate-Specific Antigen"[mhe]	33
10	#9 OR #8 OR #7 OR #6 OR #3 OR #2 OR #1	242
9	(Confirm* or diagnos*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)	72
8	(Assess* or investigat* or test* or screen* or detect*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)	195
7	(Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)	144
6	#5 AND #4	6
5	(Prostat*)	442
4	"Early Detection of Cancer"[mh]	59
3	((PCa or PrCa))	4
2	"Prostatic Intraepithelial Neoplasia"[mh]	0
1	"Prostatic Diseases"[mh]	3

Cost effectiveness searches

Databases	Date searched	Version/files	No. of results downloaded
EconLit (Ovid)	13/07/2021	1886 to July 08, 2021	7
Embase (Ovid) (apply economics filter)	13/07/2021	1974 to 2021 July 12	75
NHS Economic Evaluation Database (NHS EED) via CRD	13/07/2021	n/a	56
International Network of Agencies for Health Technology Assessment (INAHTA)	13/07/2021	n/a	62
MEDLINE (Ovid) (apply economics filter)	13/07/2021	1946 to June Week 5 2021	116
MEDLINE In-Process (Ovid) (apply economics filter)	13/07/2021	1946 to July 12, 2021	4
MEDLINE Epub Ahead of Print (apply economics filter)	13/07/2021	July 12, 2021	2
Total			***322***

Database: Ovid MEDLINE(R) <1946 to July 12, 2021>

1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 53049
2 Prostatic Intraepithelial Neoplasia/ 1377
3 (PCa or PrCa).tw. 38544
4 *Early Detection of Cancer/ and Prostat*.tw. 1514
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 15236
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 9011
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 7658
8 or/1-7 91914
9 *Prostate-Specific Antigen/ 11952
10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 9764

11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 13628
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 10044
13 or/9-12 32984
14 8 and 13 14116
15 Cost-Benefit Analysis/ 85392
16 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 12139
17 ((incremental* adj2 cost*) or ICER).tw. 12513
18 (cost adj2 utilit*).tw. 4803
19 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 1554
20 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 16692
21 (cost and (effect* or utilit*)).ti. 28668
22 or/15-21 96446
23 14 and 22 131
24 limit 23 to english language 120
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 2154852
26 24 not 25 116

Database: Ovid MEDLINE(R) In-Process & In-Data-Review Citations <1946 to July 12, 2021>

1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 0
2 Prostatic Intraepithelial Neoplasia/ 0
3 (PCa or PrCa).tw. 1253
4 *Early Detection of Cancer/ and Prostat*.tw. 0
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 412
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 192
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 216
8 or/1-7 1743
9 *Prostate-Specific Antigen/ 0

10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 204
11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 307
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 84
13 or/9-12 475
14 8 and 13 197
15 Cost-Benefit Analysis/ 0
16 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 547
17 ((incremental* adj2 cost*) or ICER).tw. 557
18 (cost adj2 utilit*).tw. 181
19 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 72
20 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 653
21 (cost and (effect* or utilit*)).ti. 732
22 or/15-21 1200
23 14 and 22 4
24 limit 23 to english language 4
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 24464
26 24 not 25 4

Database: Ovid MEDLINE(R) Epub Ahead of Print <July 12, 2021

1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 0
2 Prostatic Intraepithelial Neoplasia/ 0
3 (PCa or PrCa).tw. 983
4 *Early Detection of Cancer/ and Prostat*.tw. 0
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 307
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 188
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 164
8 or/1-7 1371
9 *Prostate-Specific Antigen/ 0

10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 159
11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 262
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 57
13 or/9-12 376
14 8 and 13 151
15 Cost-Benefit Analysis/ 0
16 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 457
17 ((incremental* adj2 cost*) or ICER).tw. 393
18 (cost adj2 utilit*).tw. 209
19 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 57
20 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 615
21 (cost and (effect* or utilit*)).ti. 620
22 or/15-21 1193
23 14 and 22 2
24 limit 23 to english language 2
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 17181
26 24 not 25 2

Database: Embase <1974 to 2021 July 12>

1 exp prostate tumor/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 111203
2 prostatic intraepithelial neoplasia/ 2927
3 (PCa or PrCa).tw. 70789
4 *early cancer diagnosis/ and Prostat*.tw.206
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 27964
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 14758
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 14006
8 or/1-7 176619
9 *prostate specific antigen/ 15111

10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 13865
11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 27668
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 12269
13 or/9-12 51765
14 8 and 13 24913
15 cost utility analysis/ 10473
16 (cost* and ((qualit* adj2 adjust* adj2 life*) or qaly*)).tw. 24853
17 ((incremental* adj2 cost*) or ICER).tw. 25449
18 (cost adj2 utilit*).tw. 9204
19 (cost* and ((net adj benefit*) or (net adj monetary adj benefit*) or (net adj health adj benefit*))).tw. 2564
20 ((cost adj2 (effect* or utilit*)) and (quality adj of adj life)).tw. 30356
21 (cost and (effect* or utilit*)).ti. 49407
22 or/15-21 77943
23 14 and 22 130
24 limit 23 to english language 124
25 Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt. 6810422
26 24 not 25 75

Database: Econlit <1886 to July 08, 2021>

1 exp Prostatic Neoplasms/ and (suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*).tw. 0
2 Prostatic Intraepithelial Neoplasia/ 0
3 (PCa or PrCa).tw. 485
4 *Early Detection of Cancer/ and Prostat*.tw. 0
5 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 6
6 ((Assess* or investigat* or test* or screen* or detect*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 17
7 ((Confirm* or diagnos*) adj2 prostat* adj2 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)).tw. 4
8 or/1-7 509
9 *Prostate-Specific Antigen/ 0

10 (Prostate* specific antigen adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 9
11 (PSA adj2 (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)).tw. 17
12 (Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3).tw. 0
13 or/9-12 20
14 8 and 13 7

Database: NHS Economic Evaluation Database (NHS EED)

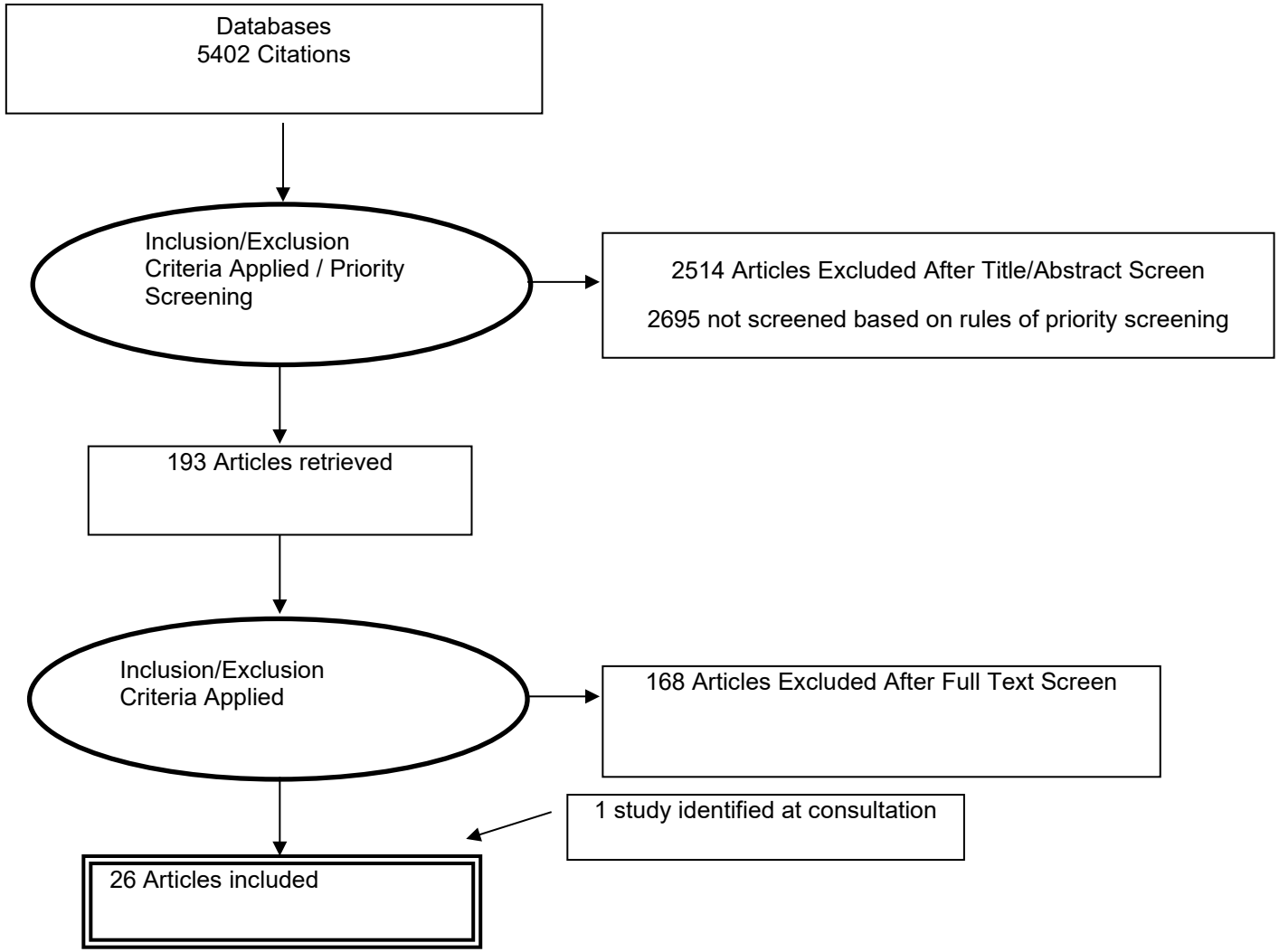
1 MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES 709
2 ((suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect)) 32541
3 #1 AND #2 297
4 MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia EXPLODE ALL TREES 2
5 ((PCa or PrCa)) 44
6 MeSH DESCRIPTOR Early Detection of Cancer EXPLODE ALL TREES 277
7 (Prostat*) 1302
8 #6 AND #7 11
9 ((Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 507
10 ((Assess* or investigat* or test* or screen* or detect*)) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 715
11 ((Confirm* or diagnos*)) AND (prostat*) AND ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*)) 331
12 #3 OR #4 OR #5 OR #8 OR #9 OR #10 OR #11 850
13 MeSH DESCRIPTOR Prostate-Specific Antigen EXPLODE ALL TREES 115
14 (Prostate* specific antigen) AND ((level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)) 184
15 (PSA) AND ((level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*)) 157
16 ((Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3)) 18

17 #13 OR #14 OR #15 OR #16 264
18 #12 AND #17 192
19 * IN DARE 45418
20 #18 AND #19 77
21 * IN HTA 17351
22 #18 AND #21 59
23 * IN NHSEED 17613
24 #18 AND #23 56

Database: International Network of Agencies for Health Technology Assessment

16 #15 AND #10 62
15 #14 OR #13 OR #12 OR #11 77
14 ((Kallikrein* or KLK3 or KLK-3 or hK3 or hK-3)) 2
13 (PSA) AND (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*) 61
12 (Prostate* specific antigen) AND (level* or test* or value* or threshold* or assess* or investigate* or screen* or densit* or ratio* or marker* or follow-up* or followup* or monitor*) 40
11 "Prostate-Specific Antigen"[mhe] 33
10 #9 OR #8 OR #7 OR #6 OR #3 OR #2 OR #1 242
9 (Confirm* or diagnos*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*) 72
8 (Assess* or investigat* or test* or screen* or detect*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*) 195
7 (Suspect* or earl* or risk* or possible* or symptomat* or asymptomatic* or detect*) AND (prostat*) AND (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump* or disease*) 144
6 #5 AND #4 6
5 (Prostat*) 442
4 "Early Detection of Cancer"[mh] 59
3 ((PCa or PrCa)) 4
2 "Prostatic Intraepithelial Neoplasia"[mh] 0
1 "Prostatic Diseases"[mh] 3

Appendix C - Diagnostic evidence study selection



Appendix D – Diagnostic test accuracy evidence tables

Abdrabo, 2011

Bibliographic Reference	Abdrabo, Abdelkarim A; Fadlalla, Adil I; Fadl-Elmula, Imad M; Significance of serum total prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer.; Saudi medical journal; 2011; vol. 32 (no. 11); 1133-6

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Sudan Setting Urology clinic in hospital Study dates August 2008- January 2010 Sources of funding Unclear - but likely to be Al Neelain University
Inclusion criteria	PSA range PSA 2.5-10 Symptoms

	Lower Urinary Tract Symptoms
Exclusion criteria	Not stated
Number of participants	n=118
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Additional comments	

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 118)**
Mean age (SD) Nominal	70
Mean age (SD) Range	56 to 83

Characteristic	Study (N = 118)
% with positive digital rectal examination Custom value	41.5%
Ethnicity Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Sample chosen based on PSA range)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Excluded people outside of the PSA range 2.5-10)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Yes - PSA measurement before biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Unclear how long after PSA measurement biopsy was performed)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes *(All included in the analysis)*

Section	Question	Answer
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of bias due to population being selected on PSA range 2.5-10)*
Overall risk of bias and directness	Directness	Partially applicable *(41.5% had positive DRE)*

Agnihotri, 2014

Bibliographic Reference	Agnihotri, Shalini; Mittal, R D; Kapoor, R; Mandhani, Anil; Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy.; The Indian journal of medical research; 2014; vol. 139 (no. 6); 851-6

Study Characteristics

Study type	Cross-sectional study
Study details	Study location

	Lucknow, India Setting department of Urology Study dates January 2000- June 2011 Sources of funding Indian Council of Medical Research (ICMR
Inclusion criteria	PSA range >4ng/ml or positive DRE Symptoms LUTS
Exclusion criteria	Excluded: Five hundred and seventeen men, who did not have biopsy due to associated morbidity and discretion of the treating urologist (taking into account the age of the patient, DRE finding and PSA levels) were excluded from the final analysis Excluded: clinical evidence of prostatitis, positive urine culture, patients on urethral catheter, 5α blocker reductase inhibitors and those who had surgery or biopsy on prostate in the preceding three months
Number of participants	n=875
Length of follow-up	N/A

Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 875)**
Mean age (SD) Mean (SD)	65.72 (7.4)
% with positive digital rectal examination Custom value	51.2%
Ethnicity Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Patients included based on having a DRE exam and PSA testing)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(People with negative DRE and PSA <4 excluded by default.)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(>50% had a positive DRE - an excluded population as these people would have been referred for biopsy regardless of PSA)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Likely as patients selected on PSA testing before biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes *(All included in analysis)*
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Greater than 50% had positive DRE, and those with PSA <4 had positive DRE)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Partially applicable

Catalona, 1994

Bibliographic Reference	Catalona, William J; Hudson, M'liss A; Scardino, Peter T; Richie, Jerome P; Ahmann, Frederick R; Flanigan, Robert C; DeKernion, Jean B; Ratliff, Timothy L; Kavoussi, Louis R; Dalkin, Bruce L; Waters, W Bedford; MacFarlane, Michael T; Southwick, Paula C; Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves.; The Journal of urology; 1994; vol. 152 (no. 6pt1); 2037-42

Study Characteristics

Study type	Cross-sectional study
Study details	Study location USA Setting 6 medical centres Study dates May 1991 - September 1992 Sources of funding not clear

Inclusion criteria	PSA range PSA >4ng/ml DRE Abnormal DRE
Exclusion criteria	Excluded: Those outside inclusion criteria
Number of participants	n=1167
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold stratified by age
Reference standard (s)	Biopsy
Subgroup analyses	XX Subgroup analysis by age

Population characteristics

Study-level characteristics

Characteristic	Study (N = 1167)
% with positive digital rectal examination Custom value	Unclear for those biopsied
median age Custom value	63
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Chosen based on greater than 4ng/ml PSA and abnormal DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Unclear what percentage of biopsied population have positive DRE, but this is used as inclusion criteria)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Used as selection criteria for biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Threshold for inclusion in study)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(ref standard done based on knowledge of PSA)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear

Section	Question	Answer
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes *(All included in this analysis)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(>4ng/ml PSA or abnormal DRE as selection criteria)*
Overall risk of bias and directness	Directness	Indirectly applicable *(Screening population and unclear what proportion of those biopsied had positive DRE but this was used as an inclusion criteria)*

Clark, 1997

Bibliographic Reference	Clark, T W; Goldenberg, L; Cooperberg, P L; Wong, A D; Singer, J; Stratification of prostate-specific antigen level and results of transrectal ultrasonography and digital rectal examination as predictors of positive prostate biopsy.; Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes; 1997; vol. 48 (no. 4); 252-8

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Vancouver, Canada Setting tertiary care hospital Study dates Unclear - 24 month period Sources of funding Unclear
Inclusion criteria	Symptoms Referred by urologist for a combination of abnormal DRE, elevated or rising PSA, strong family history, or voiding symptoms
Exclusion criteria	Excluded: Those without either abnormal DRE, high or rising PSA, a strong family history of prostate cancer or voiding symptoms
Number of participants	n=1330
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold

	PSA age adjusted
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 1330)**
Mean age (SD) Mean (SD)	66 (8.4)
% with positive digital rectal examination Custom value	59.25%
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Based on elevated or rising PSA, abnormal DRE, family history of symptoms)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Those outside the inclusion for biopsy criteria)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(>59.25% had abnormal DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Elevated or rising PSA a criteria to do biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(No threshold was pre-stated)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA levels used as indicator for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Knowledge of PSA levels and other referral criteria)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(No pre-specified PSA referral threshold but 'rising /elevated PSA' used as criteria for biopsy)*
Overall risk of bias and directness	Directness	Partially applicable *(>30% had abnormal DRE)*

Crawford, 1999

Bibliographic Reference	Crawford, E D; Leewansangtong, S; Goktas, S; Holthaus, K; Baier, M; Efficiency of prostate-specific antigen and digital rectal examination in screening, using 4.0 ng/ml and age-specific reference range as a cutoff for abnormal values.; The Prostate; 1999; vol. 38 (no. 4); 296-302

Study Characteristics

Study type	Cross-sectional study
Study details	Study location USA Setting Division of Urology (Prostate Cancer Awareness Week database) Study dates 1992-1995 Sources of funding not stated
Inclusion criteria	PSA range Abnormal PSA DRE Abnormal DRE

Number of participants	n=3029 (included in this analysis)
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA age adjusted
Reference standard (s)	Biopsy
Additional comments	

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 3029)**
Mean age (SD) Range	40 to 79
% with positive digital rectal examination Custom value	69.8%
Ethnic group Custom value	Unclear for population in this analysis

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Selected based on >4ng/ml PSA or Abnormal DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(69.8% with an abnormal DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(Data determined from a database)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(4ng/ml specified as inclusion criteria)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes *(All with biopsy)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(>4ng/ml PSA or abnormal DRE selection criteria)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Indirectly applicable *(69.8% with positive DRE and screening population)*

Dalva, 1999

Bibliographic Reference	Dalva, I; Akan, H; Yildiz, O; Telli, C; Bingol, N; The clinical value of the ratio of free prostate specific antigen to total prostate specific antigen.; International urology and nephrology; 1999; vol. 31 (no. 5); 675-80

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Turkey Setting Outpatient urology department Study dates Study dates not stated Sources of funding Funding source not stated
Inclusion criteria	PSA range

	Above 4ng/ml DRE Positive DRE or PSA >4ng/ml or FPSA/TPSA ratio lower than 0.15
Exclusion criteria	Excluded: Negative DRE or PSA <4 or FPSA/TPSA ratio >0.15
Number of participants	n=76
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	None
Additional comments	Only patients biopsied included in totals

Population characteristics

Study-level characteristics

Characteristic	Study (N = 76)
Mean age (SD) Mean (SD)	69.11 (1.48)
% with positive digital rectal examination Custom value	Unclear
Ethnicity Custom value	Ethnicity not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Participants chosen for biopsy by DRE, PSA or F/T PSA ratio status)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(People with <4ng/ml and negative DRE excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Some patients have a positive DRE - unclear how many as a percentage)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Yes as biopsy (ref standard) only given based on PSA results, therefore PSA test done prior to ref standard)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	High *(Yes - those with index test /PSA below a specified threshold of 4 were not biopsied)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(Biopsy done based on PSA results)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Ref standard only given to those above a pre-specified index test threshold)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Section	Question	Answer
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes *(Not all patients included in the study, but all included in this analysis)*
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	No *(Not in the authors analysis)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High
Overall risk of bias and directness	Directness	Partially applicable *(Unclear what percentage had positive DRE)*

Djavan, 2002

Bibliographic Reference	Djavan, Bob; Remzi, Mesut; Zlotta, Alexandre; Seitz, Christian; Snow, Peter; Marberger, Michael; Novel artificial neural network for early detection of prostate cancer.; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2002; vol. 20 (no. 4); 921-9

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Vienna based multicentre database - Europe Setting referral database Study dates January 1997-January 2000 Sources of funding Unclear
Inclusion criteria	PSA range 2.5-10ng/ml Symptoms LUTS
Exclusion criteria	Excluded: Patients with a family history of prostate cancer were excluded from the study
Number of participants	n=1246
Length of follow-up	N/A

Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	PSA thresholds 2.5-4,ng/ml, 4-10ng/ml
Additional comments	Unclear what percentage had positive DRE, but this was measured

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 1246)**
Mean age (SD) Mean (SD)	67.25 (8.13)
% with positive digital rectal examination Custom value	Unclear
Ethnic group Custom value	Not given

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(based on PSA criteria)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Patients with a family history of prostate cancer excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Only patients with PSA >2.5ng/ml - 10ng/ml selected)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Only patients in 2.5-10ng/ml range selected)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Partially applicable *(Some of the population had positive DRE ('suggestive of cancer') but unclear what percentage)*

Filella, 1996

Bibliographic Reference	Filella, X; Molina, R; Ballesta, A M; Gil, M J; Allepuz, C; Rioja, L A; Value of PSA (prostate-specific antigen) in the detection of prostate cancer in patients with urological symptoms. Results of a multicentre study.; European journal of cancer (Oxford, England : 1990); 1996; vol. 32a (no. 7); 1125-8

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Spain Setting 19 hospital urology departments Study dates Unclear Sources of funding Unclear

Inclusion criteria	Age >50
Exclusion criteria	Excluded: Patients with a previous history of prostate cancer, clinically suspected acute prostatitis, concomitant severe organic disease, or treated with corticosteroids, anti-androgens or LH-RI-I analogues within 3 months prior to inclusion PSA <3ng/ml and negative DRE
Number of participants	n=587
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	None

Population characteristics

Study-level characteristics

Characteristic	Study (N = 587)
Mean age (SD) Mean (SD)	66.6 (*empty data*)
% with positive digital rectal examination Custom value	30.83%
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Patients selected on PSA status)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(Only patients with >3ng/ml PSA included)*

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Greater than 30% or participants had positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(Biopsy conducted based on results of index test)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear

Section	Question	Answer
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Based on population selected due to PSA >3 and lack of information about timing of PSA test in relation to biopsy)*
Overall risk of bias and directness	Directness	Partially applicable *(Based on % with positive DRE in population)*

Gilbert, 2018

Bibliographic Reference	Gilbert, Rebecca; Tilling, Kate; Lane, J. Athene; Davis, Michael; Donovan, Jenny L.; Metcalfe, Chris; Martin, Richard M.; Hamdy, Freddie C.; Neal, David E.; Developing new age-specific prostate-specific antigen thresholds for testing for prostate cancer; Cancer Causes and Control; 2018; vol. 29 (no. 3); 383-388

Study Characteristics

Study type	Cross-sectional study

Study details	Study location UK Setting prostate check clinic Study dates 2001 and 2009 Sources of funding RG is funded by a Cancer Research UK Population Research Postdoctoral Fellowship (C31211/A15194). The study is supported by the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, HTA
Inclusion criteria	PSA range <10ng/ml Age 50-69
Exclusion criteria	Not stated
Number of participants	N=8016 in this analysis. Those with PSA <3ng/ml excluded from population total as biopsy/ref standard not done.
Length of follow-up	N/A
Loss to follow-up	N/A

Index test(s)	PSA fixed threshold PSA age adjusted
Reference standard (s)	Biopsy
Additional comments	

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 8016)**
Mean age (SD) Custom value	With PC - 62.4
Mean age (SD) Custom value	Without/low risk PC: 59.3
% with positive digital rectal examination Custom value	Not stated
Ethnicity Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear
Patient selection: risk of bias	Was a case-control design avoided?	yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Excluded ages outside 50-69 - and excluded those with PSA >10ng/ml)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Men from a screening population)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA >3 used as criteria for biopsy)*

Section	Question	Answer
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	No *(Those with PSA <3 didn't receive biopsy - numbers excluded from this analysis)*
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	No *(Those with PSA <3 excluded from this analysis. 9 people excluded from study analysis due to missing clinical information)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Age range 50-69, those with PSA <3ng/ml not biopsied and only included those with PSA <10ng/ml in study.)*
Overall risk of bias and directness	Directness	Indirectly applicable *(Screening population used)*

Kikuchi, 2000

Bibliographic Reference	Kikuchi, E; Nakashima, J; Ishibashi, M; Ohigashi, T; Asakura, H; Tachibana, M; Murai, M; Prostate specific antigen adjusted for transition zone volume: the most powerful method for detecting prostate carcinoma.; Cancer; 2000; vol. 89 (no. 4); 842-9

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Tokyo Setting Department of Urology, Keio University School of Medicine, Study dates October 1997 - August 1999 Sources of funding Unclear
Inclusion criteria	PSA range PSA >4ng/ml DRE Suspicious DRE
Exclusion criteria	Excluded:

	No patients with a prior diagnosis of prostate carcinoma or hormonal manipulation were included. PSA <4ng/ml
Number of participants	n=281
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	None
Additional comments	

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 281)**
Mean age (SD) Mean (SD)	68.4 (0.5)

Characteristic	Study (N = 281)
% with positive digital rectal examination Custom value	55.2
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Population chosen based on PSA >4ng or suspicious DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(PSA >4ng inclusion criteria)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(44.8% with positive DRE)*

Section	Question	Answer
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(PSA value was decision threshold for biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Threshold used for inclusion in study)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA used as decision threshold for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(PSA would have been known before results)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Due to population selection with PSA>4 and % with positive DRE)*
Overall risk of bias and directness	Directness	Partially applicable *(55.2% had suspicious DRE)*

Kobayashi, 2005

Bibliographic Reference	Kobayashi, Takashi; Kamoto, Toshiyuki; Nishizawa, Koji; Mitsumori, Kenji; Ogura, Keiji; Ide, Yoshihiro; Prostate-specific antigen (PSA) complexed to alpha1-antichymotrypsin improves prostate cancer detection using total PSA in Japanese patients with total PSA levels of 2.0-4.0 ng/mL.; BJU international; 2005; vol. 95 (no. 6); 761-5

Study Characteristics

Study type	Cross-sectional study
Study details	Study location

	Japan Setting Departments of Urology and Surgical Pathology, Hamamatsu Rosai Hospital, Hamamatsu, and Urology, Kyoto University Graduate School of Medicine, Kyoto, Study dates April 2001-June 2003 Sources of funding Japanese Labour Welfare Corporation
Inclusion criteria	Symptoms LUTS Age <79 years
Exclusion criteria	PSA PSA <2 or 1.5 if abnormal DRE
Number of participants	n=315
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold

Reference standard (s)	Biopsy
Subgroup analyses	None

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 315)**
% with positive digital rectal examination Custom value	43%
Mean age Custom value	67.1 (SD 8)
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(PSA level of ≥ 2.0 ng/m or 1.5 with abonormal DRE chosen for biopsy)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(People with PSA <2 excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(>40% have positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Threshold for inclusion/biopsy)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Knowledge of PSA)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes *(all included in analysis)*
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(Exclusion criteria PSA <2)*
Overall risk of bias and directness	Directness	Partially applicable *(>40% with positive DRE)*

Martinez-Pineiro, 2000

Bibliographic Reference	Martinez-Pineiro, L; Tabernero, A; Contreras, T; Madero, R; Lozano, D; Lopez-Tello, J; Alonso-Dorrego, J M; Picazo, M L; Gonzalez Gancedo, P; Martinez-Pineiro, J A; de La Pena, J J; Determination of the percentage of free prostate-specific antigen helps to avoid unnecessary biopsies in men with normal rectal examinations and total prostate-specific antigen of 4-10 ng/ml.; European urology; 2000; vol. 37 (no. 3); 289-96

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Spain Setting outpatient clinic Study dates January 1995 - October 1998 Sources of funding Unclear
Inclusion criteria	PSA range 4-10ng/ml DRE Negative DRE
Exclusion criteria	Excluded:

	Patients on finasteride and those with acute prostatitis, urinary tract infection or recent manipulation of the lower urinary tract, which could elicit a change in total serum PSA concentration
Number of participants	n=180
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 180)**
Mean age (SD) Mean (SD)	67.29 (7.43)
% with positive digital rectal examination Custom value	0%
Ethnic group	not stated

Characteristic	Study (N = 180)
Custom value	

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Selected for biopsy based on PSA 4-10ng/ml)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(PSA <4 excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(threshold for inclusion)*

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Done with knowledge of PSA threshold)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(index test taken 'before' biopsy but unclear how long before)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Only patients within PSA 4-10 selected)*
Overall risk of bias and directness	Directness	Directly applicable

McArdle, 2004

Bibliographic Reference	McArdle, P A; Pollock, M A; Wallace, A M; McMillan, D C; Crooks, J E; Underwood, M A; Comparison of total, complexed and free prostate-specific antigens and their ratios in the detection of prostate cancer in a non-screened population.; Annals of clinical biochemistry; 2004; vol. 41 (no. pt3); 201-6

Study Characteristics

Study type	Cross-sectional study
Study details	Study location UK Setting Hospital Study dates

	Unclear Sources of funding Unclear. Bayer Plc provided PSA complexed PSA assay kits
Inclusion criteria	PSA range 4-10ng/ml DRE Abnormal DRE
Exclusion criteria	PSA PSA <4ng/ml and >10ng/ml
Number of participants	n=171
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	Study (N = 171)
% with positive digital rectal examination Custom value	Not stated
median age Custom value	66 – benign group, 69 cancer
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Selected based on PSA range)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(Excluded PSA <4ng/ml)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Not clear what % had positive DRE but this was an inclusion criteria for those with <4ng/ml)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(threshold for inclusion)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA threshold used as criteria for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	High *(Based on PSA inclusion criteria)*
Overall risk of bias and directness	Directness	Partially applicable *(Some of population had a positive DRE - unclear what %)*

Mitchell, 2001

Bibliographic Reference	Mitchell, I D; Croal, B L; Dickie, A; Cohen, N P; Ross, I; A prospective study to evaluate the role of complexed prostate specific antigen and free/total prostate specific antigen ratio for the diagnosis of prostate cancer.; The Journal of urology; 2001; vol. 165 (no. 5); 1549-53

Study Characteristics

Study type	Cross-sectional study

Study details	Study location UK Setting Hospital Study dates Feb 1998 - Aug 1999 Sources of funding Unclear
Inclusion criteria	PSA range previously recorded total PSA measurement (range 2.6 to 20 ng./ml.).
Exclusion criteria	Excluded: Patients in whom recorded total PSA may have been increased by urinary tract infection, urinary retention or instrumentation
Number of participants	n=160
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold

Reference standard (s)	Biopsy
Subgroup analyses	None

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 160)**
Mean age (SD) Custom value	68.9
% with positive digital rectal examination Custom value	51%
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear *(Unclear if previously recoded PSA 2.6-20 was basis for inclusion)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Unclear
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(>50% with positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Unclear
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(Previously assessed PSA range of 2.6-20 chosen, but new PSA tests done for study)*
Overall risk of bias and directness	Directness	Partially applicable *(>50% of population had positive DRE)*

Mutlu, 2009

Bibliographic Reference	Mutlu, Nilgun; Turkeri, Levent N; Yencilek, Faruk; Demir, Aslan; Emerk, Kaya; Complexed prostate specific antigen: better test in the diagnosis of prostate cancer for the clinically relevant 2.5-4 ng/ml total PSA range.; The Canadian journal of urology; 2009; vol. 16 (no. 2); 4558-67

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Turkey Setting Hospital Study dates April 2006-Oct 2007 Sources of funding Unclear
Inclusion criteria	PSA range >2.5 DRE Suspicious DRE

Exclusion criteria	Excluded: Previous history of elevated PSA, established BPH, Chronic prostatis, prostate cancer, on testosterone or finasteride therapy, underwent prior resection of prostate
Number of participants	n=177
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	PSA thresholds
Additional comments	

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 315)**
% with positive digital rectal examination Custom value	not stated

Characteristic	Study (N = 315)
Mean age Custom value	65 (SD 7.2) cancer group 64.3 (9.1) benign group
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(PSA >2.5 or suspicious DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes *(<2.5ng/ml PSA)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Unclear *(Unclear what % had positive DRE)*

Section	Question	Answer
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Done before Biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(for inclusion)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Knowledge of PSA)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(PSA >2.5 inclusion criteria)*
Overall risk of bias and directness	Directness	Partially applicable *(Unclear what % had positive DRE)*

Putra, 2019

Bibliographic Reference	Putra, Prima Ciko Ade; Umbas, Rainy; Hamid, Agus Rizal Ardy Hariandy; Mochtar, Chaidir Arif; Age, prostate volume, prostate-specific antigen and prostate-specific antigen density as predictor factors in results of transrectal ultrasonography-guided prostate biopsy; F1000Research; 2019; vol. 8; 875

Study Characteristics

Study type	Cross-sectional study
Study details	Study location

	Jakarta Setting Hospital Study dates Jan 2008 - Dec 2013 Sources of funding The author(s) declared that no grants were involved in supporting this work
Inclusion criteria	PSA range PSA >4ng/ml Symptoms LUTS DRE Abnormal DRE Age >45
Exclusion criteria	Excluded: underwent transperineal prostate biopsy or had been biopsied previously
Number of participants	n=1232

Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 1232)**
% with positive digital rectal examination Custom value	not stated
Median age - PC group Custom value	68 (35-89)
Median age - Benign group Custom value	65 (40-83)
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Over 4ng/ml or positive DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes *(PSA <4ng/ml)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Unclear what % had positive DRE but used as inclusion criteria)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Threshold for inclusion)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear *(data collected from a database - unclear in which order)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(Doesn't specify interval)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(Only those with >4 PSA selected)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Partially applicable *(Some of the population have positive/abnormal DRE - unclear what %)*

Rahardjo, 2000

Bibliographic Reference	Rahardjo, Djoko; Gardian, Siti Tersiani Kamil; New cutoff point of prostate-specific antigen (PSA) and PSA density (PSAD) to enhance diagnostic specificity for prostate cancer (Pca) in country with low prostate cancer incidence; Medical Journal of Indonesia; 2000; vol. 9 (no. 1); 35-42

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Indonesia Setting Hospital Study dates Sept 1994 - August 1997 Sources of funding Unclear

Inclusion criteria	Symptoms prostate symptoms without acute urinary retention
Exclusion criteria	Not stated
Number of participants	n=118 (biopsied)
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 118)**
Mean age (SD) Custom value	64.37 (8.22) non PCa, 73 (6.08) PCa
% with positive digital rectal examination Custom value	unclear

Characteristic	Study (N = 118)
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient selection: risk of bias	Was a case-control design avoided?	Unclear
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear *(It's unclear if patients were selected due to symptoms or based on a diagnosis)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear

Section	Question	Answer
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear *(Unclear if PSA taken before or after biopsy)*
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear *(interval not stated)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes *(All biopsed)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate (unclear how patients were selected and the interval between index and reference standard)
Overall risk of bias and directness	Directness	Partially applicable *(Unclear what % had a positive DRE)*

Rajandram/Kuppasamy, 2018

Bibliographic Reference	Rajandram, Retnagowri; Kuppusamy, Shanggar; Razack, Azad Hassan Abdul; Quek, Kia Fatt; Dublin, Norman; Revisiting prostate specific antigen density (PSAD): A prospective analysis in predicting the histology of prostate biopsy; International Journal of Clinical and Experimental Medicine; 2018; vol. 11 (no. 4); 3873-3879

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Kuala Lumpur Setting University Malaya Medical Centre

	Study dates Unclear Sources of funding Unclear - likely University of Malaya
Inclusion criteria	PSA range 4.1-30ng/ml DRE with our without abnormal DRE First time biopsy
Exclusion criteria	Excluded: Taking 5a reductase inhibitor Biopsy done previously Continuous bladder drainage PSA PSA <4.1
Number of participants	286
Length of follow-up	N/A
Loss to follow-up	N/A

Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Additional comments	No

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 286)**
Mean age (SD) Standardised Mean (SD)	69.01 (7.5)
% with positive digital rectal examination Custom value	25.8%
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(based on PSA 4.1-30 range)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(PSA <4.1ng/ml excluded)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low *(<30% with positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Threshold for inclusion pre-specified)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(Knowledge of PSA)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High (<4.1 and >30 patients excluded)
Overall risk of bias and directness	Directness	Partially applicable *(25.8% with positive DRE)*

Rashid, 2012

Bibliographic Reference	Rashid, M M; Alam, A K M K; Habib, A K M K; Rahman, H; Hossain, A K M S; Salam, M A; Rahman, S; Efficacy of lower cut off value of serum prostate specific antigen in diagnosis of prostate cancer.; Bangladesh Medical Research Council bulletin; 2012; vol. 38 (no. 3); 90-3

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Dhaka Setting Hospital Study dates July 2009 - October 2010 Sources of funding Unclear
Inclusion criteria	PSA range >2.5ng/ml Symptoms LUTS Age

	>50
Exclusion criteria	Excluded: patient with bleeding disorder, anorectal pathology, active UTI or prostatitis PSA <2.5
Number of participants	n=206
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 206)**
Mean age (SD) Custom value	not stated

Characteristic	Study (N = 206)
% with positive digital rectal examination Custom value	not stated
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Chosen based on PSA >2.5)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes *(PSA <2.5)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(PSA used as decision threshold for biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(Biopsy done based on PSA threshold)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(knowledge of PSA levels prior to biopsy)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes

Section	Question	Answer
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate *(<2.5 ng/ml PSA excluded)*
Overall risk of bias and directness	Directness	Directly applicable

Reljic, 2004

Bibliographic Reference	Reljic, Ante; Tomaskovic, Igor; Simundic, Ana-Marija; Kruslin, Bozo; Diagnostic value of age specific prostate specific antigen in prostate cancer patients; Acta Clinica Croatica; 2004; vol. 43 (no. 4); 379-383

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Croatia

	Setting Hospital Study dates April 2001-September 2002 Sources of funding Unclear
Inclusion criteria	DRE Negative DRE required
Exclusion criteria	Excluded: Patients with positive or suspect digitorectal finding, patients previously diagnosed with prostate cancer, and patients on medicamentous or previous surgical therapy for benign prostate hyperplasia (BPH) were excluded from the study
Number of participants	n=80 (in this analysis)
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA age adjusted
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	Study (N = 80)
Mean age (SD) Custom value	46-87 (unclear in population selected for age adjusted analysis)
% with positive digital rectal examination Custom value	0%
Ethnic group Custom value	Not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Biopsied patients had PSA between 4-9.9ng/ml)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes

Section	Question	Answer
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Age specific thresholds pre-stated)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA used as criteria for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes *(In this analysis)*
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(All patients with PSA 4-9.9ng/ml)*
Overall risk of bias and directness	Directness	Partially applicable *(Negative DRE but no symptoms recorded)*

Senra-Varela, 2004

Bibliographic Reference	Senra-Varela, Avelino; Otero, Milagros; Saez Martin, Jose Luis; Duran Munoz, Borja; Vieito Fuentes, Juan; Ojea, Antonio; Lopez-Saez, Juan-Bosco; Prospective observational study to assess value of prostate cancer diagnostic methods; Journal of Diagnostic Medical Sonography; 2004; vol. 20 (no. 6); 383-393

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Spain Setting Hospital Study dates January 1997 - November 2003 Sources of funding Unclear - likely University Hospital of Puerto Real, Cádiz, Spain
Inclusion criteria	Criteria X DRE and/or serial PSA pathologies who were referred for TRUS.
Number of participants	n= 556
Length of follow-up	N/A
Loss to follow-up	N/A

Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	None

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 556)**
Mean age (SD) Mean (SD)	68.53 (0.96)
% with positive digital rectal examination Custom value	34.2%
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Yes
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(34.2% with positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Before biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear

Section	Question	Answer
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes *(3 weeks before/after biopsy)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Partially applicable *(34.2% positive DRE)*

Shim, 2007

Bibliographic Reference	Shim, Hong Bang; Lee, Sang Eun; Park, Hyoung Keun; Ku, Ja Hyeon; Histological diagnosis of prostate cancer in Korean men aged 70-79 years.; Japanese journal of clinical oncology; 2007; vol. 37 (no. 10); 782-7

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Korea Setting Hospital Study dates July 2003 - June 2005 Sources of funding Unclear
Inclusion criteria	PSA range >2ng/ml DRE or abnormal DRE Age 70-79

Exclusion criteria	Excluded: Younger than 70, over 80, had previously undergone prostate biopsy, had received a prior diagnosis of prostate cancer, had undergone prostate surgery or radiation treatment, had received 5a-reductase inhibitors, had acute urinary retention or an indwelling catheter, had gone more than 3 months between PSA measurement and biopsy or had evidence of acute urinary infection (pyuria and bacteriuria) on urinalysis.
Number of participants	n=344
Length of follow-up	n/a
Loss to follow-up	n/a
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	Study (N = 344)
% with positive digital rectal examination Custom value	29%
Ethnic group Custom value	not stated
Median age PCa group Custom value	73
Median age non-PCa group Custom value	73

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Chosen on basis of abnormal DRE and PSA>2)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(<2ng/ml PSA with normal DRE excluded)*

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(29% had positive DRE and some (unclear what %) came from a screening population)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes *(Done before biopsy)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(inclusion threshold)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA threshold chosen as basis for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High *(foreknowledge of PSA)*
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low

Section	Question	Answer
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	High *(<2 PSA excluded but also those aged <70 and >80)*
Overall risk of bias and directness	Directness	Partially applicable *(29% positive DRE (below <30%) but also some patients from a screening population (unclear what %))*

Sozen, 2005

Bibliographic Reference	Sozen, Sinan; Eskicorapci, Saadettin; Kupeli, Bora; Irkilata, Lokman; Altinel, Mert; Ozer, Gokhan; Uygur, Cemil; Alkibay, Turgut; Ozen, Haluk; Complexed prostate specific antigen density is better than the other PSA derivatives for detection of prostate cancer in men with total PSA between 2.5 and 20 ng/ml: results of a prospective multicenter study.; European urology; 2005; vol. 47 (no. 3); 302-7

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Turkey Setting Urology department Study dates September 2002 - August 2003 Sources of funding Unclear
Inclusion criteria	PSA range PSA 2.5- 20 ng/ml Symptoms LUTS
Exclusion criteria	Excluded: men who had received testosterone or finasteride and had undergone transurethral resection of the prostate, no matter how remote in time.
Number of participants	n=351 (normal DRE)
Length of follow-up	N/A

Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy
Subgroup analyses	XX Separate analysis provided for negative DRE population

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 351)**
% with positive digital rectal examination Custom value	0% (in analyis)
PCa mean age Mean (SD)	65 (7.8)
Non-PCa mean age Mean (SD)	62.3 (7.9)
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Patients chosen on PSA range 2.5-20)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No *(<2.5ng/ml PSA and >20ng/ml)*
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(PSA threshold used as basis for inclusion)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(Biopsy done based on knowledge of previous PSA threshold)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes *(10-15 mins before biopsy)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Moderate *(Risk of bias moderate due to exclusion of PSA <2.5 ng/ml and above 20)*
Overall risk of bias and directness	Directness	Directly applicable

Tan, 1995

Bibliographic Reference	Tan, H H; Gan, E; Rekhraj, I; Cheng, C; Li, M K; Thng, P; Tan, I K; Yo, S L; Poh, W T; Foo, K T; Use of prostate specific antigen (PSA) and transrectal ultrasound (TRUS) in the diagnosis of prostate cancer--a local experience.; Annals of the Academy of Medicine, Singapore; 1995; vol. 24 (no. 4); 550-6

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Singapore Setting Hospital Study dates August 1991-October 1994 Sources of funding

	Unclear
Inclusion criteria	PSA range Abnormal/elevated PSA DRE Abnormal DRE
Exclusion criteria	Excluded: Those outside the inclusion criteria
Number of participants	n=579
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA age adjusted
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	Study (N = 579)
Mean age (SD) Mean (SD)	71 (*empty data*)
% with positive digital rectal examination Custom value	30.4%
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Selected based on abnormal DRE/elevated PSA)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High

Section	Question	Answer
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No *(No threshold specified - rising/elevated PSA)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(elevated/rising PSA used as criteria for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Unclear

Section	Question	Answer
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Unclear
Overall risk of bias and directness	Risk of Bias	Moderate
Overall risk of bias and directness	Directness	Partially applicable *(>30% abnormal DRE)*

Veltri, 2002

Bibliographic Reference	Veltri, Robert W; Miller, M Craig; O'dowd, Gerard J; Partin, Alan W; Impact of age on total and complexed prostate-specific antigen cutoffs in a contemporary referral series of men with prostate cancer.; Urology; 2002; vol. 60 (no. 4suppl1); 47-52

Study Characteristics

Study type	Cross-sectional study
Study details	Study location

	USA Setting Several urology clinical practices Study dates June 1999 - October 2000 Sources of funding Unclear
Inclusion criteria	no previous history of prostate cancer diagnosed by our laboratory; a minimum of 6 locations of the prostate sampled; (4) a biopsy diagnosis of either no evidence of malignancy (NEM) or prostate cancer (ie, no diagnosis of prostatic intraepithelial neoplasia or suspicious if cancer was not present); (5) a tPSA and cPSA serum assay performed within 90 days before the biopsy procedure; and PSA range PSA between 2 and 20ng/mL. Age >45
Exclusion criteria	Excluded: Those outside of inclusion criteria
Number of participants	n=3597
Length of follow-up	N/A

Loss to follow-up	N/A
Index test(s)	PSA fixed threshold Stratified by age
Reference standard (s)	Biopsy
Subgroup analyses	Subgroup analysis by age category

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 3597)**
Mean age (SD) Mean (SD)	66.9 (8.4)
% with positive digital rectal examination Custom value	Unclear
Ethnic group Custom value	not stated

Critical appraisal - GUT QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	No *(Chosen from a database based on PSA 2-20ng/ml. Patients biopsied based on elevated PSA or abnormal DRE)*
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	No
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(Unclear % with DRE but stated as one of the criteria for biopsy)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear *(All information taken from a database)*
Index tests: risk of bias	If a threshold was used, was it pre-specified?	Yes *(Inclusion criteria threshold stated)*
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low

Section	Question	Answer
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	No *(PSA levels were reason for referral for biopsy)*
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	High
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes *(PSA taken within 90 days of biopsy)*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Moderate *(2-20ng/ml PSA as selection criteria)*

Section	Question	Answer
Overall risk of bias and directness	Directness	Indirectly applicable *(No symptoms stated by authors and a some referred due to positive DRE)*

Vukotic, 2005

Bibliographic Reference	Vukotic, V; Cerovic, S; Kozomara, M; Lazic, M; The predictive value of PSA in diagnosis of prostate cancer in non screened population.; Acta chirurgica Iugoslavica; 2005; vol. 52 (no. 4); 81-7

Study Characteristics

Study type	Cross-sectional study
Study details	Study location Serbia Setting Urology clinic Study dates 1997-2000 Sources of funding Unclear
Inclusion criteria	Criteria X

	indication for biopsy was not made according strict criteria but rather on clinical suspicion of prostate cancer considering PSA, free/total PSA, DRE, TRUS
Exclusion criteria	Not stated
Number of participants	n=579
Length of follow-up	N/A
Loss to follow-up	N/A
Index test(s)	PSA fixed threshold
Reference standard (s)	Biopsy

Population characteristics

Study-level characteristics

Characteristic	**Study (N = 579)**
Mean age (SD) Custom value	67.5
% with positive digital rectal examination Custom value	60.8%
Ethnic group	not stated

Characteristic	Study (N = 579)
Custom value	

Critical appraisal - GUT QUADAS-2

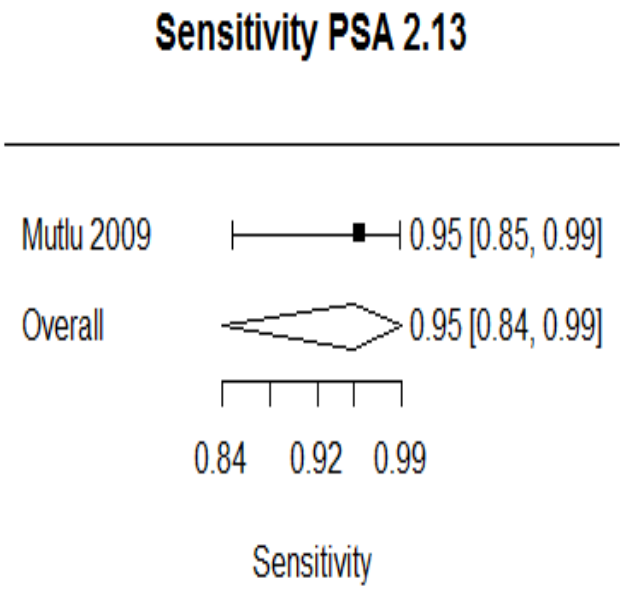
Section	Question	Answer
Patient selection: risk of bias	Was a consecutive or random sample of patients enrolled?	Unclear
Patient selection: risk of bias	Was a case-control design avoided?	Yes
Patient selection: risk of bias	Did the study avoid inappropriate exclusions?	Yes
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Unclear
Patient selection: applicability	Are there concerns that included patients do not match the review question?	High *(60.8% with positive DRE)*
Index tests: risk of bias	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
Index tests: risk of bias	If a threshold was used, was it pre-specified?	No
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Unclear

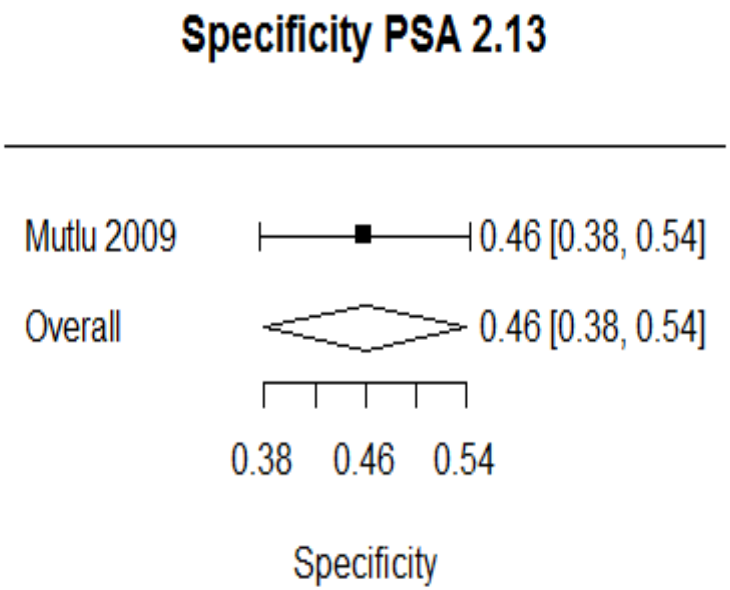
Section	Question	Answer
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Is the reference standard likely to correctly classify the target condition?	Unclear
Reference standard: risk of bias	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Was there an appropriate interval between index test(s) and reference standard?	Yes *(likely - 'prior to biopsy')*
Flow and timing: risk of bias	Did all patients receive a reference standard?	Yes
Flow and timing: risk of bias	Did patients receive the same reference standard?	Yes
Flow and timing: risk of bias	Were all patients included in the analysis?	Yes
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low

Section	Question	Answer
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Partially applicable *(>60% of patients with positive DRE)*

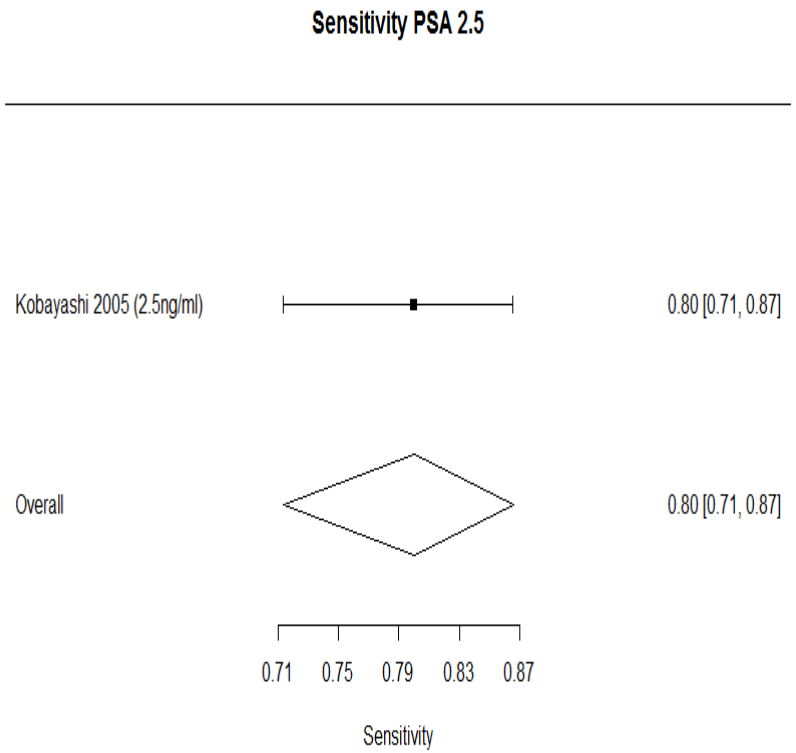
Appendix E – Forest plots

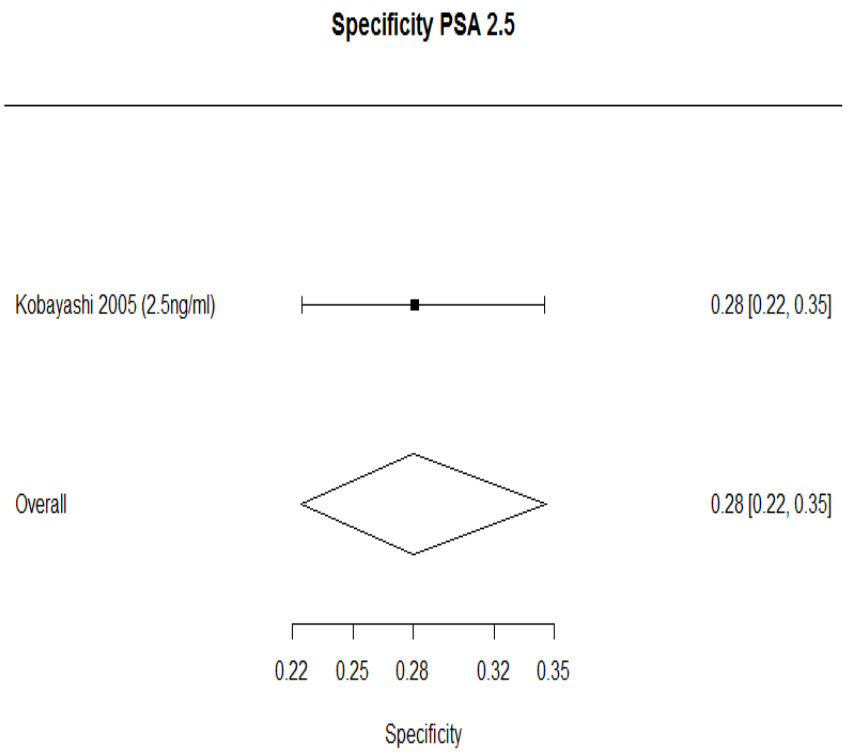
Fixed PSA threshold 2.13mg/l (GRADE table 11)



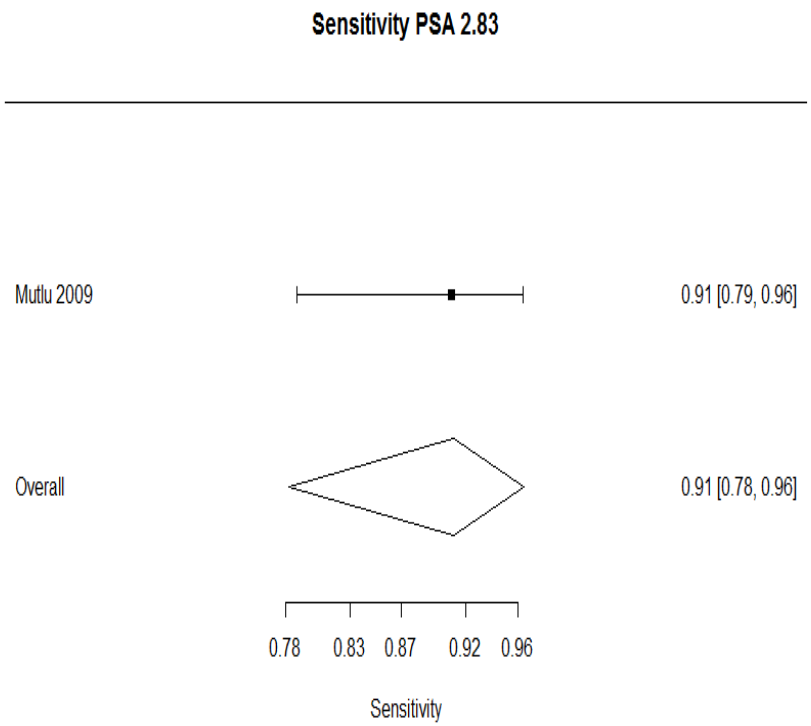


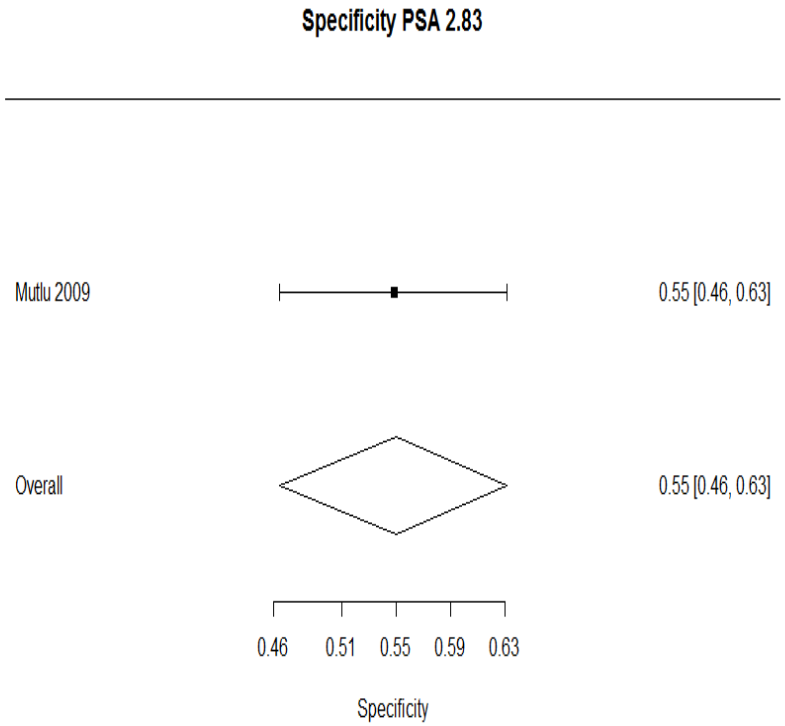
Fixed PSA threshold 2.5mg/l (GRADE table 11)



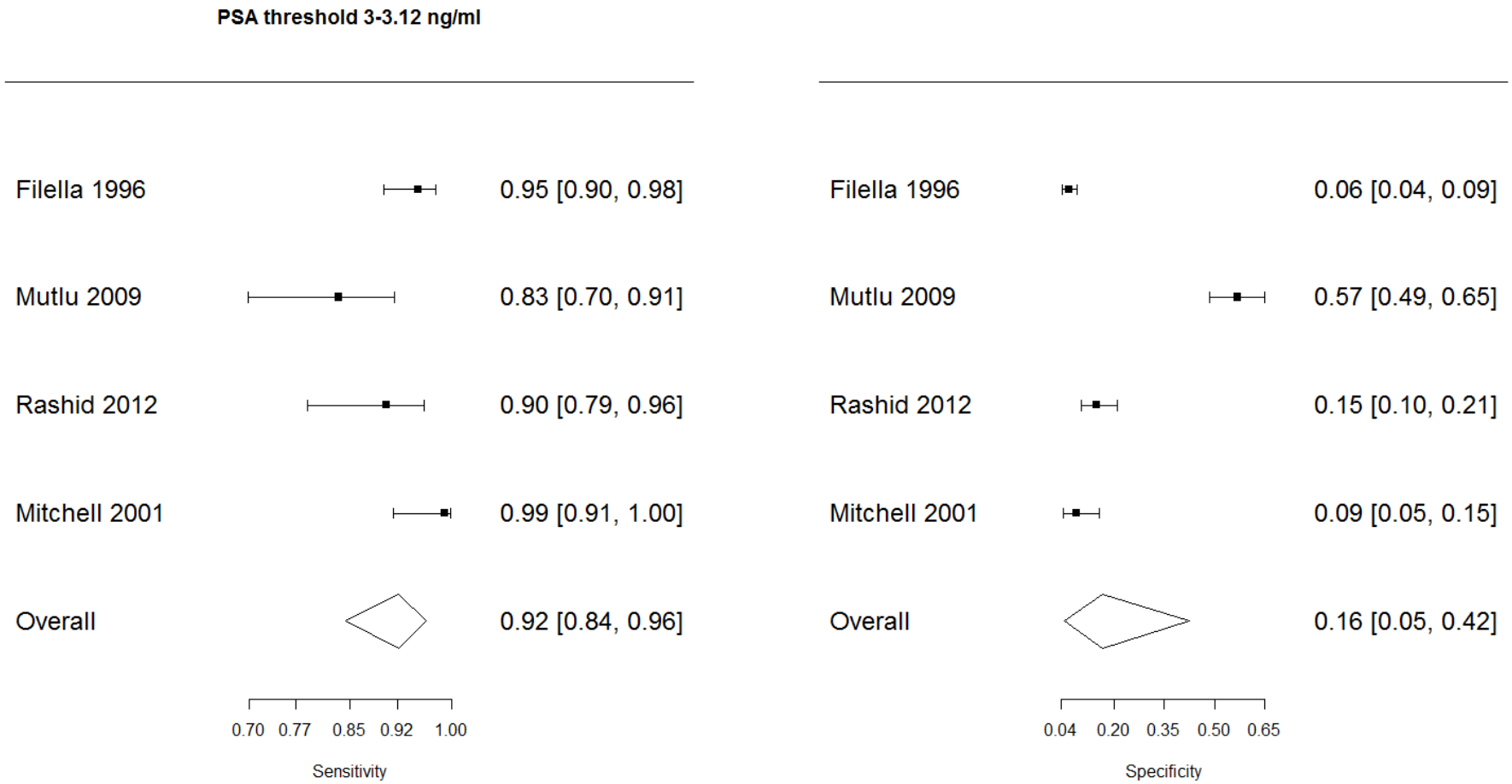


Fixed PSA threshold 2.83mg/l (GRADE table 11)



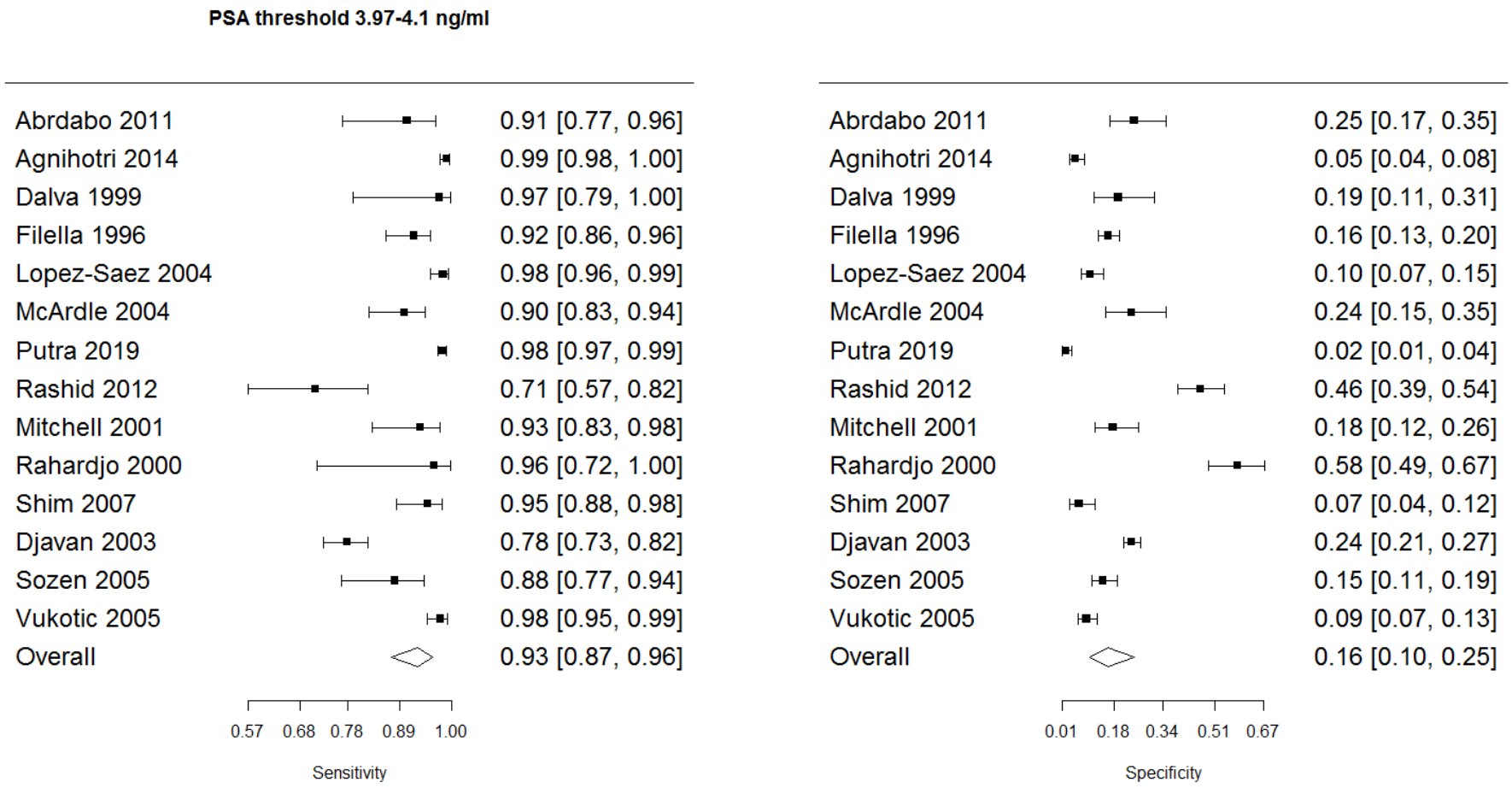


Fixed PSA threshold 3-3.12mg/l (GRADE table 11)



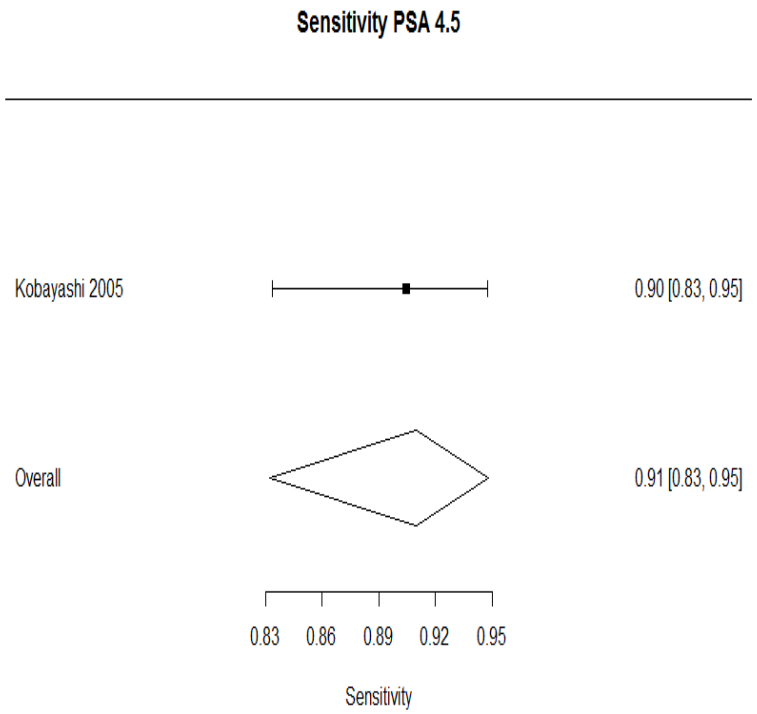
Sensitivity: $I^2 = 36.8\%$

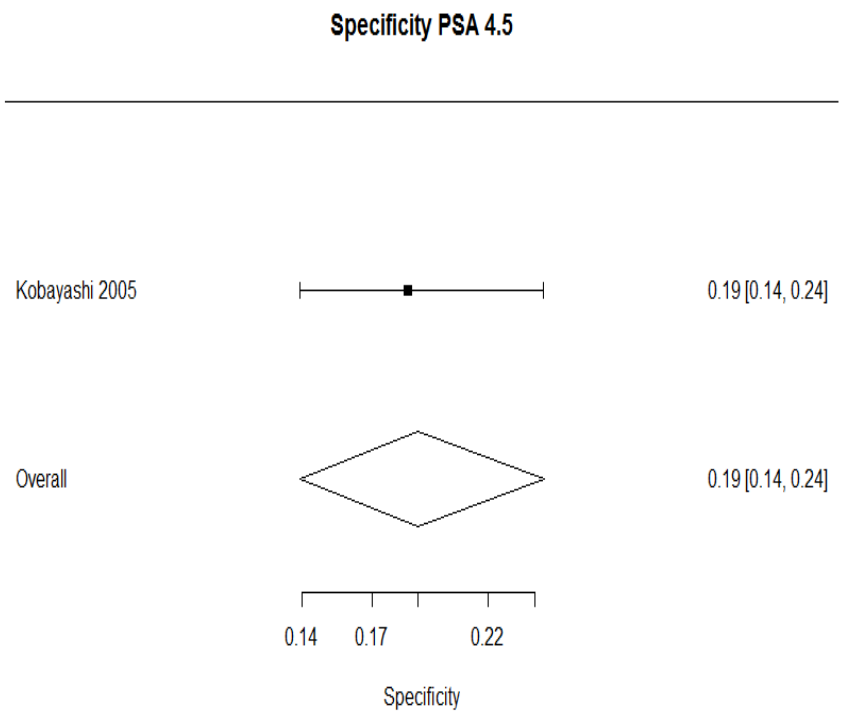
Fixed PSA threshold 3.97-4.1mg/l (GRADE table 11)



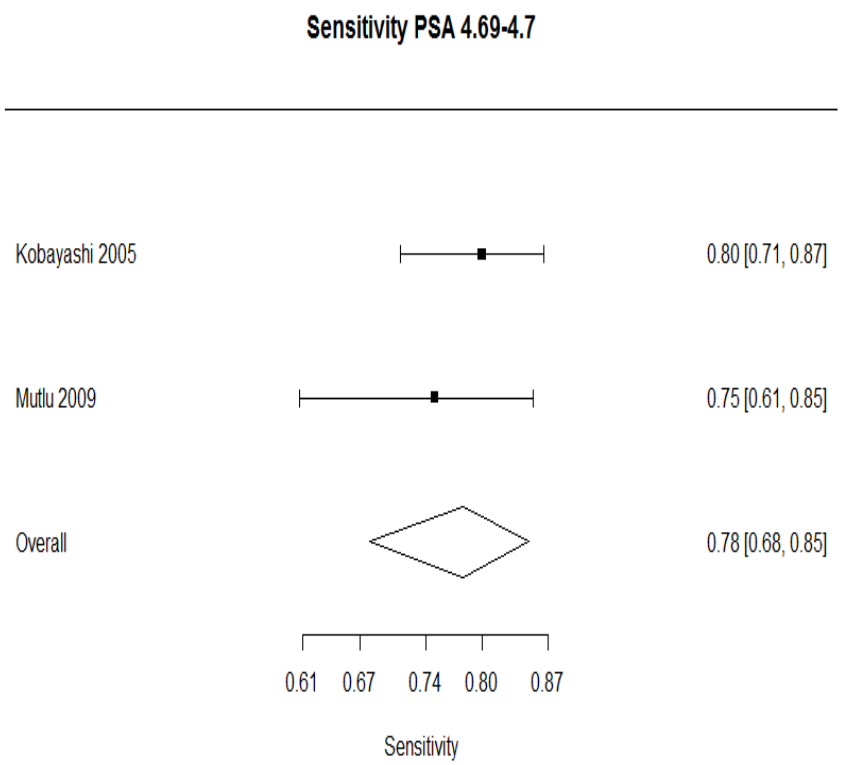
Sensitivity: $I^2 = 91.6\%$

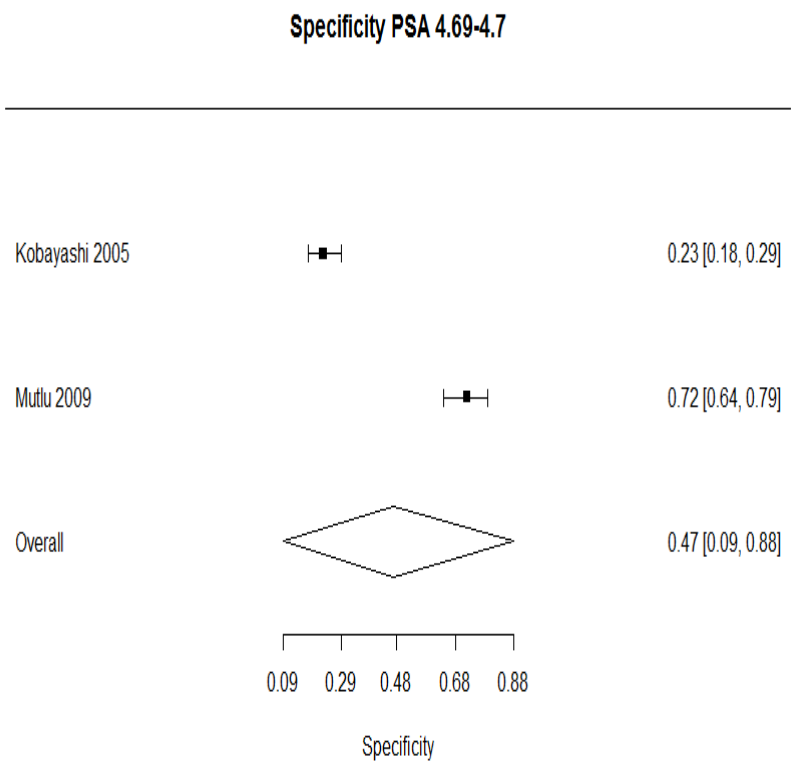
Fixed PSA threshold 4.5mg/l (GRADE table 11)





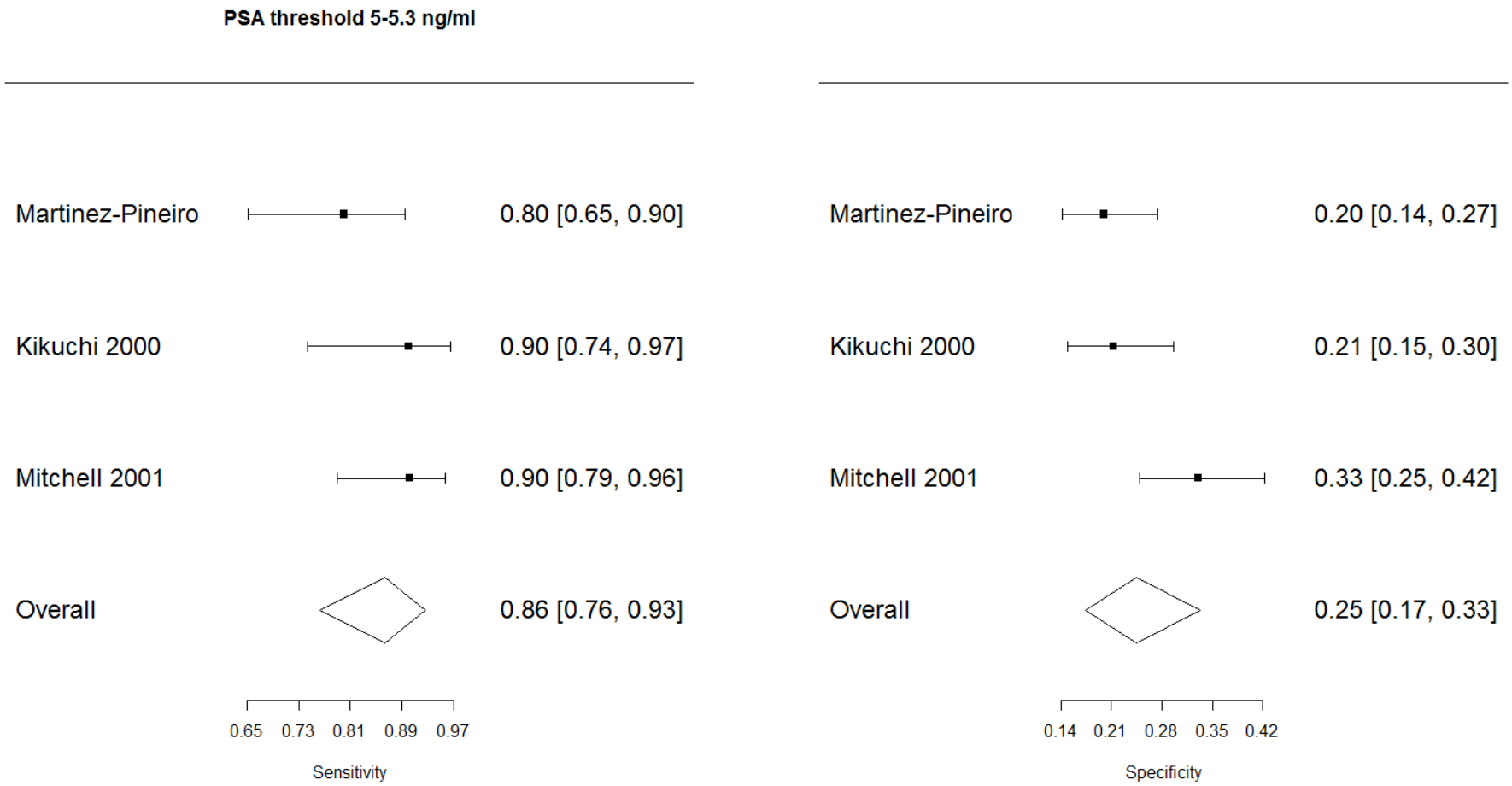
Fixed PSA threshold 4.69-4.7mg/l (GRADE table 11)





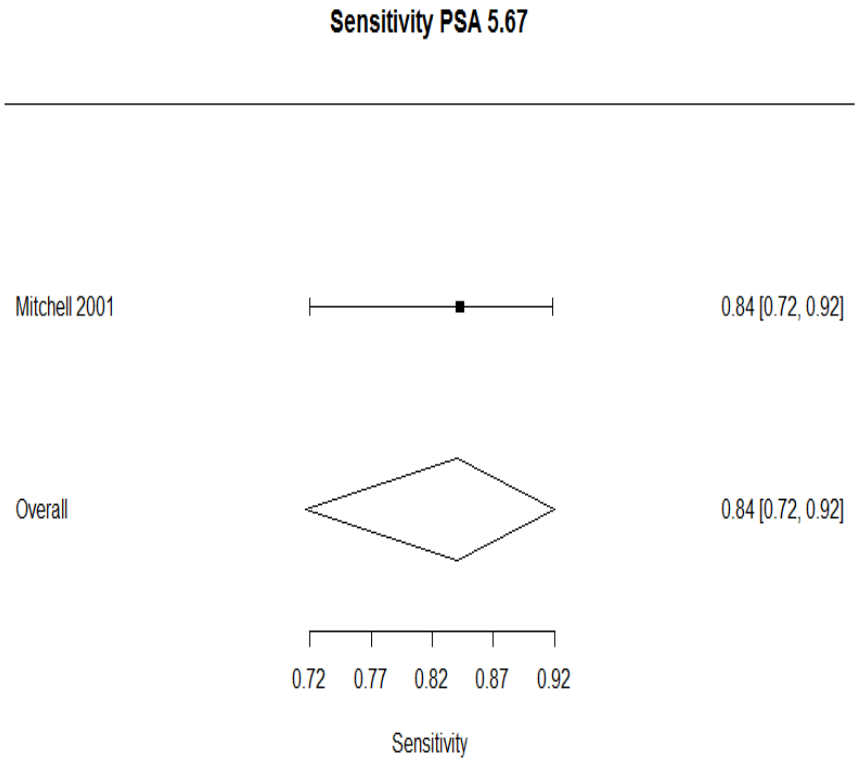
Sensitivity: $I^2 = 0\%$

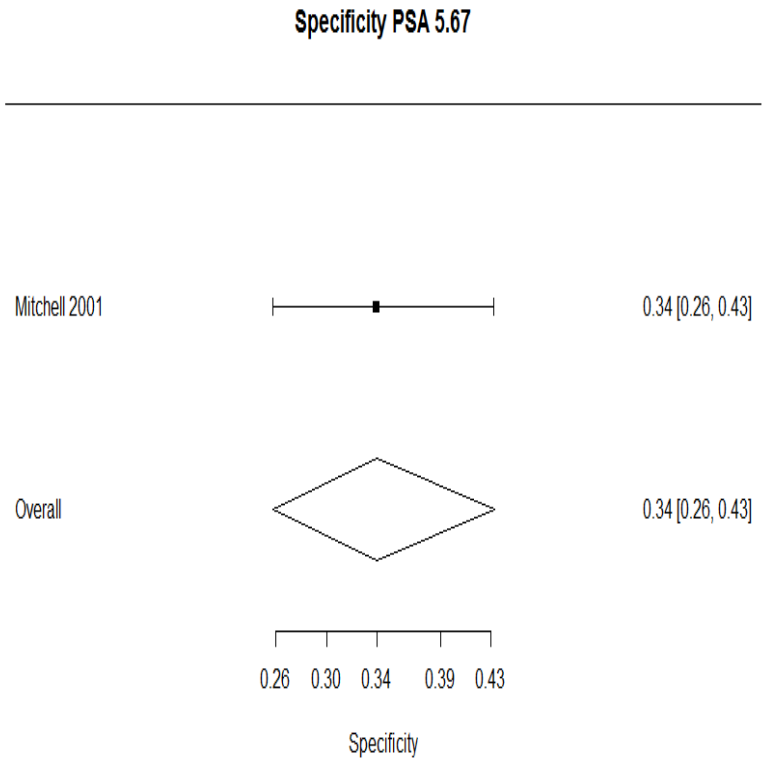
Fixed PSA threshold 5-5.3ng/ml (GRADE table 11)



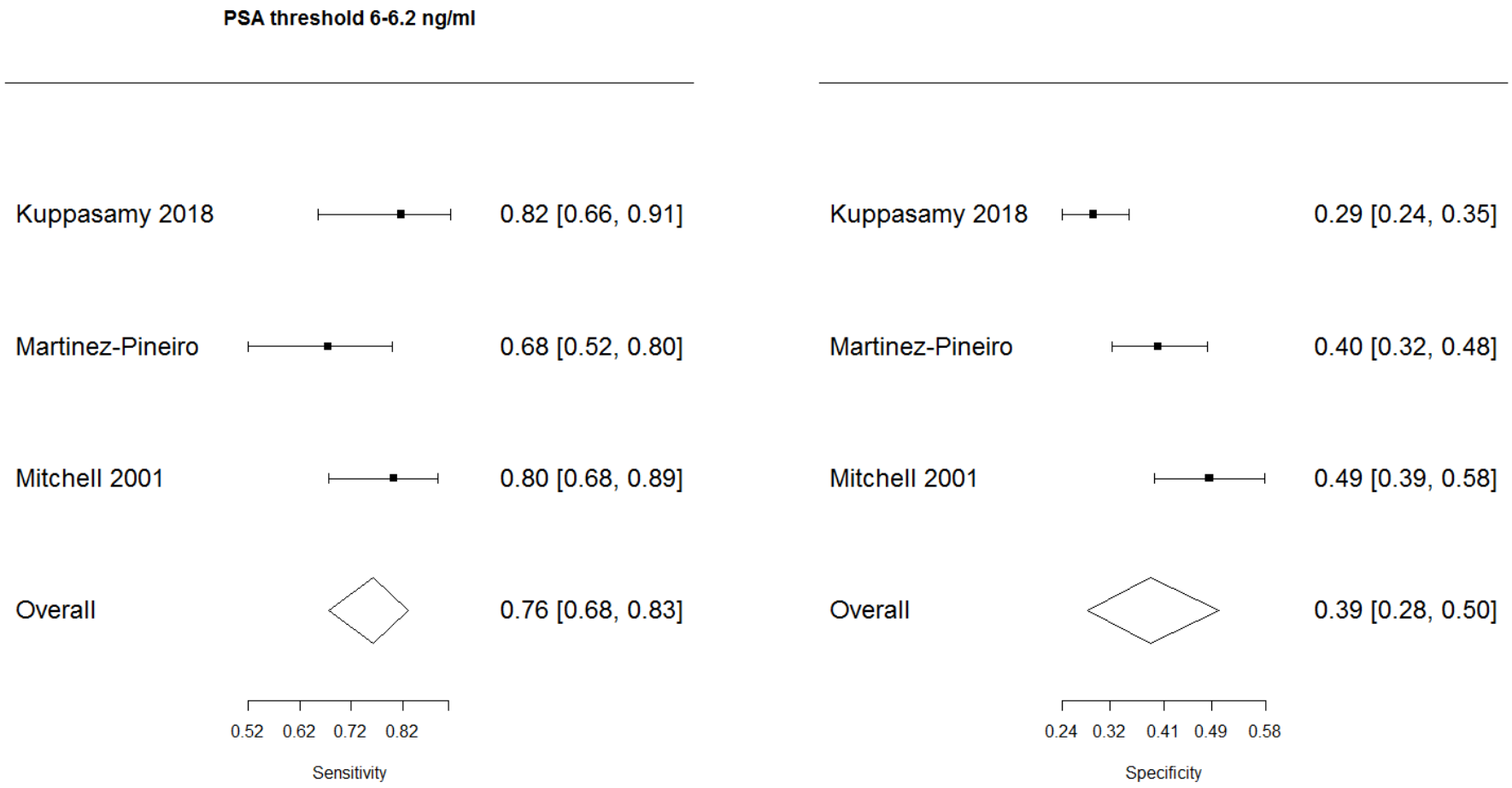
Sensitivity: $I^2 = 13.3\%$

Fixed PSA threshold 5.67mg/l (GRADE table 11)



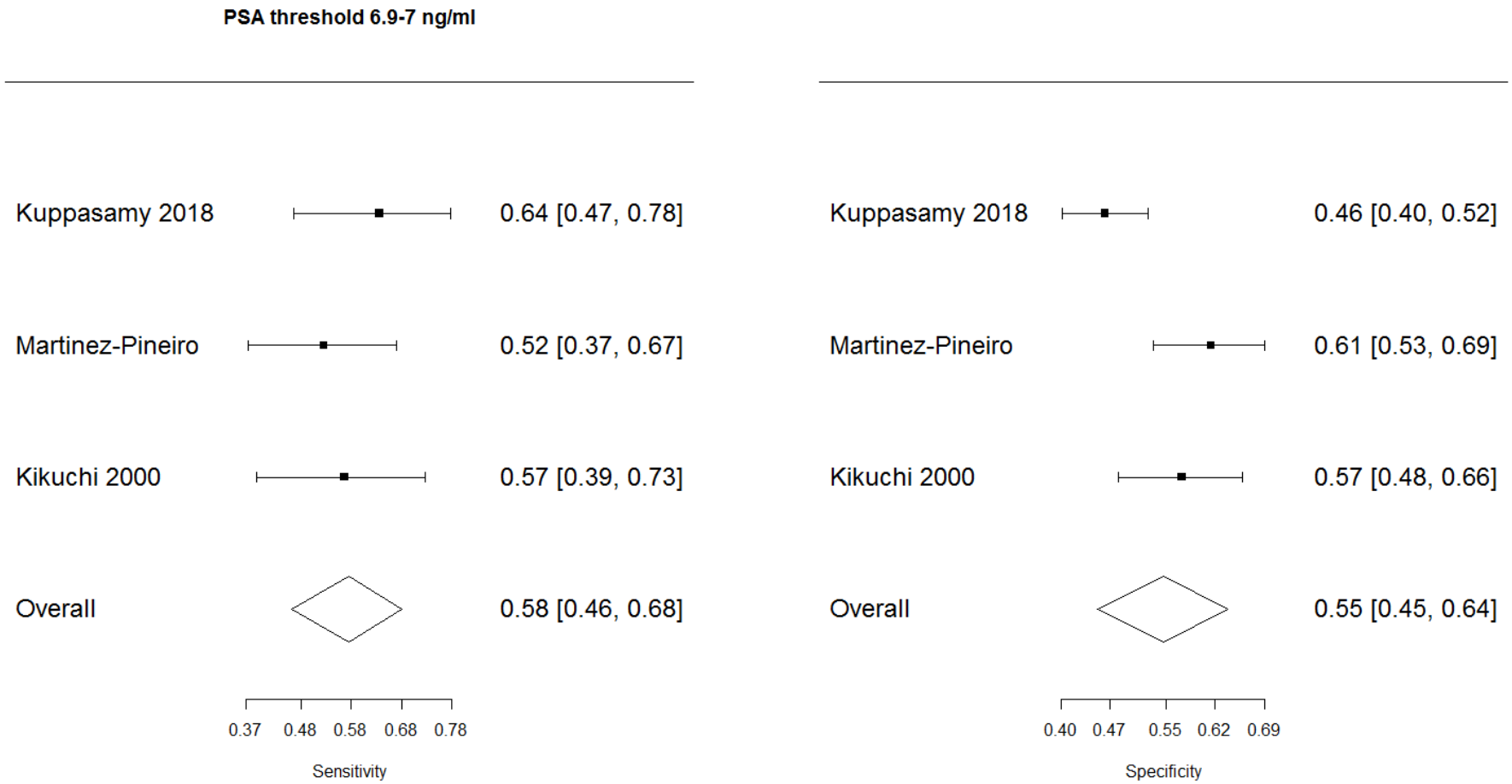


Fixed PSA threshold 6-6.2mg/l (GRADE table 11)



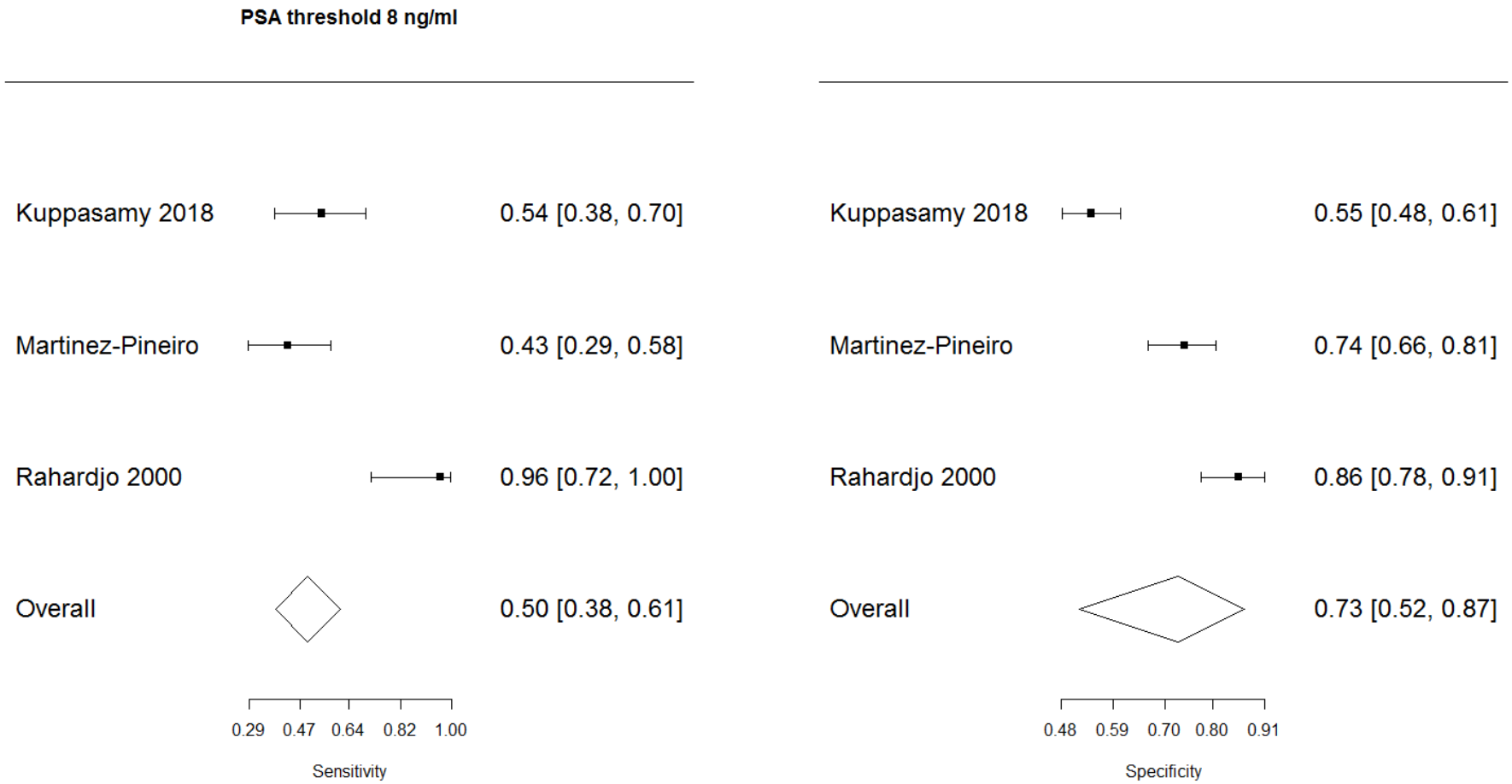
Sensitivity: $I^2 = 26\%$

Fixed PSA threshold 6.9-7 (GRADE table 11)



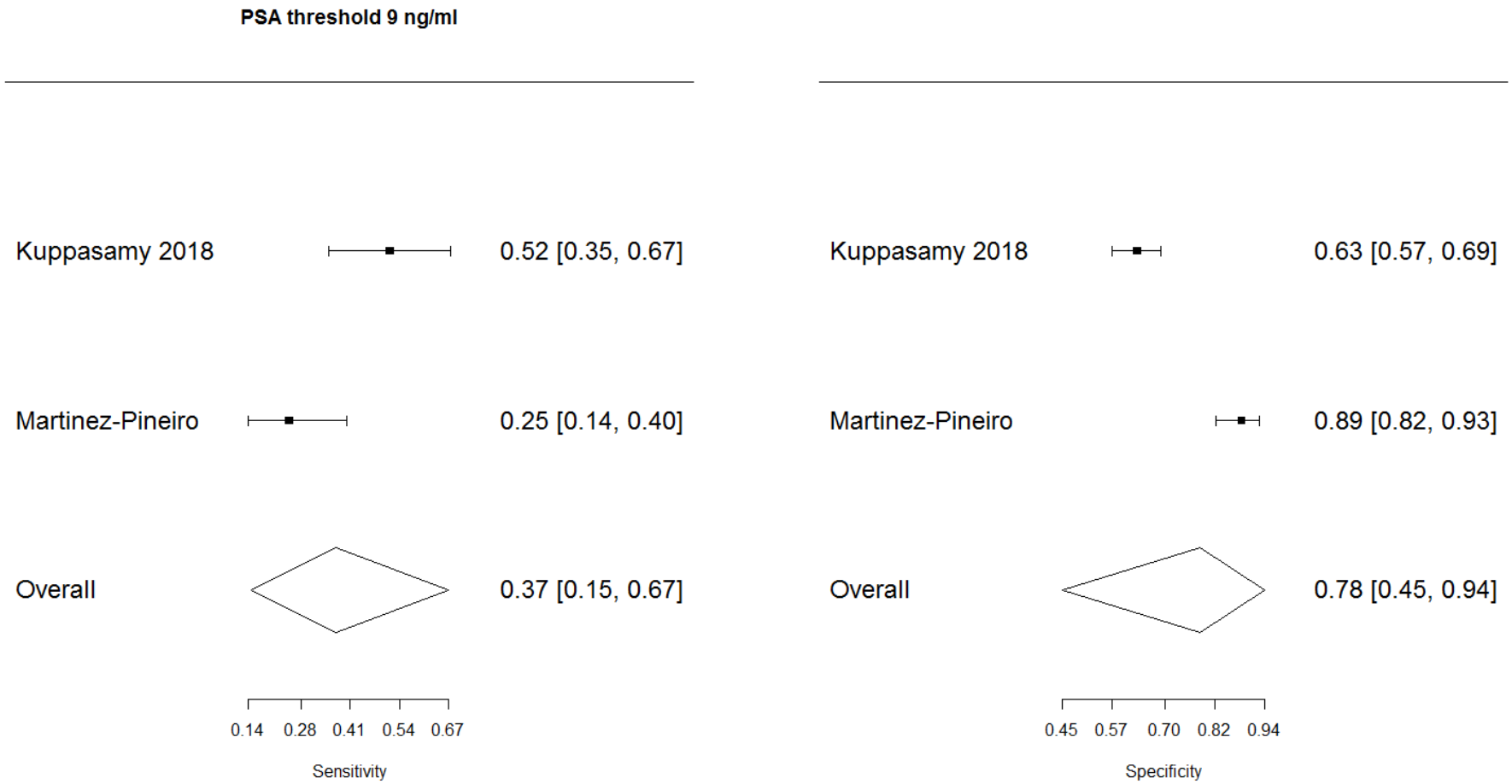
Sensitivity: $I^2 = 0\%$

Fixed PSA threshold 8mg/l (GRADE table 11)



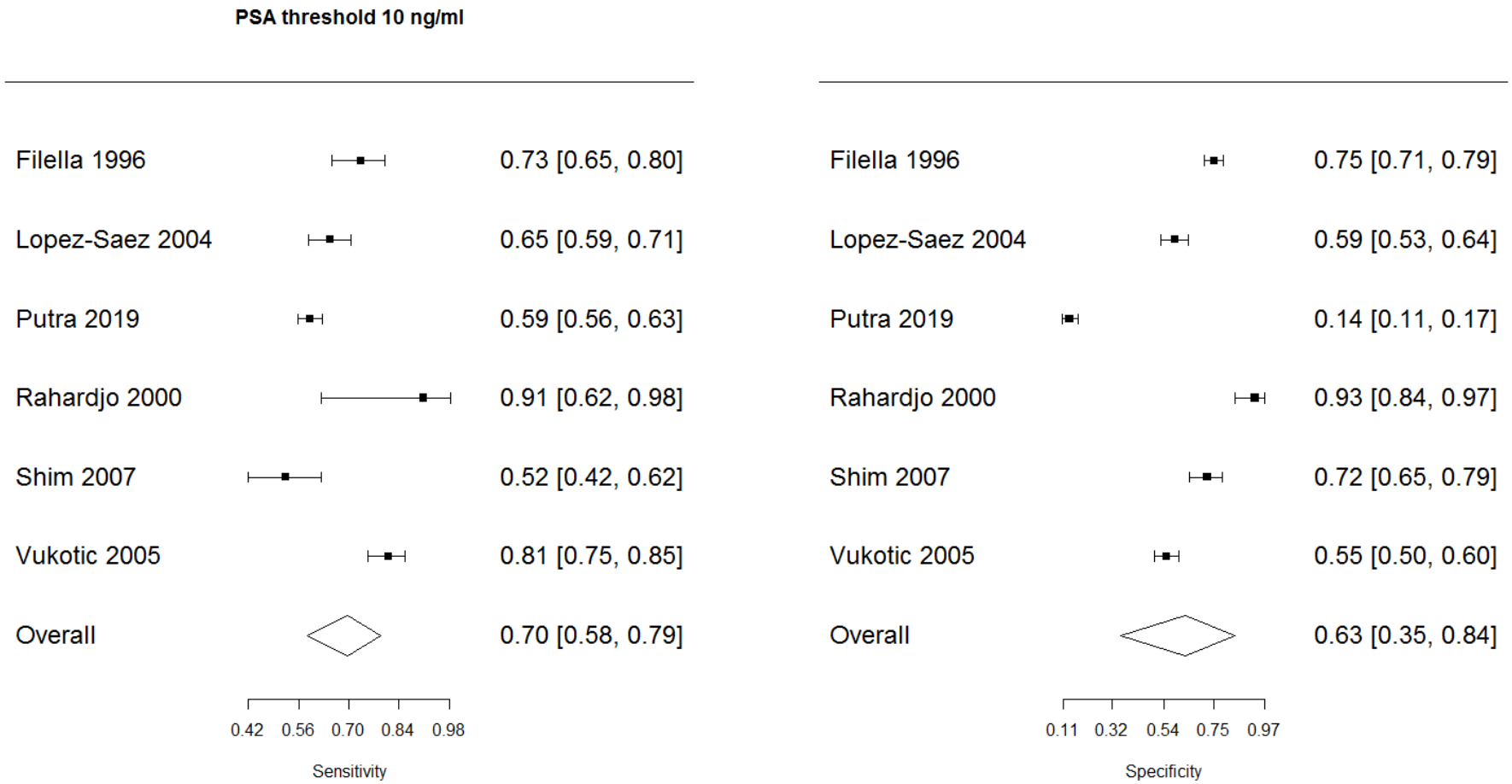
Sensitivity: $I^2 = 67.5\%$

Fixed PSA threshold 9ng/ml (GRADE table 11)



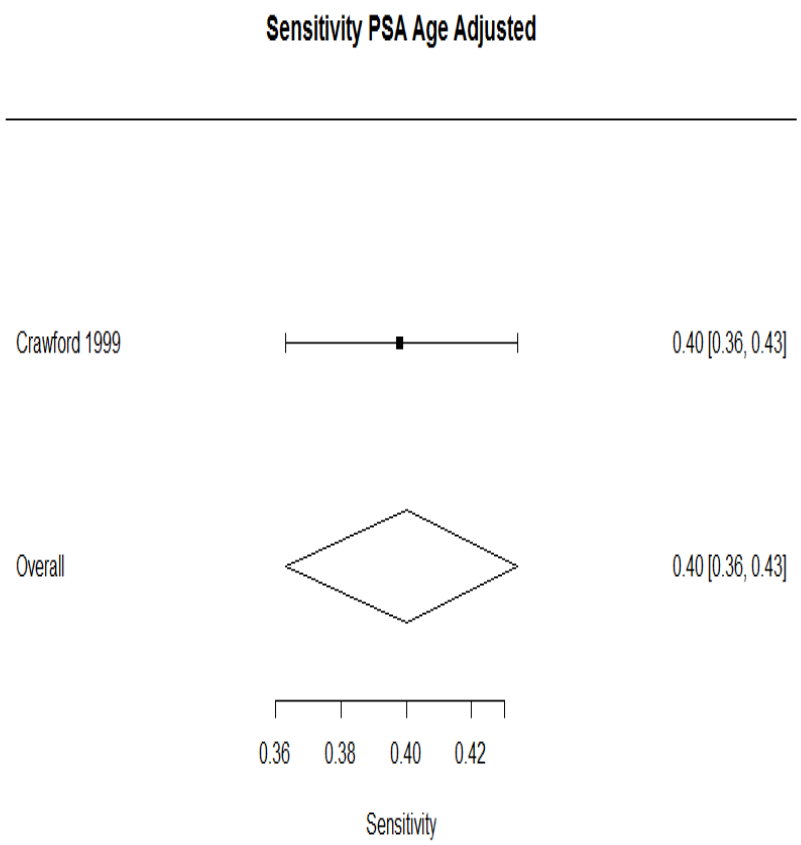
Sensitivity: $I^2 = 81\%$

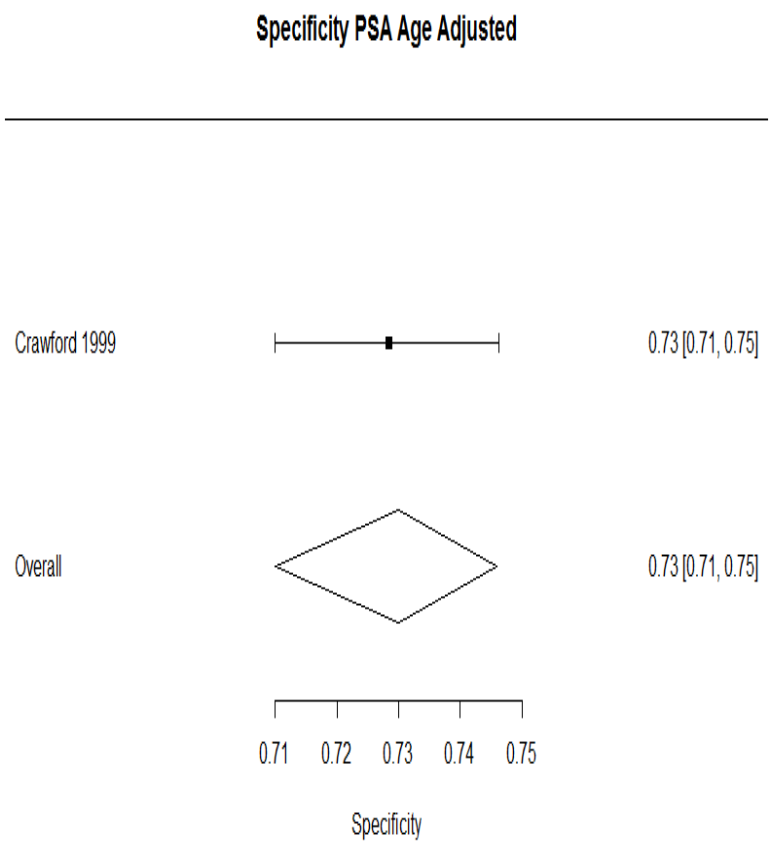
Fixed PSA threshold 10ng/ml (GRADE table 11)



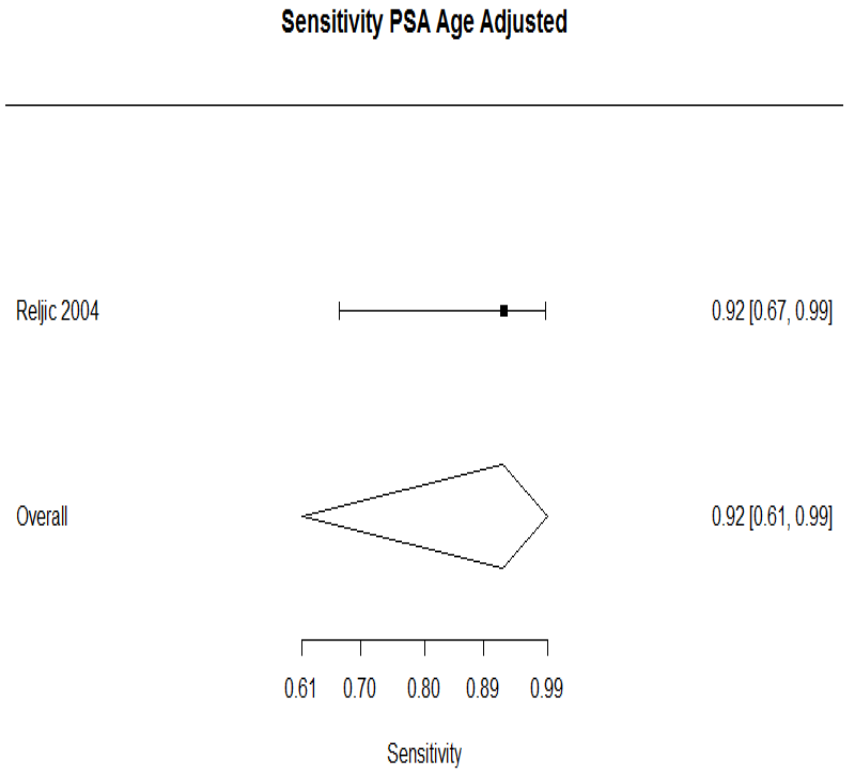
Sensitivity: $I^2 = 91.8\%$

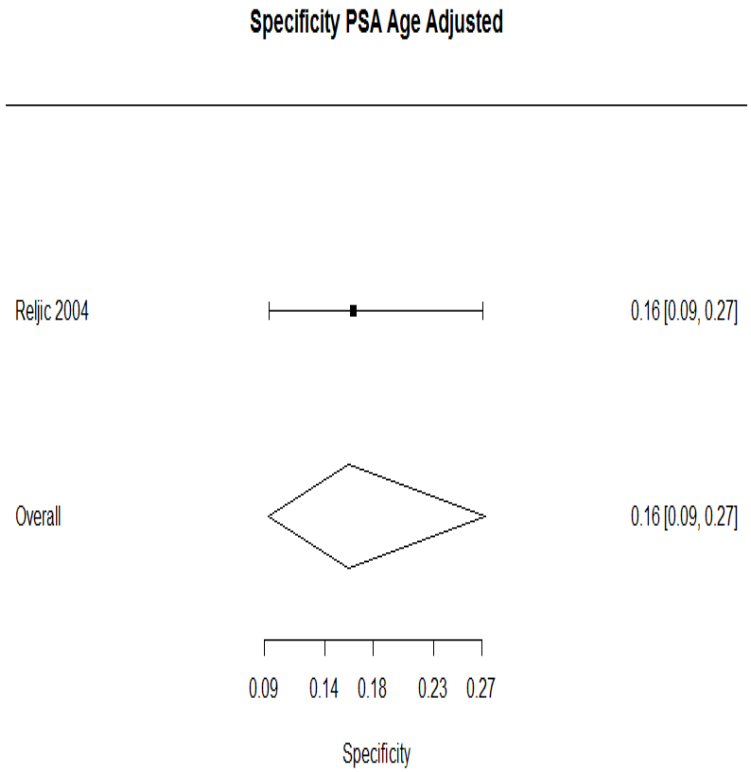
PSA Age Adjusted – without symptoms (GRADE table 12). Thresholds: 40-49: 2.4mg/l, 50-59: 3.8mg/l, 60-69: 5.6mg/l, 70-79 – 6.9mg/l



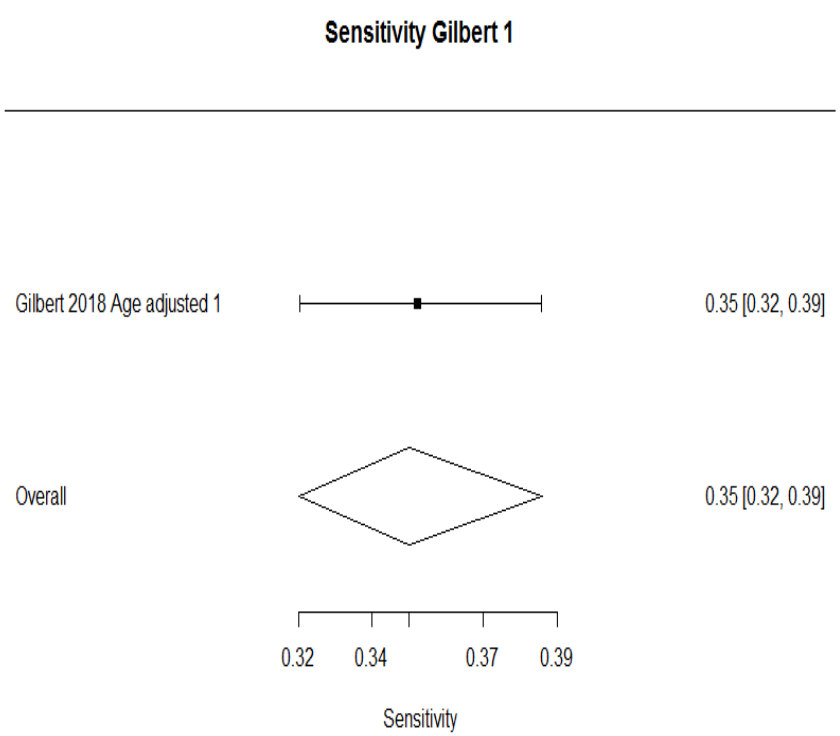


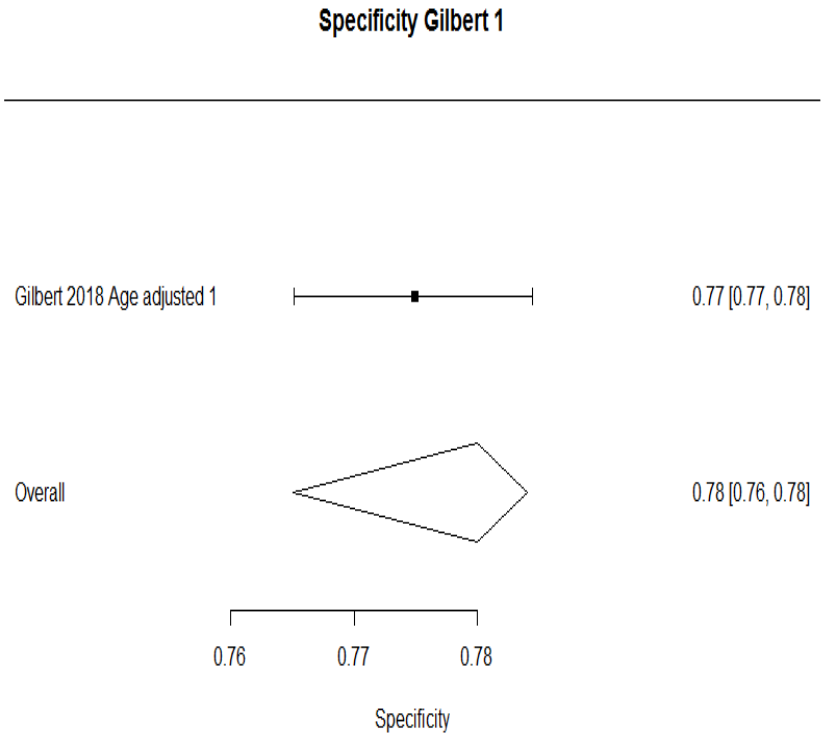
PSA Age Adjusted – without symptoms (GRADE table 12). Thresholds: 40-49: 2.5mg/l, 50-59: 3.5mg/l, 60-69: 4.5mg/l, 70-79: 6.5mg/l



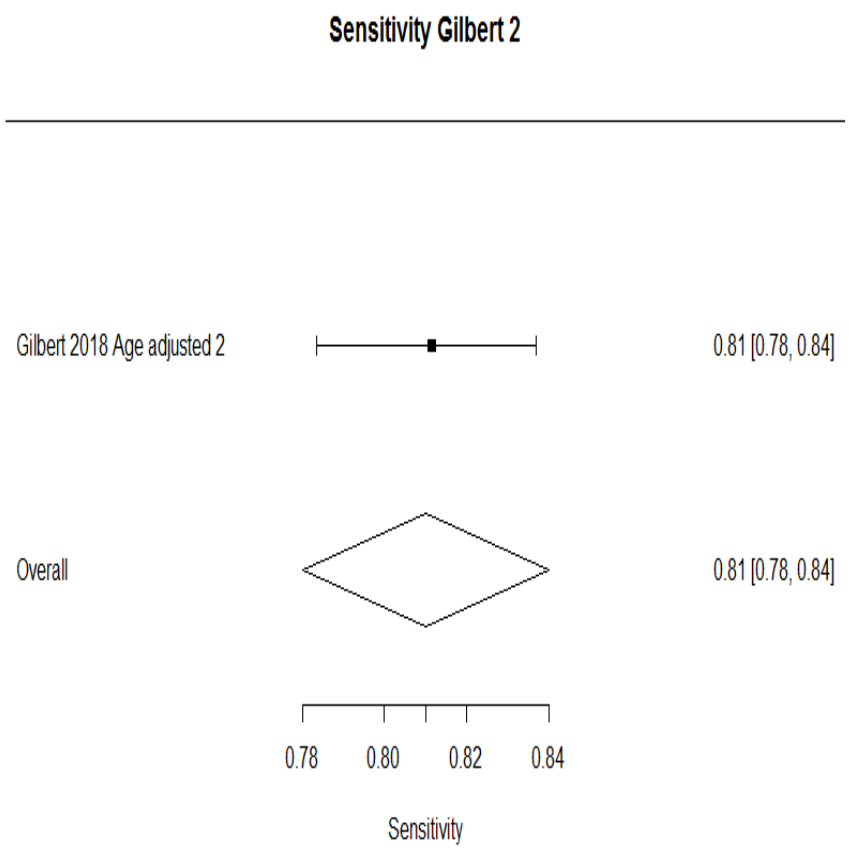


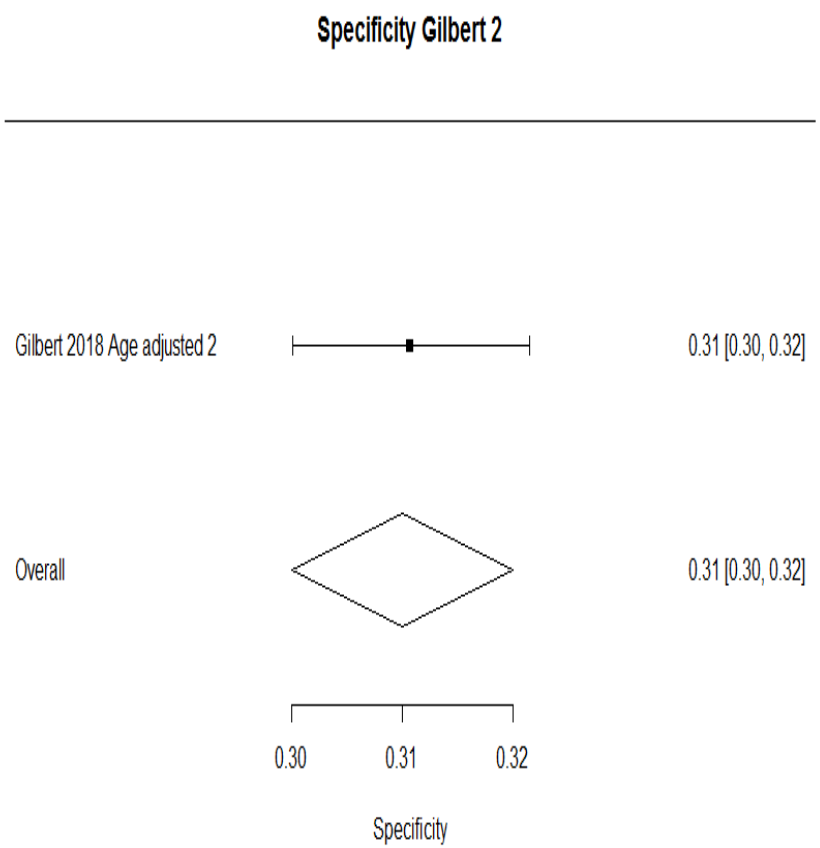
PSA age adjusted – without symptoms (GRADE table 12). Thresholds: age (years): PSA (ng/mL): 50:2.8, 51:3.0, 52:3.2, 53:3.4, 54:3.6, 55:3.8, 56:4, 57:4.2, 58:4.6, 59:4.9, 60:5.2, 61:5.6, 62:6.1, 63:6.5, 64:7, 65:7.6, 66:8.3, 67:9, 68:9.8, 69:10.4, 70:11.3



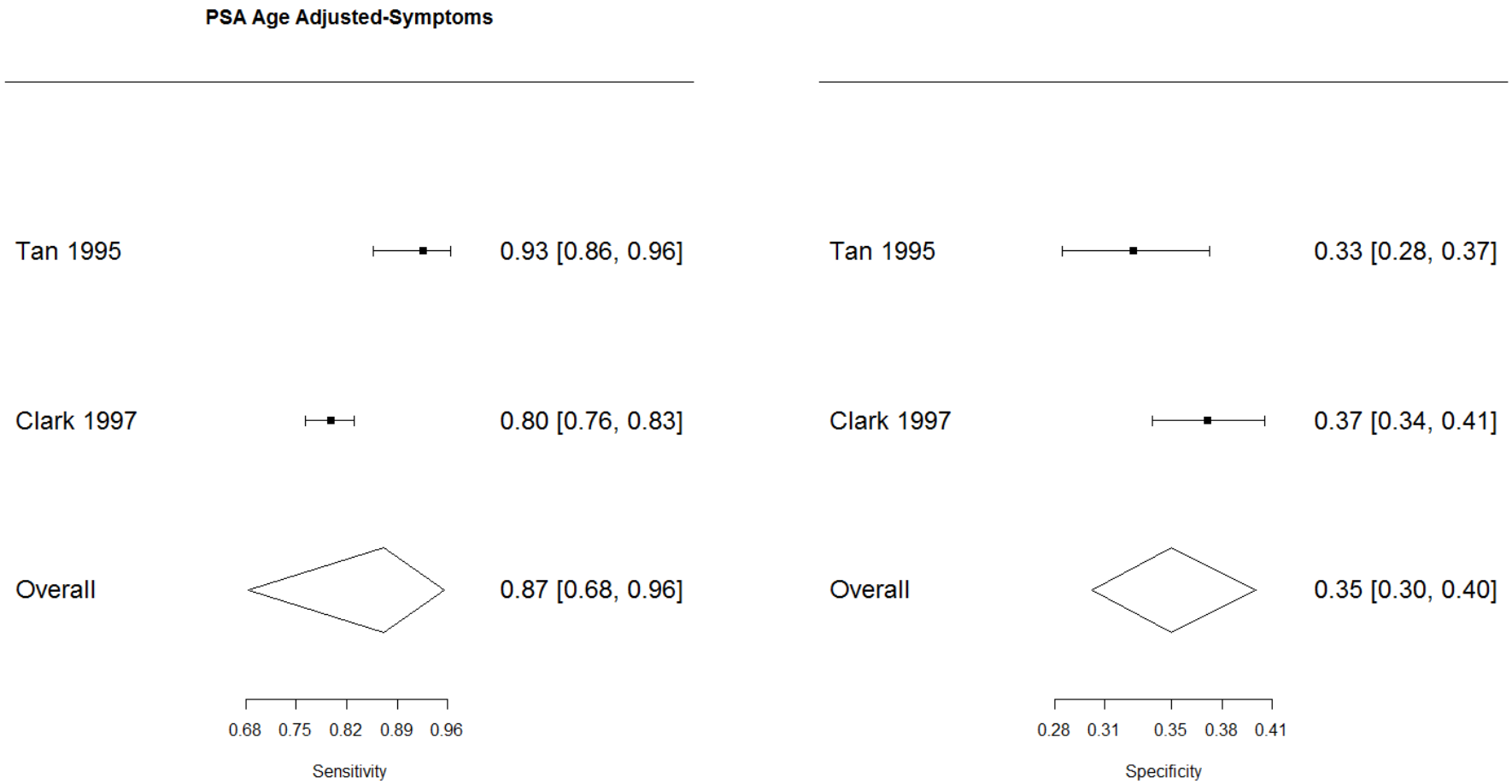


PSA age adjusted – without symptoms (GRADE table 12). Thresholds: 50–59: PSA = 3 ng/mL; age 60–70: PSA = 4 ng/mL; age ≥ 70: PSA = 5 ng/mL)



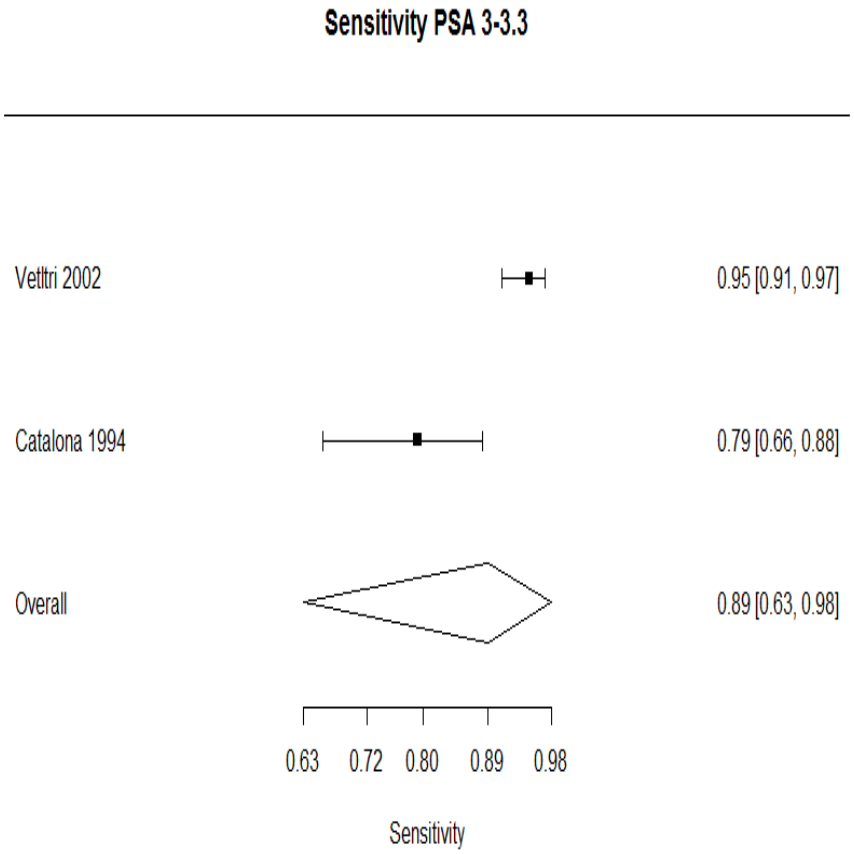


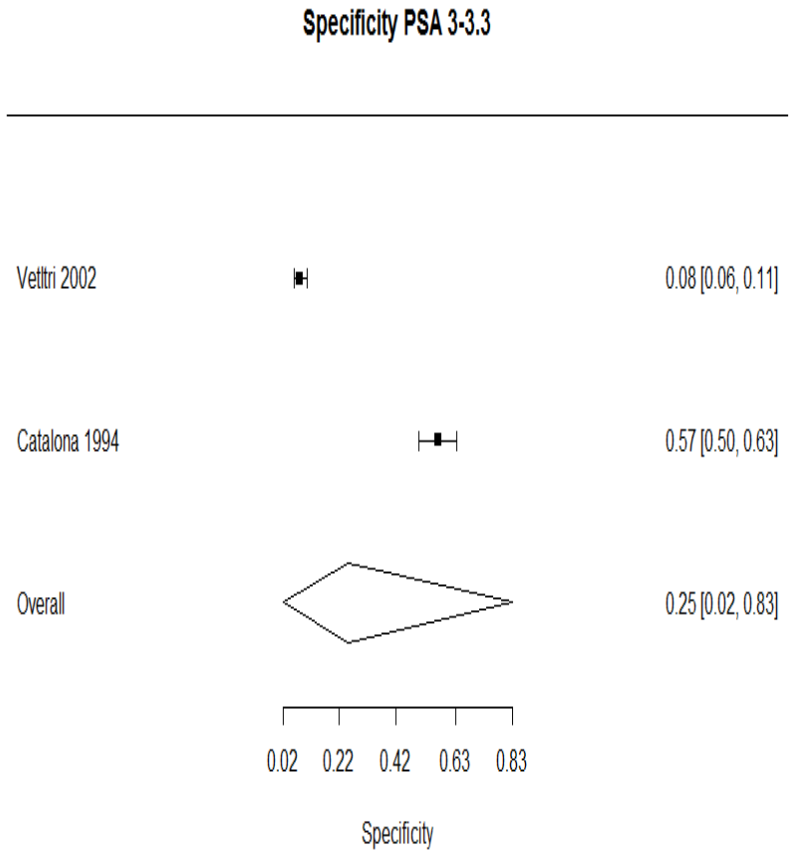
PSA Age Adjusted – with symptoms (GRADE table 13)



Sensitivity: $I^2 = 98.7\%$

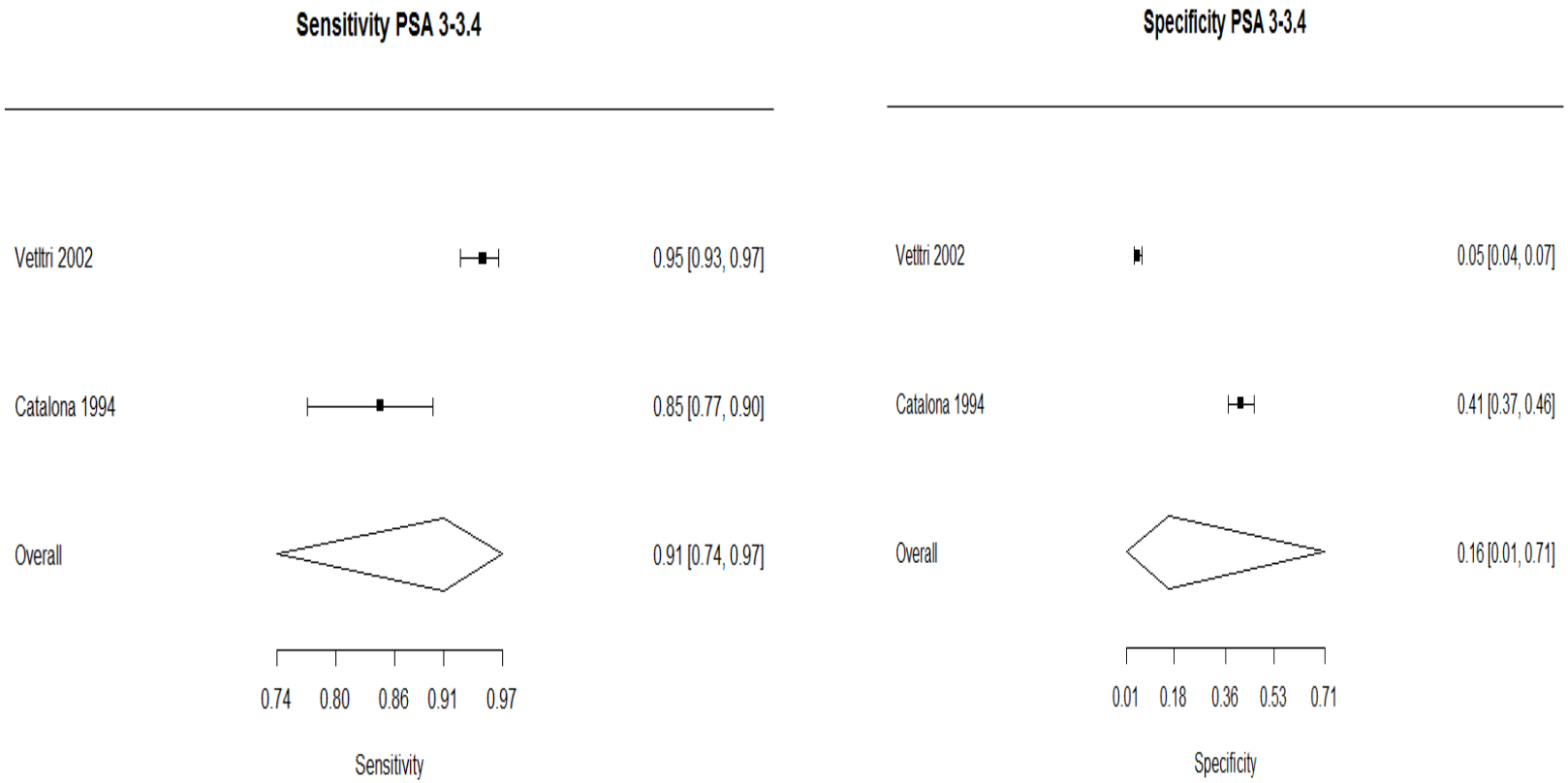
PSA 3-3.3mg/l Age 45-59 (GRADE table 14)





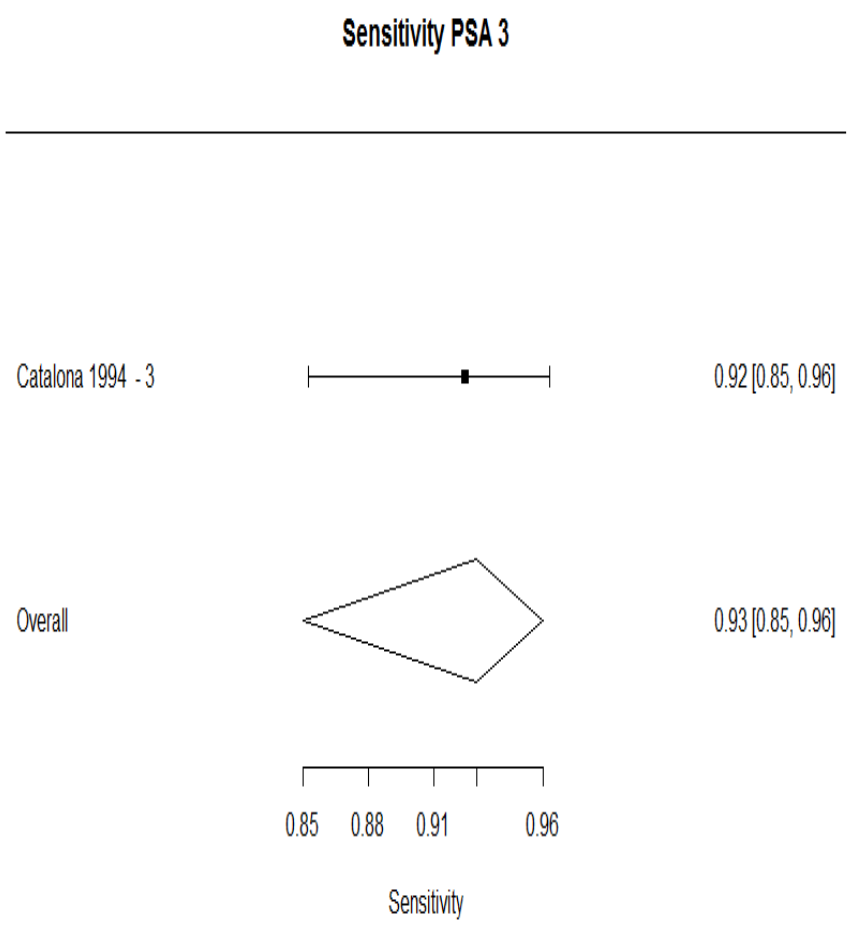
Sensitivity: $I^2 = 91.2\%$

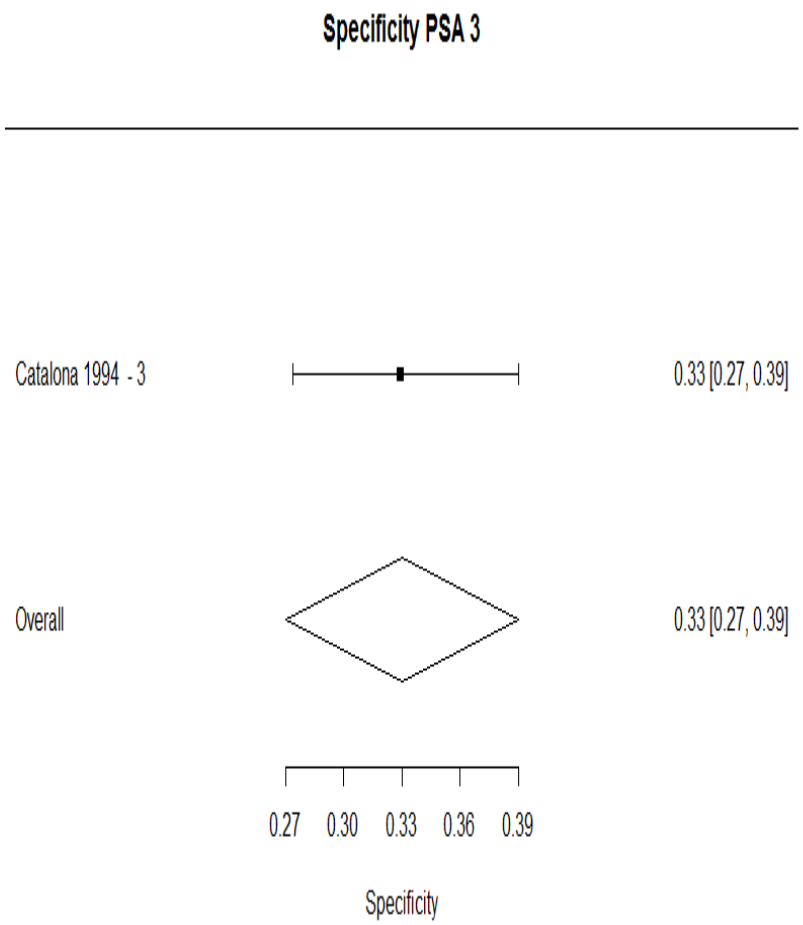
PSA 3-3.4mg/l Age 60-69 (GRADE table 14)



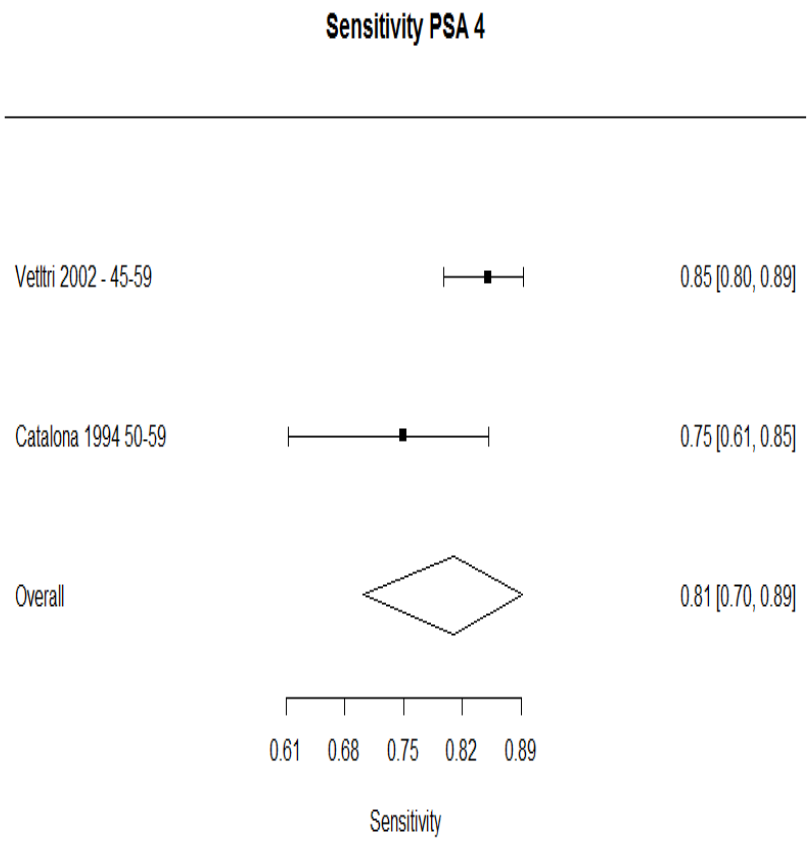
Sensitivity: I^2 =93.3%

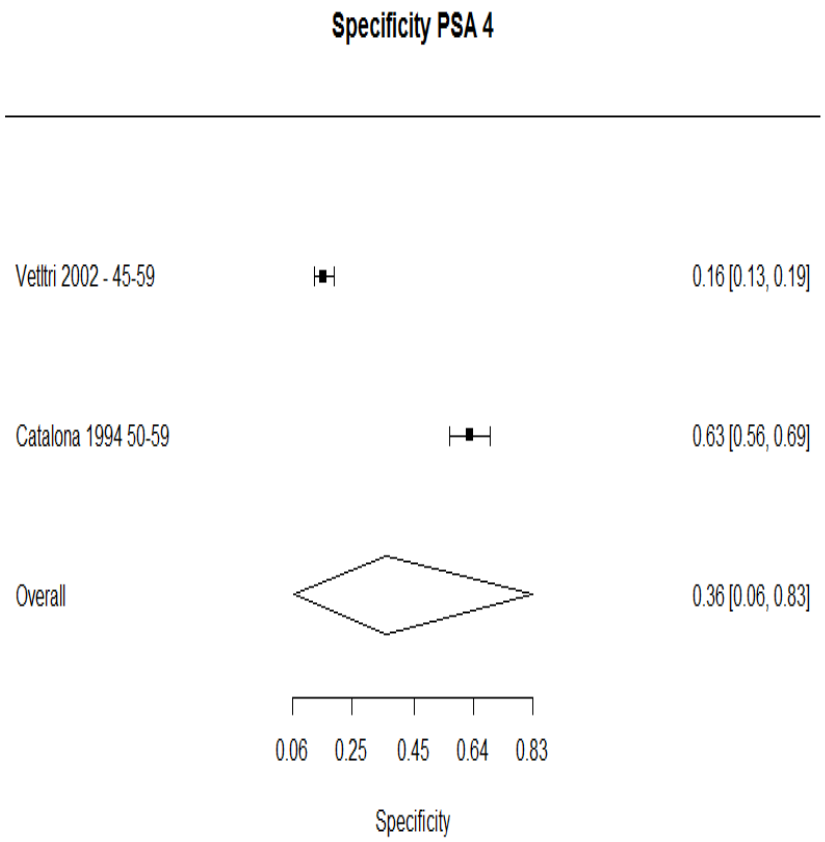
PSA 3mg/l Age 70-96 (GRADE table 14)





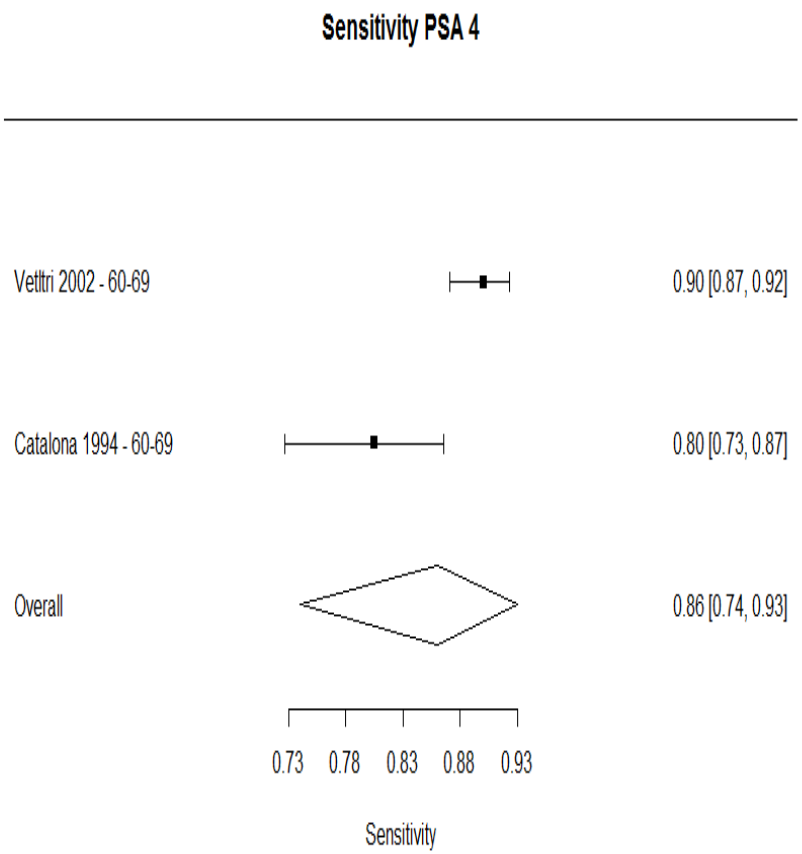
PSA 4mg/ml Age 45-59 (GRADE table 14)

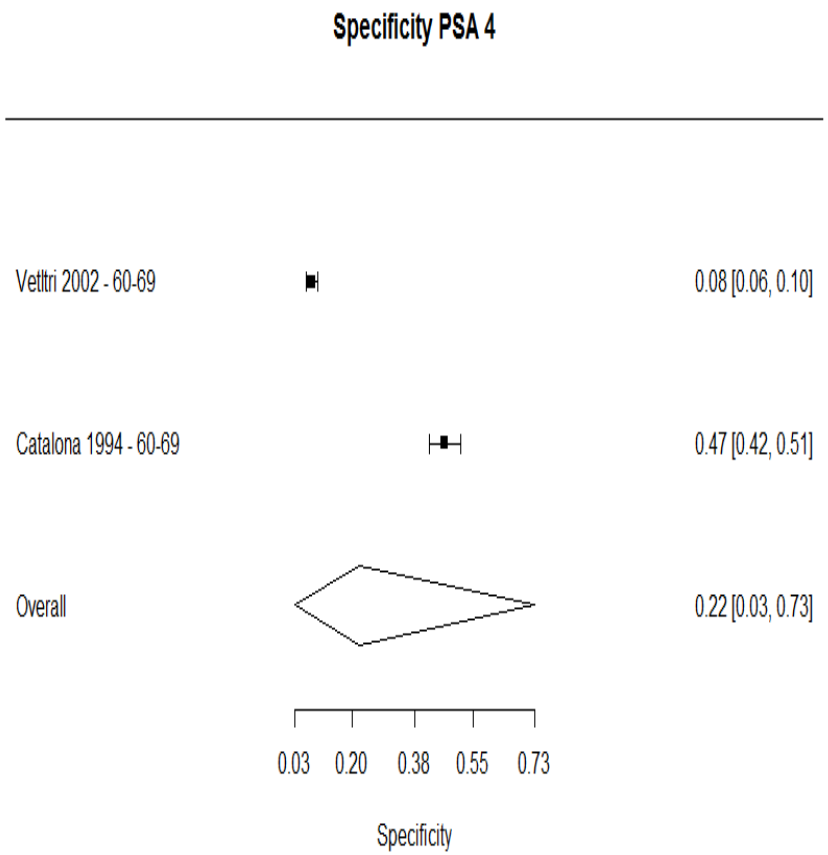




Sensitivity: $I^2 = 64.5\%$

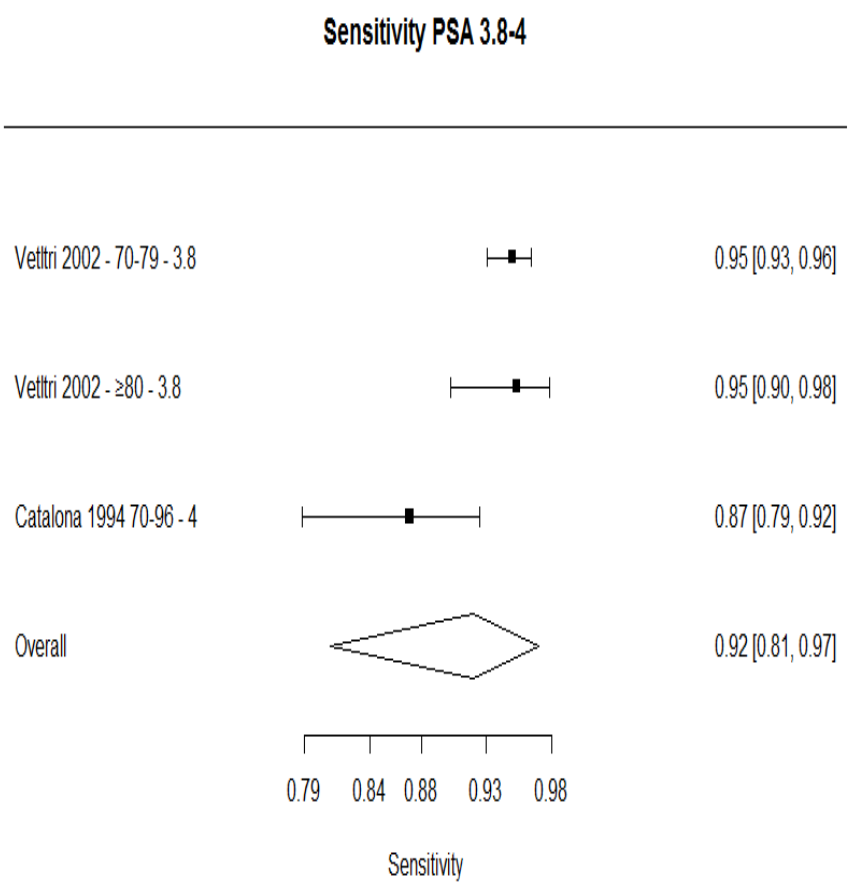
PSA 4mg/l Age 60-69 (GRADE table 14)

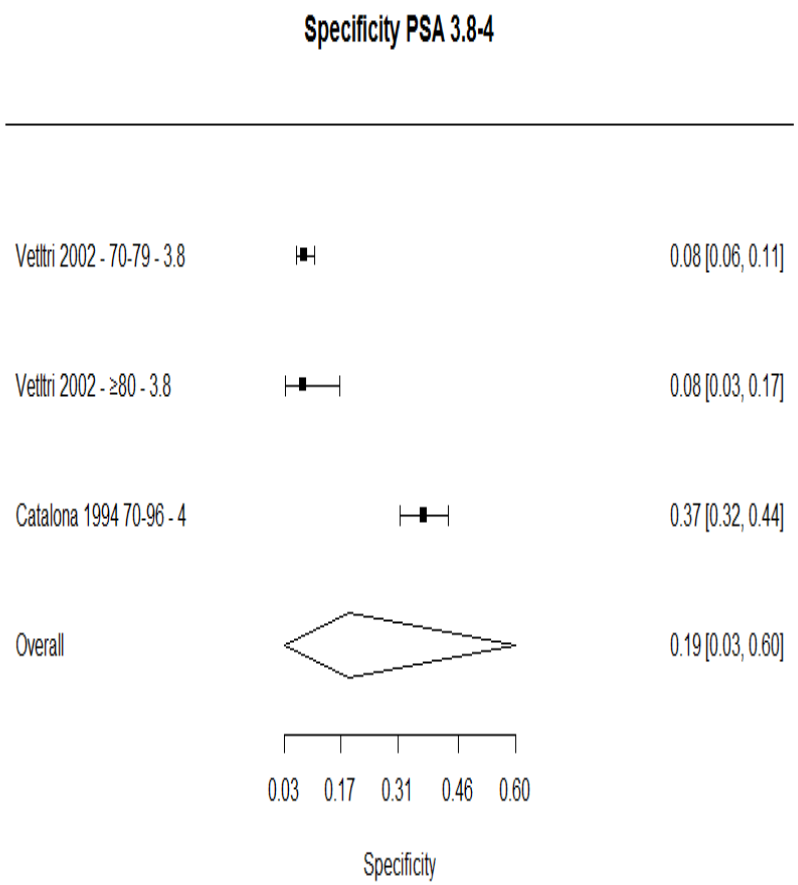




Sensitivity: $I^2 = 87.9\%$

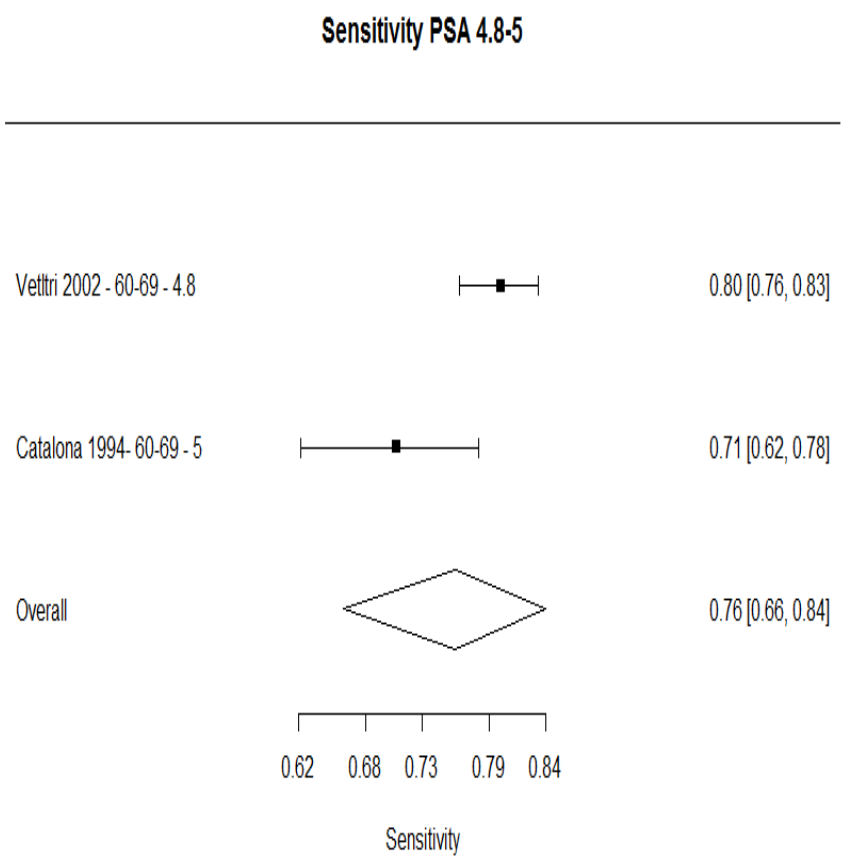
PSA 3.8-4mg/l Age 70-96 (GRADE table 14)

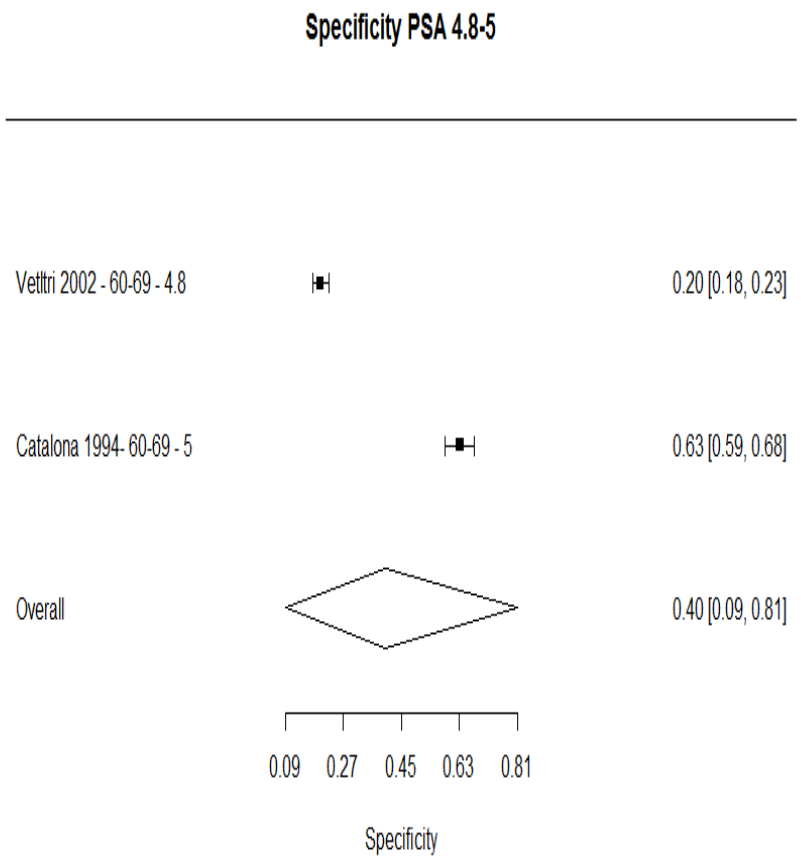




Sensitivity: $I^2 = 77.9\%$

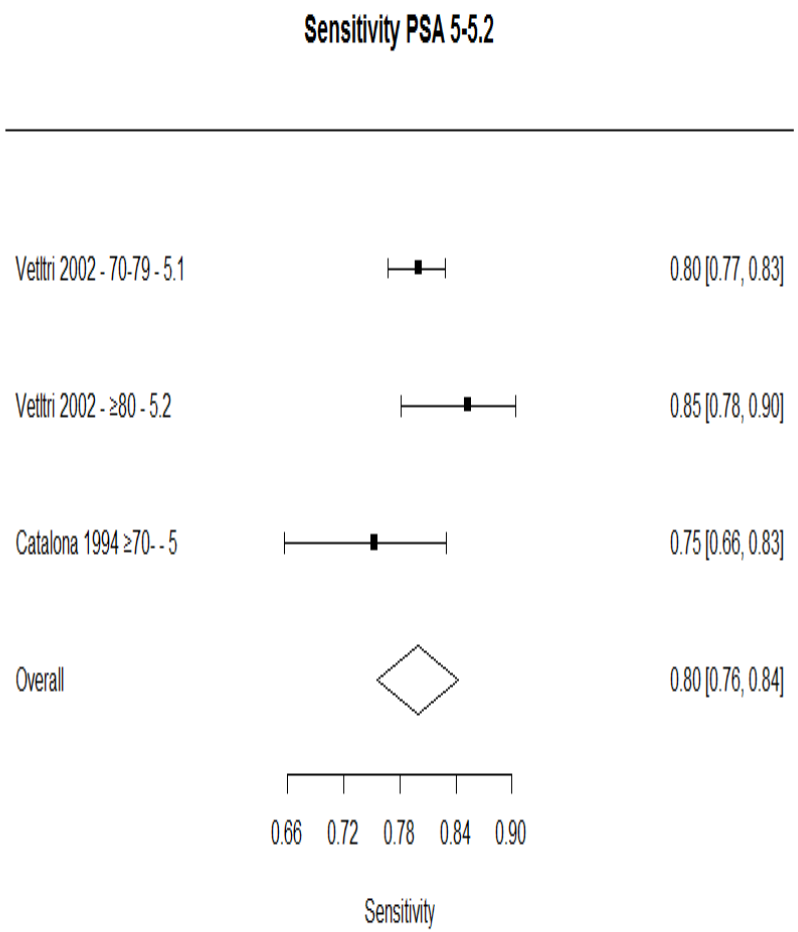
PSA 4.8-5mg/l Age 60-69 (GRADE table 14)

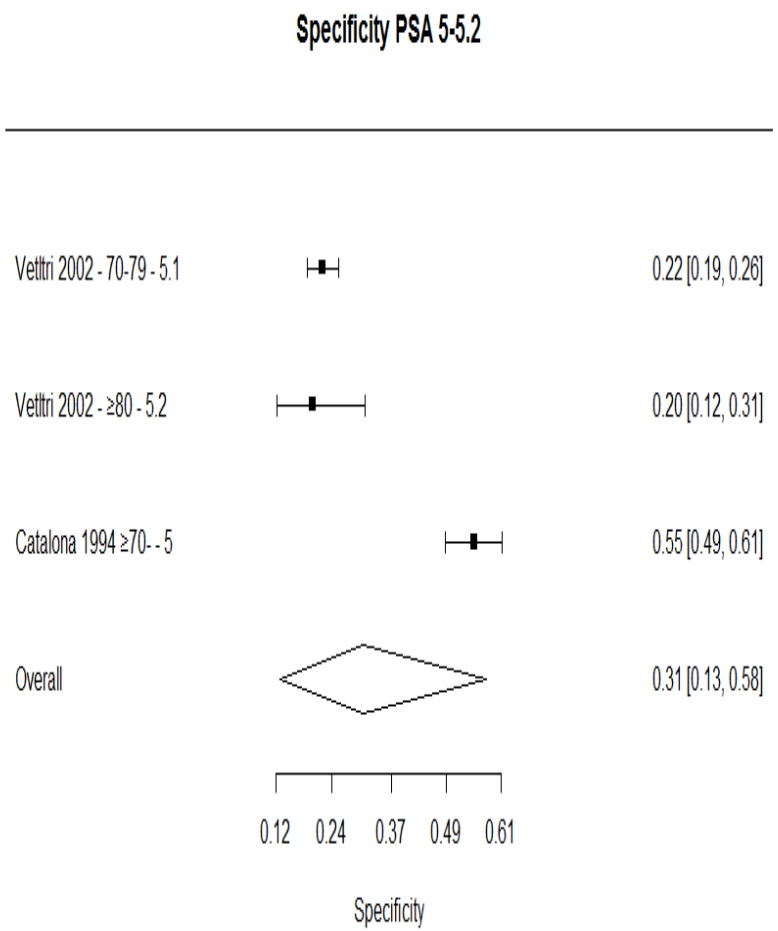




Sensitivity: $I^2 = 79.8\%$

PSA 5-5.2mg/l Age 70-96 (GRADE table 14)





Sensitivity: $I^2 = 42.9$

Appendix F – GRADE tables

Table 11: Fixed thresholds:

No. of studies	Study design	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1[9]	Cross-sectional	177	2.13mg/l	0.95 (0.84-0.99)	0.46(0.38-0.54)	0.10%	0.18% (0.14-0.21)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						1.60%	2.28% (2.16-3.38)	Serious risk of bias[1]	Serious indirectness[3]	N/A	Serious imprecision[7]	Very Low
						6.10%	10.3% (8.1-12.27)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
1[10]	Cross-sectional	315	2.5mg/l	0.8 (0.71-0.87)	0.28 (0.22-0.35)	0.10%	0.11% (0.09-0.13)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						1.60%	1.78% (1.47-2.11)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						6.10%	6.74% (5.63-7.92)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
1[9]	Cross-sectional	177	2.83mg/l	0.91 (0.78 - 0.97	0.55 (0.46 - 0.63)	0.10%	0.2% (0.15-0.26)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						1.60%	3.17% (2.32-4.08)	Serious risk of bias[1]	Serious indirectness[3]	N/A	Serious imprecision[7]	Very low
						6.10%	11.58% (8.66-14.52)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
4[11]	Cross-sectional	1068	3-3.12mg/l	0.92 (0.84-0.96)	0.16 (0.05-0.42)	0.10%	0.11% (0.09-0.17)	Serious risk of bias[1]	Serious indirectness[3]	Serious inconsistency[5]	No serious imprecision	Very Low

						1.60%	1.75% (1.42-2.62)	Serious risk of bias[1]	Serious indirectness[3]	Serious inconsistency[5]	No serious imprecision	Very Low
						6.10%	6.64% (5.4-9.71)	Serious risk of bias[1]	Serious indirectness[3]	Serious inconsistency[5]	No serious imprecision	Very Low
14[12]	Cross-sectional	6387	3.97-4.1mg/l	0.93 (0.87-0.96)	0.16 (0.1-0.25)	0.10%	0.11% (0.1-0.13)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low
						1.60%	1.7% (1.5-2.04)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low
						6.10%	6.7% (5.9-7.7)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low
1[10]	Cross-sectional	315	4.5mg/l	0.91 (0.83-0.948)	0.19 (0.14-0.24)	0.10%	0.11% (0.10-0.13)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						1.60%	1.78% (1.55-2)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						6.10%	6.74% (5.9-7.53)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
2 [9, 10]	Cross-sectional	492	4.69-4.7mg/l	0.78 (0.68-0.85)	0.47 (0.09-0.88)	0.10%	0.15% (0.07-0.7)	Serious risk of bias[1]	Serious indirectness[3]	No serious inconsistency	Serious imprecision[7]	Very Low
						1.60%	2.34% (1.2-10.33)	Serious risk of bias[1]	Serious indirectness[3]	No serious inconsistency	Serious imprecision[7]	Very Low
						6.10%	8.73% (4.63-31.51)	Serious risk of bias[1]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low

3[13]	Cross-sectional	487	5-5.3mg/l	0.86 (0.76-0.93)	0.25 (0.17-0.33)	0.10%	0.11% (0.09-0.14)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
						1.60%	1.8% (1.47-2.21)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
						6.10%	6.9% (5.6-8.27)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
1[14]	Cross-sectional	160	5.67mg/l	0.84 (0.716-0.92)	0.34 (0.257-0.433)	0.10%	0.13% (0.1-0.16%	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						1.60%	2% (1.54-2.57)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
						6.10%	7.65% (5.9-9.54)	Serious risk of bias[1]	Serious indirectness[3]	N/A	No serious imprecision	Low
3[15]	Cross-sectional	626	6-6.2mg/l	0.76 (0.68-0.83)	0.39 (0.28-0.50)	0.10%	0.12% (0.09-0.17)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
						1.60%	2% (1.51-2.63)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
						6.10%	7.49% (5.8-9.73)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
3[16]	Cross-sectional	613	6.9-7mg/l	0.58 (0.46-0.68)	0.55 (0.45-0.64)	0.10%	0.13% (0.08-0.19)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low

						1.60%	2.1% (1.34-2.98)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
						6.10%	7.73% (5.2-10.93)	Very serious risk of bias [2]	Serious indirectness[3]	No serious inconsistency	No serious imprecision	Very Low
3[17]	Cross-sectional	586	8mg/l	0.5 (0.38-0.61)	0.73 (0.52-0.87)	0.10%	0.2% (0.08-0.5)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	Serious imprecision[7]	Very Low
						1.60%	2.9% (1.27-7.09)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	Serious imprecision[7]	Very Low
						6.10%	10.74% (4.9-23.36)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low
2[18]	Cross-sectional	466	9mg/l	0.37 (0.15-0.67)	0.78 (0.45-0.94)	0.10%	0.19% (0.03-1.1)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	Serious imprecision[7]	Very Low
						1.60%	2.7% (0.44-15.37)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	Very serious imprecision[8]	Very Low
						6.10%	9.85% (1.7-42.04)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	Serious imprecision[7]	Very Low
6[19]	Cross-Sectional	3225	10mg/l	0.70 (0.58-0.79)	0.63 (0.35-0.84)	0.10%	0.19% (0.09-0.49)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low
						1.60%	2.98% (1.4-7.4)	Very serious	Serious indirectness[3]	Very serious inconsistency[6]	Serious imprecision[7]	Very Low

								risk of bias [2]				
						6.10%	10.95 (5.48-24.3)	Very serious risk of bias [2]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very Low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. >33.3% of weighted data from studies at high risk of bias
3. >33.3% of weighted data from indirect or partially indirect studies
4. >33.3% of weighted data from indirect studies
5. i-squared >33%
6. i-squared >66%
7. 95% confidence interval for positive predictive value crosses one end of a clinical decision threshold interval – (0.5, 3)
8. 95% confidence interval for positive predictive value crosses both ends of a clinical decision threshold interval – (0.5, 3)
9. Mutlu 2009
10. Kobayashi 2005
11. Filella 1996, Mutlu 2009, Rashid 2012, Mitchell 2001
12. Abdrabo 2011 , Agnihotri 2014, Dalva 1999, Filella 1996, Lopez-Saez 2004, McArdle 2004, Putra 2019, Rashid 2012, Mitchell 2001, Rahardjo 2000, Shim 2007, Djavan 2002, Sozen 2005, Vukotic 2005
13. Martinez-Pineiro, Kikuchi 2000, Mitchell 2001
14. Mitchell 2001
15. Kuppasamy 2018, Martinez-Pineiro, Mitchell 2001
16. Kuppasamy 2018, Martinez-Pineiro, Kikuchi 2000
17. Kuppasamy 2018, Martinez-Pineiro, Rahardjo 2000
18. Kuppasamy 2018, Martinez-Pineiro
19. Filella 1996, Lopez-Saez 2004, Putra 2019, Rahardjo 2000, Shim 2007, Vukotic 2005

Table 12: Age Adjusted – without symptoms

No. of studies	Study design	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1[11]	Cross-Sectional	3029	Age Adjusted[9]	0.4 (0.36-0.43)	0.73 (0.71-0.75)	0.10%	0.15% (0.13-0.17)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low
						1.60%	2.32% (2-2.7)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low
						6.10%	8.68% (7.52-10)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low
1[12]	Cross-sectional	80	Age Adjusted[10]	0.92 (0.61-0.99)	0.16 (0.09-0.27)	0.10%	0.1% (0.07-0.14)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	1.76% (1.08-2.16)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						6.10%	6.7% (4.18-8.12)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
1[15]	Cross-sectional	8016	Age Adjusted[13]	0.35 (0.32-0.39)	0.78 (0.77-0.784)	0.10%	0.16% (0.14-0.18)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	2.48% (2.17-2.82)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low

						6.10%	9.23% (8.13-10.40)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
1[15]	Cross-sectional	8016	Age Adjusted[14]	0.81 (0.78-0.84)	0.31 (0.3-0.32)	0.10%	0.12% (0.11-0.12)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	1.87% (1.78-1.97)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						6.10%	7.09% (6.75-7.43)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low

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4. >33.3% of weighted data from indirect studies
5. i-squared >33%
6. i-squared >66%
7. 95% confidence interval for positive predictive value crosses one end of a clinical decision threshold interval – (0.5, 3)
8. 95% confidence interval for positive predictive value crosses both ends of a clinical decision threshold interval – (0.5, 3)
9. Age adjusted cut offs: 40-49: 2.4mg/l, 50-59: 3.8mg/l, 60-69: 5.6mg/l, 70-79 – 6.9mg/l
10. Age adjusted cut offs: 40-49: 2.5mg/l, 50-59: 3.5mg/l, 60-69: 4.5mg/l, 70-79: 6.5mg/l
11. Crawford 1999
12. Reljic 2004
13. Age adjusted cut offs: age (years): PSA (ng/mL): 50:2.8, 51:3.0, 52:3.2, 53:3.4, 54:3.6, 55:3.8, 56:4, 57:4.2, 58:4.6, 59:4.9, 60:5.2, 61:5.6, 62:6.1, 63:6.5, 64:7, 65:7.6, 66:8.3, 67:9, 68:9.8, 69:10.4, 70:11.3
14. Age adjusted cut offs: 50–59: PSA = 3 ng/mL; age 60–70: PSA = 4 ng/mL; age ≥ 70: PSA = 5 ng/mL)
15. Gilbert 2018

Table 13 Age Adjusted – Population with symptoms

No. of studies	Study design	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
2[10]	Cross-Sectional	1857	Age Adjusted[9]	0.87 (0.68-0.96)	0.35 (0.30-0.40)	0.10%	0.13% (0.1-0.16)	Serious risk of bias[1]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very low
						1.60%	2.13% (1.55-2.54)	Serious risk of bias[1]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very low
						6.10%	8% (5.94-9.42)	Serious risk of bias[1]	Serious indirectness[3]	Very serious inconsistency[6]	No serious imprecision	Very low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. >33.3% of weighted data from studies at high risk of bias
3. >33.3% of weighted data from indirect or partially indirect studies
4. >33.3% of weighted data from indirect studies
5. i-squared >33%
6. i-squared >66%
7. 95% confidence interval for positive predictive value crosses one end of a clinical decision threshold interval – (0.5, 3)
8. 95% confidence interval for positive predictive value crosses both ends of a clinical decision threshold interval – (0.5, 3)
9. Age adjusted cut offs: 40-49: 2.5mg/l, 50-59: 3.5mg/l, 60-69: 4.5mg/l, 70-79: 6.5ng/ml
10. Clark 1997, Tan 1995

Table 14: Age stratified fixed thresholds – without symptoms:

No. of studies	Study design	Sample size	PSA cut-off	Sensitivity (95%CI)	Specificity (95%CI)	Prevalence	PPV (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

2[9]	Cross-Sectional	1004	Age 45-59: 3-3.3ng/ml	0.89 (0.63-0.98)	0.25 (0.02-0.83)	0.10%	0.1% (0.06-0.6)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						1.60%	1.9% (1.03-8.57)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						6.10%	7.16% (4-27.25)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
2[9]	Cross-Sectional	1997	Age 60-69: 3-3.4ng/ml	0.91 (0.74-0.97)	0.16 (0.01-0.71)	0.10%	0.1% (0.07-0.3)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
						1.60%	1.7% (1.2-5.16)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						6.10%	6.58% (4.6-17.85)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
1[10]	Cross-Sectional	342	Age 70-96: 3ng/ml	0.93 (0.85-0.96	0.33 (0.27-0.39)	0.10%	0.14% (0.12 - 0.2)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low
						1.60%	2.2% (1.86-2.5)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low
						6.10%	8.27% (7-9.28)	Very serious risk of bias[2]	Very serious indirectness[4]	N/A	No serious imprecision	Very low

2[9]	Cross-Sectional	1004	Age 45-59: 4mg/l	0.81 (0.7-0.9)	0.36 (0.06-0.83)	0.10%	0.13% (0.07-0.52)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low
						1.60%	2.03% (1.2-7.85)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low
						6.10%	7.65% (4.64-25.4)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low
2[9]	Cross-Sectional	1997	Age 60-69: 4ng/ml	0.86 (0.74-0.93)	0.22 (0.03-0.73)	0.10%	0.1% (0.08-0.3)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
						1.60%	1.8% (1.2-5.3)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						6.10%	6.68% (4.7-18.3)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
2[9]	Cross-Sectional	1763	Age 70-96: 3.8-4 ng/ml	0.92 (0.81-0.97)	0.19 (0.03-0.6)	0.10%	0.1% (0.08-0.2)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
						1.60%	1.8% (1.3-3.8)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						6.10%	6.9% (5.1-13.6)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low

2[9]	Cross-Sectional	1997	Age 60-69: 4.8 - 5ng/ml	0.76 (0.66-0.84)	0.40 (0.09-0.81)	0.10%	0.1% (0.07-0.4)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
						1.60%	2% (1.12-6.7)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	Serious imprecision[7]	Very low
						6.10%	7.6% (4.5-22.3)	Very serious risk of bias[2]	Very serious indirectness[4]	Very serious inconsistency[6]	No serious imprecision	Very low
2[9]	Cross-Sectional	1763	Age 70-96: 5 - 5.2ng/ml	0.8 (0.76-0.84)	0.31 (0.13-0.57)	0.10%	0.12% (0.09-0.2)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low
						1.60%	1.86% (1.39-3.14)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low
						6.10%	7.03% (5.33-11.46)	Very serious risk of bias[2]	Very serious indirectness[4]	Serious inconsistency[5]	No serious imprecision	Very low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. >33.3% of weighted data from studies at high risk of bias
3. >33.3% of weighted data from indirect or partially indirect studies
4. >33.3% of weighted data from indirect studies
5. i-squared >33%
6. i-squared >66%
7. 95% confidence interval for positive predictive value crosses one end of a clinical decision threshold interval – (0.5, 3)
8. 95% confidence interval for positive predictive value crosses both ends of a clinical decision threshold interval – (0.5, 3)
9. Veltri 2002, Catalona 1994
10. Catalona 1994

Table 15: Age adjusted split into age categories: population without symptoms

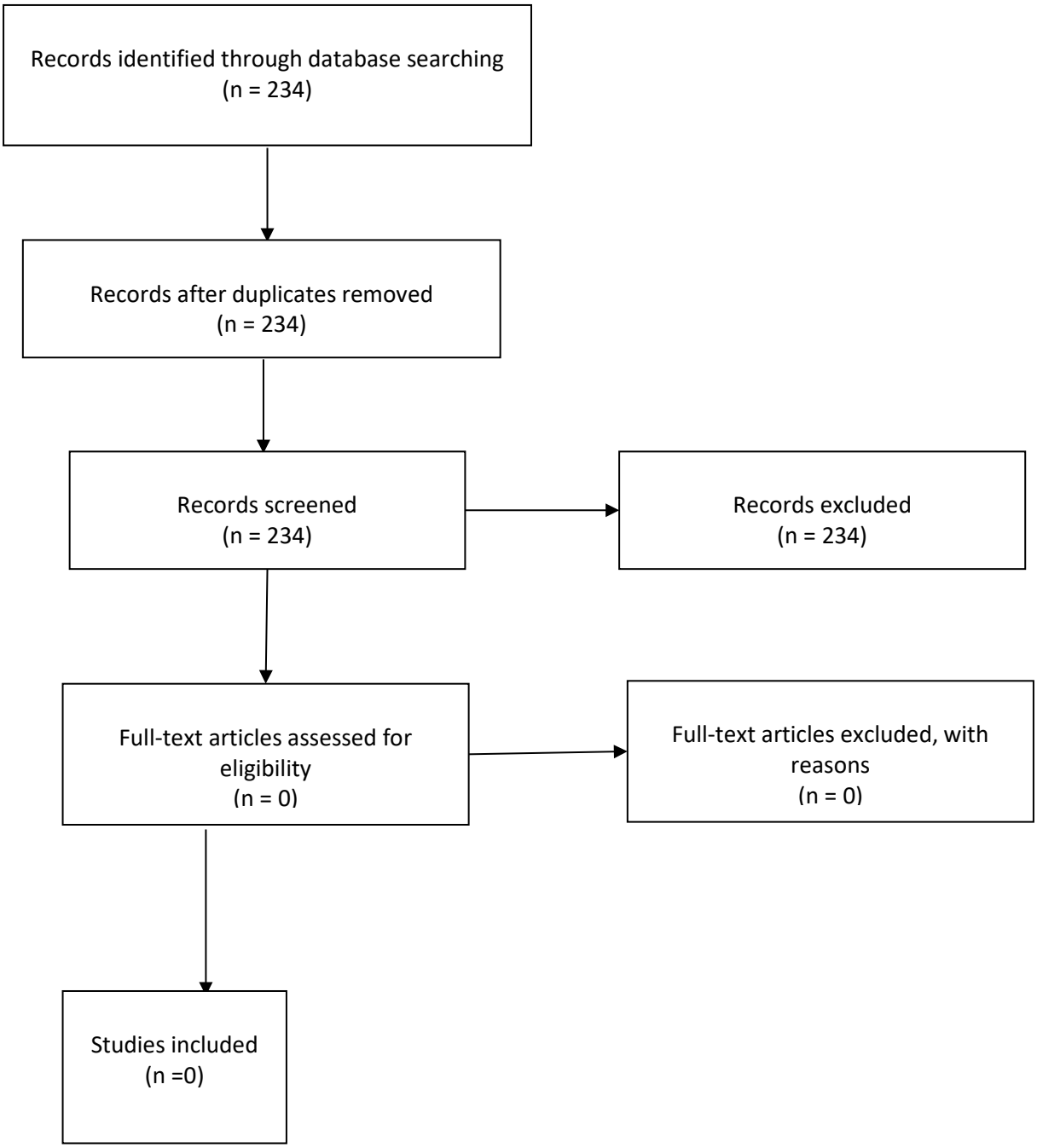
Age 50-54 **Age adjusted thresholds 1:** age (years):PSA (ng/mL) - 50:2.8, 51:3.0, 52:3.2, 53:3.4, 54:3.6												
1[4]	Cross-sectional	857	Age adjusted	0.87 (0.78 – 0.93)	0.26 (0.23-0.29)	0.10%	0.12% (0.1-0.13	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	1.87% (1.62-2.08)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						6.10%	7.09% (6.17-7.81)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
Age group 55–59 years **Age adjusted thresholds 1** age (years): PSA (ng/mL) - 56:4, 57:4.2, 58:4.6, 59:4.9												
1[4]	Cross-sectional	1,878	Age adjusted	0.63 (0.55-0.695)	0.63(0.6-0.65)	0.10%	0.17%(0.14-0.2)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	2.67% (2.23-3.14)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	Serious imprecision[5]	Very low
						6.10%	9.87% (8.35-11.45)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
Age group 60-64: **Age adjusted thresholds 2:** age 50–59: PSA = 3 ng/mL; age 60–70: PSA = 4 ng/ mL; age ≥ 70: PSA = 5 ng/mL)												
1[4]	Cross-sectional	2618	Age adjusted	0.7 (0.64-0.75)	0.47 (0.45-0.49)	0.10%	0.13% (0.12-0.15)	Very serious	Serious indirectness[3]	N/A	No serious imprecision	Very low

								risk of bias[2]				
						1.60%	2.1% (1.86-2.34)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						6.10%	7.89% (7.03-8.74)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
Age group 60-64: **Adjusted thresholds 1:** age (years): PSA (ng/mL) - 60:5.2, 61:5.6, 62:6.1, 63:6.5, 64:7												
1[4]	Cross-sectional	2618	Age adjusted	0.33 (0.27-0.39)	0.85 (0.831-0.86)	0.10%	0.21% (0.16-0.28)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	3.38% (2.59-4.3)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	Serious imprecision[5]	Very low
						6.10%	12.25% (9.59-15.32)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
Age group >65 Age adjusted thresholds 2: age 50–59: PSA = 3 ng/mL; age 60–70: PSA = 4 ng/mL; age ≥ 70: PSA = 5 ng/mL)												
1[4]	Cross-sectional	2663	Age adjusted	0.75 (0.696-0.794)	0.48 (0.45-0.495)	0.10%	0.14% (0.13-0.16)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
						1.60%	2.26% (2.03-2.49)	Very serious	Serious indirectness[3]	N/A	No serious imprecision	Very low

								risk of bias[2]				
						6.10%	8.47% (7.66-9.27)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low
Age group >65: **Age adjusted thresholds 1** age (years): 65:7.6, 66:8.3, 67:9, 68:9.8, 69:10.4, 70:11.3												
1[4]	Cross-sectional	2663	Age adjusted	0.07 (0.043-0.1)	0.98 (0.97-0.983)	0.10%	0.3% (0.15-0.59)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	Serious imprecision[5]	Very low
						1.60%	4.65% (2.35-8.73)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	Serious imprecision[5]	Very low
						6.10%	16.31% (8.79-27.65)	Very serious risk of bias[2]	Serious indirectness[3]	N/A	No serious imprecision	Very low

1. >33.3% of weighted data from studies at moderate or high risk of bias
2. >33.3% of weighted data from studies at high risk of bias
3. >33.3% of weighted data from indirect or partially indirect studies
4. Gilbert, R, 2018
5. 95% CI crosses one end of the MID threshold (0.5 or 3)

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

There are no included studies in this review question.

Appendix I – Health economic model

There is no original modelling in this review question

Appendix J – Excluded studies

Table 16: Diagnostic accuracy evidence – excluded studies

Study	Reason for exclusion
Abedi, Amir-Reza, Allameh, Farzad, Ranjbar, Arash et al. (2018) Incidental prostate cancer: A 10-year review of a tertiary center, Tehran, Iran. Research and Reports in Urology 10: 1-6	- Exclude *unable to tell if PSA taken at time of biopsy*
Abrate, A, Lazzeri, M, Lughezzani, G et al. (2015) Clinical performance of the Prostate Health Index (PHI) for the prediction of prostate cancer in obese men: data from the PROMEtheuS project, a multicentre European prospective study. BJU international 115(4): 537-545	- Exclude - no symptoms, fixed threshold
Ahn, Jae Hyun, Lee, Jeong Zoo, Chung, Moon Kee et al. (2014) Nomogram for prediction of prostate cancer with serum prostate specific antigen less than 10 ng/mL. Journal of Korean medical science 29(3): 338-42	- Exclude *2x2 data for cut off not included*
Akbas, Alpaslan, Gulpinar, Murat Tolga, Sancak, Eyup Burak et al. (2015) Is PSA still the best marker in diagnosis and monitoring of prostate cancer?. European Journal of General Medicine 12(2): 187-193	- Exclude *Review article not a study*
Al Rumaihi, Khalid, Al Jalham, Khalid, Younes, Nagy et al. (2013) The role of an abnormal prostate-specific antigen level and an abnormal digital rectal examination in the diagnosis of prostate cancer: A cross-sectional study in Qatar. Arab Journal of Urology 11(4): 355-360	- Exclude - no symptoms, fixed threshold
Arai, Y, Maeda, H, Ishitoya, S et al. (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. The Journal of urology 158(3pt1): 861-4	- 2x2 diagnostic data on PSA cut off not extractable
Asafudullah, S.M.; Badruddoza, S.M.; Salam, M.A. (2011) Evaluation of diagnostic accuracy of different biomarkers for prostate cancer. Pakistan Journal of Medical Sciences 27(1): 48-51	- Population does not match the protocol *Population all DRE positive*

Study	Reason for exclusion
Babaian, R J and Camps, J L (1991) The role of prostate-specific antigen as part of the diagnostic triad and as a guide when to perform a biopsy. Cancer 68(9): 2060-3	- no symptoms, fixed threshold
Babaian, R.J., Dinney, C.P.N., Ramirez, E.I. et al. (1993) Diagnostic testing for prostate cancer detection: Less is best. Urology 41(5): 421-425	- no symptoms, fixed threshold
Bakir, M Adel and Abo-daher, Dima (2012) Age-specific reference ranges for prostate-specific antigen among healthy Syrian men. The International journal of biological markers 27(2): e152-9	- Exclude *Not a diagnostic accuracy study*
Bangma, C H, Rietbergen, J B, Kranse, R et al. (1997) The free-to-total prostate specific antigen ratio improves the specificity of prostate specific antigen in screening for prostate cancer in the general population. The Journal of urology 157(6): 2191-6	- no symptoms, fixed threshold
Bangma, C H; Rietbergen, J B; Schroder, F H (1997) Prostate-specific antigen as a screening test. The Netherlands experience. The Urologic clinics of North America 24(2): 307-14	- no symptoms, fixed threshold
Barutcuoglu, Burcu, Bozdemir, A. Erkin, Kabaroglu, Ceyda et al. (2009) Performance of total prostate specific antigen and free prostate specific antigen ratio for screening prostate cancer in a Turkish population. Turkish Journal of Cancer 39(1): 18-25	- no symptoms, fixed threshold
Battikhi, M N G and Hussein, I (2006) Age-specific reference ranges for prostate specific antigen-total and free in patients with prostatitis symptoms and patients at risk. International urology and nephrology 38(34): 559-64	- Exclude *Not a diagnostic accuracy of PSA thresholds study*
Becker, C, Piironen, T, Pettersson, K et al. (2000) Clinical value of human glandular kallikrein 2 and free and total prostate-specific antigen in serum from a population of men with prostate-specific antigen levels 3.0 ng/mL or greater. Urology 55(5): 694-9	- no symptoms, fixed threshold
Belbase, Narayan Prasad, Agrawal, Chandra Shekhar, Pokharel, Paras Kumar et al. (2013) Prostate cancer screening in a healthy	- no symptoms, fixed threshold

Study	Reason for exclusion
population cohort in eastern Nepal: an explanatory trial study. Asian Pacific journal of cancer prevention : APJCP 14(5): 2835-8	
Berg, W, Linder, C, Eschholz, G et al. (2001) Pilot study of the practical relevance of a one-step test for prostate-specific antigen in capillary blood to improve the acceptance rate in the early detection program of prostate carcinoma. International urology and nephrology 32(3): 381-8	- Exclude *Not a diagnostic accuracy of PSA thresholds study*
Bott, Simon R J, Foley, Charlotte L, Bull, Matthew D et al. (2007) Are prostatic biopsies necessary in men aged > or =80 years?. BJU international 99(2): 335-8	- 2x2 diagnostic data on PSA cut off not extractable
Bunker, Clareann H, Patrick, Alan L, Miljkovic-Gacic, Iva et al. (2004) Prostate cancer screening parameters in a high-risk African-Caribbean population. Urology 63(4): 737-41	- no symptoms, fixed threshold
Caliskan, Selahattin (2017) Diagnostic efficacy of free prostate-specific antigen/total prostate-specific antigen ratio for the diagnosis of prostate cancer in low concentration (<=4 ng/ml) and intermediate levels of total prostate-specific antigen (4.01-10.0 ng/ml). Journal of cancer research and therapeutics 13(2): 279-283	- 2x2 diagnostic data on PSA cut off not extractable *fPSA measured*
Camdzic, Nina, Kuskunovic-Vlahovljak, Suada, Doric, Mirsad et al. (2021) Serum total prostate-specific antigen (tPSA): correlation with diagnosis and grading of prostate cancer in core needle biopsy. Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina 18(1): 122-127	- Study design does not match review protocol *Reported as retrospective. No indication of when PSA measured relative to biopsy so not clear if was cross sectional.*
Catalona, W J, Partin, A W, Slawin, K M et al. (2000) Percentage of free PSA in black versus white men for detection and staging of prostate cancer: a prospective multicenter clinical trial. Urology 55(3): 372-6	- Exclude *2x2 data for PSA cut off not extractable*
Catalona, W J, Richie, J P, deKernion, J B et al. (1994) Comparison of prostate specific antigen concentration versus prostate specific antigen density in the early detection of prostate cancer: receiver operating characteristic curves. The Journal of urology 152(6pt1): 2031-6	- no symptoms, fixed threshold

Study	Reason for exclusion
Catalona, W J, Southwick, P C, Slawin, K M et al. (2000) Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology 56(2): 255-60	- Exclude *Case-control study*
Chen, Rui, Gao, Xu, Xu, Chuanliang et al. (2015) Percent free prostate-specific antigen for prostate cancer diagnosis in Chinese men with a PSA of 4.0e10.0 ng/mL: Results from the Chinese Prostate Cancer Consortium. Asian Journal of Urology 2(2): 107-113	- 2x2 diagnostic data on PSA cut off not extractable
Chen, Rui, Huang, Yiran, Cai, Xiaobing et al. (2015) Age-Specific Cutoff Value for the Application of Percent Free Prostate-Specific Antigen (PSA) in Chinese Men with Serum PSA Levels of 4.0-10.0 ng/ml. PloS one 10(6): e0130308	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *Age adjusted fPSA thresholds used*
Chen, Rui, Zhou, Li-Qun, Cai, Xiao-Bing et al. (2015) Percent free prostate-specific antigen is effective to predict prostate biopsy outcome in Chinese men with prostate-specific antigen between 10.1 and 20.0 ng ml(-1). Asian journal of andrology 17(6): 1017-21	- 2x2 diagnostic data on PSA cut off not extractable *fPSA assessed*
Cheng, Yung-Ting, Chiang, Chih-Hung, Pu, Yeong-Shiau et al. (2019) The application of p2PSA% and prostate health index in prostate cancer detection: A prospective cohort in a Tertiary Medical Center. Journal of the Formosan Medical Association = Taiwan yi zhi 118(1pt2): 260-267	- Exclude *2x2 data not extractable*
Ciatto, S, Bonardi, R, Mazzotta, A et al. (1995) Comparing two modalities of screening for prostate cancer: digital rectal examination + transrectal ultrasonography vs. prostate-specific antigen. Tumori 81(4): 225-9	- no symptoms, fixed threshold
Ciatto, Stefano, Rubeca, Tiziana, Confortini, Massimo et al. (2004) Free to total PSA ratio is not a reliable predictor of prostate biopsy outcome. Tumori 90(3): 324-7	- no symptoms, fixed threshold
Cooke, R R, Nacey, J N, Beeston, R E et al. (1992) The efficacy of serum prostate specific antigen as a tumour marker in prostatic	- no symptoms, fixed threshold

Study	Reason for exclusion
carcinoma: a comparison with serum acid phosphatase. The New Zealand medical journal 105(941): 345-7	
Cookson, M S, Floyd, M K, Ball, T P Jr et al. (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. The Journal of urology 154(3): 1070-3	- Index test does not match protocol
Coric, Jozo, Mujic, Jasminka, Kucukalic, Elma et al. (2015) Prostate-specific antigen (PSA) and prostate volume: Better predictor of prostate cancer for Bosnian and Herzegovina men. Open Biochemistry Journal 9(1): 34-36	- Exclude *2x2 data on PSA cut off not extractable*
Dadkhah, Farid, Amini, Erfan, Lashay, Ali R. et al. (2010) Utility of prostate specific antigen density and free to total prostate specific antigen ratio for detecting prostate cancer in Iranian men: A prospective study of 187 cases. Current Urology 4(1): 1-5	- 2x2 diagnostic data on PSA cut off not extractable *No confidence intervals on PPV and NPV*
Dincel, C, Caskurlu, T, Tasci, A I et al. (1999) Prospective evaluation of prostate specific antigen (PSA), PSA density, free-to-total PSA ratio and a new formula (prostate malignancy index) for detecting prostate cancer and preventing negative biopsies in patients with normal rectal examinations and intermediate PSA levels. International urology and nephrology 31(4): 497-509	- no symptoms, fixed threshold
Djavan, B, Zlotta, A, Kratzik, C et al. (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. Urology 54(3): 517-22	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *F/T PSA and PSA-TZ*
Djavan, Bob, Remzi, Mesut, Zlotta, Alexandre R et al. (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	- no symptoms, fixed threshold

Study	Reason for exclusion
multicenter European trial. Urology 60(4suppl1): 4-9	
Eekers, Danielle Berty Petra, Laschet, Andrea, de Groot, Monique et al. (2008) Why determine only the total prostate-specific antigen, if the free-to-total ratio contains the information?. Annals of clinical biochemistry 45(pt3): 270-4	- no symptoms, fixed threshold
Egawa, S, Suyama, K, Takashima, R et al. (1999) Prospective evaluation of prostate cancer detection by prostate-specific antigen-related parameters. International journal of urology : official journal of the Japanese Urological Association 6(10): 493-501	- 2x2 diagnostic data on PSA cut off not extractable *TP and TN not clear for 4.1-10 subgroup that Sens/Spec provided for*
el-Galley, R E, Petros, J A, Sanders, W H et al. (1995) Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma. Urology 46(2): 200-4	- 2x2 diagnostic data on PSA cut off not extractable *Unclear if analysis based on entire population or just those biopsied*
Etzioni, R, Shen, Y, Petteway, J C et al. (1996) Age-specific prostate-specific antigen: a reassessment. The Prostate. Supplement 7: 70-7	- Study design does not match review protocol
Fan, Yu-Hua, Pan, Po-Hsun, Lin, Tzu-Ping et al. (2019) Prostate Health Index outperforms other PSA derivatives in predicting a positive biopsy in men with tPSA <10 ng/mL: Largest prospective cohort in Taiwan. Journal of the Chinese Medical Association : JCMA 82(10): 772-777	- no symptoms, fixed threshold
Ferreira, Marcos D and Koff, Walter J (2005) Assessment of serum level of prostate-specific antigen adjusted for the transition zone volume in early detection of prostate cancer. International braz j urol : official journal of the Brazilian Society of Urology 31(2): 137-146	- Exclude *2x2 data for PSA cut off not provided / CI's not provided*
Fossati, Nicola, Lazzeri, Massimo, Haese, Alexander et al. (2015) Clinical performance of serum isoform [-2]proPSA (p2PSA), and its derivatives %p2PSA and the Prostate Health Index, in men aged <60 years: results from a multicentric European study. BJU international 115(6): 913-20	- no symptoms, fixed threshold
Fowler, J E Jr, Sanders, J, Bigler, S A et al. (2000) Percent free prostate specific antigen	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
and cancer detection in black and white men with total prostate specific antigen 2.5 to 9.9 ng./ml. The Journal of urology 163(5): 1467-70	
Froehner, Michael, Buck, Lena Marie, Koch, Rainer et al. (2009) Derivatives of prostate-specific antigen as predictors of incidental prostate cancer. BJU international 104(1): 25-8	- Population does not match the protocol *Population was people undergoing prostate resection.*
Furuya, Kazuhiro, Kawahara, Takashi, Narahara, Masaki et al. (2017) Measurement of serum isoform [-2]proPSA derivatives shows superior accuracy to magnetic resonance imaging in the diagnosis of prostate cancer in patients with a total prostate-specific antigen level of 2-10 ng/ml. Scandinavian journal of urology 51(4): 251-257	- no symptoms, fixed threshold
Gerstenbluth, Robert E, Seftel, Allen D, Hampel, Nehemia et al. (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?. The Journal of urology 168(5): 1990-3	- PSA thresholds outside relevant range (>10ng/ml)
Ghafoori, Mahyar, Varedi, Peyman, Hosseini, Seyed Jalil et al. (2009) Value of prostate-specific antigen and prostate-specific antigen density in detection of prostate cancer in an Iranian population of men. Urology journal 6(3): 182-8	- no symptoms, fixed threshold
Gohji, K, Nomi, M, Egawa, S et al. (1997) Detection of prostate carcinoma using prostate specific antigen, its density, and the density of the transition zone in Japanese men with intermediate serum prostate specific antigen concentrations. Cancer 79(10): 1969-76	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *PSAD not PSA*
Gray, Marion A (2005) Clinical use of serum prostate-specific antigen: a review. Clinical laboratory 51(34): 127-33	- Study design does not match review protocol *Narrative review*
Guazzoni, Giorgio, Nava, Luciano, Lazzeri, Massimo et al. (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	- no symptoms, fixed threshold

Study	Reason for exclusion
prospective study in a clinical setting. European urology 60(2): 214-22	
Guillet, J, Role, C, Duc, A T et al. (1988) Prostate-specific antigen (PSA) in the management of 500 prostatic patients. American journal of clinical oncology 11suppl2: 61-2	- Reference standard does not match protocol *Details of reference standard not reported.*
Hara, Noboru, Kitamura, Yasuo, Saito, Toshihiro et al. (2006) Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations. Asian journal of andrology 8(4): 429-34	- no symptoms, fixed threshold
Harvey, Philip, Basuita, Amman, Endersby, Deborah et al. (2009) A systematic review of the diagnostic accuracy of prostate specific antigen. BMC urology 9: 14	- Exclude *Unclear which PSA cut off / age adjusted cut offs were used for 2x2 data from each primary study. Also not all studies used biopsies as ref standard*
Heidegger, Isabel, Fritz, Josef, Klocker, Helmut et al. (2015) Age-Adjusted PSA Levels in Prostate Cancer Prediction: Updated Results of the Tyrol Prostate Cancer Early Detection Program. PloS one 10(7): e0134134	- 2x2 diagnostic data on PSA cut off not extractable *fPSA incorporated into cut offs*
Heyns, C F, Naude, A M, Ahmed, G et al. (2001) Serum prostate-specific antigen as surrogate for the histological diagnosis of prostate cancer. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 91(8): 685-9	- Reference standard does not match protocol *Not clear how many patients were biopsied*
Higashihara, E, Nutahara, K, Kojima, M et al. (1996) Significance of free prostate-specific antigen and gamma-seminoprotein in the screening of prostate cancer. The Prostate. Supplement 7: 40-7	- Earlier version of included study
Higashihara, E, Nutahara, K, Kojima, M et al. (1996) Significance of serum free prostate specific antigen in the screening of prostate cancer. The Journal of urology 156(6): 1964-8	- no symptoms, fixed threshold
Hofer, C, Sauerstein, P, Wolter, C et al. (2000) Value of free prostate-specific antigen (Hybritech Tandem-R) in symptomatic patients consulting the urologist. Urologia internationalis 64(1): 18-23	- Study design does not match review protocol

Study	Reason for exclusion
Hoffman, Richard M, Gilliland, Frank D, Adams-Cameron, Meg et al. (2002) Prostate-specific antigen testing accuracy in community practice. BMC family practice 3: 19	- Too long between index test and ref standard
Horninger, W, Reissigl, A, Klocker, H et al. (1998) Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent free PSA in addition to total PSA levels. The Prostate 37(3): 133-9	- 2x2 diagnostic data on PSA cut off not extractable
Horninger, Wolfgang, Cheli, Carol D, Babaian, Richard J et al. (2002) Complexed prostate-specific antigen for early detection of prostate cancer in men with serum prostate-specific antigen levels of 2 to 4 nanograms per milliliter. Urology 60(4suppl1): 31-5	- no symptoms, fixed threshold
Hoshii, Tatsuhiko, Nishiyama, Tsutomu, Toyabe, Shinichi et al. (2007) Evaluation of magnetic resonance imaging-based prostate-specific antigen density of the prostate in the diagnosis of prostate cancer. International journal of urology : official journal of the Japanese Urological Association 14(4): 305-10	- no symptoms, fixed threshold
Hsieh, Po-Fan, Chang, Chao-Hsiang, Yang, Chi-Rei et al. (2018) Prostate Health Index (PHI) improves prostate cancer detection at initial biopsy in Taiwanese men with PSA 4-10 ng/mL. The Kaohsiung journal of medical sciences 34(8): 461-466	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *PHI cut offs not PSA*
Hsieh, Po-Fan, Li, Wei-Juan, Lin, Wei-Ching et al. (2020) Combining prostate health index and multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in an Asian population. World journal of urology 38(5): 1207-1214	- 2x2 diagnostic data on PSA cut off not extractable *Association between PSA and Prostate cancer reported but not diagnostic accuracy data for particular test thresholds.*
Hua, LiXin, Qiao, Di, Xu, Bin et al. (2011) Clinical and pathological characteristics of screen-detected versus clinically diagnosed prostate cancer in Nanjing, China. Medical oncology (Northwood, London, England) 28(1): 357-64	- Study design does not match review protocol
Huang, Maping, Lin, Yurong, Xu, Abai et al. (2014) Percent free prostate-specific antigen	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: a multicenter study. Medical oncology (Northwood, London, England) 31(4): 925	
Huang, Yuan, Cheng, Gong, Liu, Bianjiang et al. (2014) A prostate biopsy strategy based on a new clinical nomogram reduces the number of biopsy cores required in high-risk patients. BMC urology 14: 8	- Study design does not match review protocol
Hugosson, J, Aus, G, Bergdahl, S et al. (2003) Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Sweden. BJU international 92suppl2: 39-43	- no symptoms, fixed threshold
Ilic, Dragan, Djulbegovic, Mia, Jung, Jae Hung et al. (2018) Prostate cancer screening with prostate-specific antigen (PSA) test: a systematic review and meta-analysis. BMJ (Clinical research ed.) 362: k3519	- Study design does not match review protocol *Systematic review of RCTs*
Ito, K, Yamamoto, T, Kubota, Y et al. (2000) Usefulness of age-specific reference range of prostate-specific antigen for Japanese men older than 60 years in mass screening for prostate cancer. Urology 56(2): 278-82	- Reference standard does not match protocol
Ito, Kazuto, Yokomizo, Akira, Tokunaga, Shoji et al. (2020) Diagnostic Impacts of Clinical Laboratory Based p2PSA Indexes on any Grade, Gleason Grade Group 2 or Greater, or 3 or Greater Prostate Cancer and Prostate Specific Antigen below 10 ng/ml. The Journal of urology 203(1): 83-91	- Reference standard does not match protocol *Only a subset of participants received reference standard (biopsy or MRI).*
Janbaziroudsari, Hamid; Mirzaei, Arezoo; Maleki, Nasrollah (2016) Association of serum prostate-specific antigen levels with the results of the prostate needle biopsy. Bulletin du cancer 103(9): 730-4	- no symptoms, fixed threshold
Jen, Hsiao-Hsuan, Chang, Wei-Jung, Hsu, Chen-Yang et al. (2020) Sojourn-time-corrected receiver operating characteristic curve (ROC) for prostate specific antigen (PSA) test in population-based prostate cancer screening. Scientific reports 10(1): 20665	- Reference standard does not match protocol *Reference standard was cancer diagnosis from registry data.*

Study	Reason for exclusion
Jeong, In Gab; Lee, Kang Hyun; Korean Urological Oncologic Society Prostate Cancer Study, Group (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 years old: a prospective multicenter study. The Journal of urology 179(1): 111-6	- PSA thresholds outside relevant range (>10ng/ml)
Jue, Joshua S, Barboza, Marcelo Panizzutti, Prakash, Nachiketh S et al. (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. Urology 105: 123-128	- no symptoms, fixed threshold
Junker, R, Brandt, B, Zechel, C et al. (1997) Comparison of prostate-specific antigen (PSA) measured by four combinations of free PSA and total PSA assays. Clinical chemistry 43(9): 1588-94	- Study design does not match review protocol: Case control design
Karamanolakis, Dimitrios, Lambou, Theocharis, Bogdanos, John et al. (2006) Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (> or =3.0 and <10.0 ng/ml). Anticancer research 26(4b): 3159-66	- 2x2 diagnostic data on PSA cut off not extractable
Khan, Masood A, Partin, Alan W, Rittenhouse, Harry G et al. (2003) Evaluation of proprostate specific antigen for early detection of prostate cancer in men with a total prostate specific antigen range of 4.0 to 10.0 ng/ml. The Journal of urology 170(3): 723-6	- no symptoms, fixed threshold
Kim, Lois, Boxall, Nicholas, George, Anne et al. (2020) Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to Reflne Mri) study. BMC medicine 18(1): 95	- HE modelling study
Kobayashi, Takashi, Kawahara, Takashi, Nishizawa, Koji et al. (2005) Value of prostate volume measurement using transabdominal ultrasonography for the improvement of prostate-speci fi c antigen-based cancer detection. International journal of urology :	- no symptoms, fixed threshold

Study	Reason for exclusion
official journal of the Japanese Urological Association 12(10): 881-5	
Kurita, Y, Terada, H, Masuda, H et al. (1998) Prostate specific antigen (PSA) value adjusted for transition zone volume and free PSA (gamma-seminoprotein)/PSA ratio in the diagnosis of prostate cancer in patients with intermediate PSA levels. British journal of urology 82(2): 224-30	- 2x2 diagnostic data on PSA cut off not extractable *PSAT cut offs not PSA*
Kuriyama, M, Uno, H, Watanabe, H et al. (1999) Determination of reference values for total PSA, F/T and PSAD according to prostatic volume in japanese prostate cancer patients with slightly elevated serum PSA levels. Japanese journal of clinical oncology 29(12): 617-22	- Population does not match the protocol
Labrie, F, Dupont, A, Suburu, R et al. (1992) Serum prostate specific antigen as pre-screening test for prostate cancer. The Journal of urology 147(3pt2): 846-2	- no symptoms, fixed threshold
Le, Brian V, Griffin, Christopher R, Loeb, Stacy et al. (2010) [-2]Proenzyme prostate specific antigen is more accurate than total and free prostate specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study. The Journal of urology 183(4): 1355-9	- 2x2 diagnostic data on PSA cut off not extractable
Lee, F, Torp-Pedersen, S, Littrup, P J et al. (1989) Hypoechoic lesions of the prostate: clinical relevance of tumor size, digital rectal examination, and prostate-specific antigen. Radiology 170(1pt1): 29-32	- 2x2 diagnostic data on PSA cut off not extractable
Leibovici, Dan, Shilo, Yaniv, Raz, Orit et al. (2013) Is the diagnostic yield of prostate needle biopsies affected by prostate volume?. Urologic oncology 31(7): 1003-5	- 2x2 diagnostic data on PSA cut off not extractable
Lin, Yu-Rong, Wei, Xing-Hua, Uhlman, Matthew et al. (2015) PSA density improves the rate of prostate cancer detection in Chinese men with a PSA between 2.5-10.0 ng ml (-1) and 10.1-20.0 ng ml (-1) : a multicenter study. Asian journal of andrology 17(3): 503-7	- no symptoms, fixed threshold
Lippi, Giuseppe; Aloe, Rosalia; Mattiuzzi, Camilla (2012) Prostate-specific antigen (PSA)	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
isoform p2PSA in prostate cancer screening: Systematic review of current evidence and further perspectives. Rivista Italiana della Medicina di Laboratorio 8(4): 231-238	
Lotfi, Mehrzad, Assadsangabi, R., Jali, R. et al. (2009) Diagnostic value of prostate specific antigen and its density in Iranian men with prostate cancer. Iranian Red Crescent Medical Journal 11(2): 170-175	- Study design does not match review protocol *Retrospective study. Not clear whether was cross sectional as no detail of timing of biopsy relative to PSA test.*
Lowe, Franklin C., Gilbert, Scott M., Cavallo, Christina B. et al. (2005) Evidence suggesting PSA cutpoint of 2.5 ng/mL for prompting prostate biopsy: Review of 36,316 biopsies. Urology 65(3): 549-553	- no symptoms, fixed threshold
Luboldt, H J, Bex, A, Swoboda, A et al. (2001) Early detection of prostate cancer in Germany: a study using digital rectal examination and 4.0 ng/ml prostate-specific antigen as cutoff. European urology 39(2): 131-7	- no symptoms, fixed threshold
Luboldt, H J, Swoboda, A, Borgermann, C et al. (2001) Clinical usefulness of free PSA in early detection of prostate cancer. Onkologie 24(1): 33-7	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *fPSA*
Luboldt, HJ, Altwein, JE, Bichler, KH et al. (1999) Early recognition of prostate carcinoma. Initial results of a prospective multicenter study in Germany. Project Group for Early Detection DGU-BDU Laboratory diagnosis Professional Circle. Der Urologe. Ausg. A 38(2): 114-123	- Publication not in English
Maattanen, L, Auvinen, A, Stenman, U H et al. (1999) European randomized study of prostate cancer screening: first-year results of the Finnish trial. British journal of cancer 79(78): 1210-4	- Study design does not match review protocol
Maeda, H, Arai, Y, Aoki, Y et al. (1999) Complexed prostate-specific antigen and its volume indexes in the detection of prostate cancer. Urology 54(2): 225-8	- no symptoms, fixed threshold

Study	Reason for exclusion
Makinen, T, Tammela, T L, Hakama, M et al. (2001) Prostate cancer screening within a prostate specific antigen range of 3 to 3.9 ng./ml.: a comparison of digital rectal examination and free prostate specific antigen as supplemental screening tests. The Journal of urology 166(4): 1339-42	- Reference standard does not match protocol
Makinen, Tuukka, Tammela, Teuvo L J, Stenman, Ulf-Hakan et al. (2002) Family history and prostate cancer screening with prostate-specific antigen. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 20(11): 2658-63	- 2x2 diagnostic data on PSA cut off not extractable *Unclear on who was biopsied in total*
Martin, B J, Cheli, C D, Sterling, K et al. (2006) Prostate specific antigen isoforms and human glandular kallikrein 2--which offers the best screening performance in a predominantly black population?. The Journal of urology 175(1): 104-7	- 2x2 diagnostic data on PSA cut off not extractable *Another paper included of the same study which contains this data*
Martin, B J, Finlay, J A, Sterling, K et al. (2004) Early detection of prostate cancer in African-American men through use of multiple biomarkers: human kallikrein 2 (hK2), prostate-specific antigen (PSA), and free PSA (fPSA). Prostate cancer and prostatic diseases 7(2): 132-7	- no symptoms, fixed threshold
Martin, B, Cheli, C D, Lifsey, D et al. (2003) Complexed PSA performance for prostate cancer detection in an African-American population. Urology 62(5): 835-9	- no symptoms, fixed threshold
Martin, E, Lujan, M, Sanchez, E et al. (1999) Final results of a screening campaign for prostate cancer. European urology 35(1): 26-31	- no symptoms, fixed threshold
Masters, J G, Keegan, P E, Hildreth, A J et al. (1998) Free/total serum prostate-specific antigen ratio: how helpful is it in detecting prostate cancer?. British journal of urology 81(3): 419-23	- no symptoms, fixed threshold
Masuda, Hiroshi, Mikami, Kosuke, Otsuka, Kotaro et al. (2021) Validation of the Effectiveness of Neutrophil-to-lymphocyte Ratio (NLR) as a Predictive Factor in Patients Undergoing Prostate Biopsy With Prostate Specific Antigen (PSA) Between 4.0 and 10.0	- Population does not match the protocol *Appears that of the eligible patients, the ones chosen for analysis were based on having/not having prostate cancer*

Study	Reason for exclusion
ng/ml. In vivo (Athens, Greece) 35(3): 1641-1646	
Mearini, Luigi, Ferri, Carla, Lazzeri, Massimo et al. (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. Urologia internationalis 93(2): 135-45	- no symptoms, fixed threshold
Michielsen, D P, De Boe, V R, Braeckman, J G et al. (1998) Specificity and accuracy of TRUS-measured PSA-density and transition zone-PSA in the diagnosis of prostate cancer. European journal of ultrasound : official journal of the European Federation of Societies for Ultrasound in Medicine and Biology 8(2): 125-8	- Index test does not match protocol
Miller, M C, O'Dowd, G J, Partin, A W et al. (2001) Contemporary use of complexed PSA and calculated percent free PSA for early detection of prostate cancer: impact of changing disease demographics. Urology 57(6): 1105-11	- Population does not match the protocol *Population chosen based on Cancer/no cancer status*
Morgan, T O, McLeod, D G, Leifer, E S et al. (1996) Prospective use of free prostate-specific antigen to avoid repeat prostate biopsies in men with elevated total prostate-specific antigen. Urology 48(6asuppl): 76-80	- Population does not match the protocol
Moul, J W (1998) Use of prostate-specific antigen in black men: age-adjusted reference ranges for maximal cancer detection. Journal of the National Medical Association 90(11suppl): 710-2	- Study design does not match review protocol
Murray, Nigel P, Reyes, Eduardo, Orellana, Nelson et al. (2014) A comparative performance analysis of total PSA, percentage free PSA, PSA velocity, and PSA density versus the detection of primary circulating prostate cells in predicting initial prostate biopsy findings in Chilean men. BioMed research international 2014: 676572	- Index test does not match protocol
Na, Rong, Wu, Yishuo, Xu, Jianfeng et al. (2013) Age-specific prostate specific antigen cutoffs for guiding biopsy decision in Chinese population. PloS one 8(6): e67585	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
	Aim was to determine age-specific cut off values but diagnostic accuracy of this strategy as a whole was not assessed.
Nadler, Robert B, Loeb, Stacy, Roehl, Kimberly A et al. (2005) Use of 2.6 ng/ml prostate specific antigen prompt for biopsy in men older than 60 years. The Journal of urology 174(6): 2154-2157	- no symptoms, fixed threshold
Ng, Tze Kiat, Vasilareas, Despina, Mitterdorfer, Andrew J et al. (2005) Prostate cancer detection with digital rectal examination, prostate-specific antigen, transrectal ultrasonography and biopsy in clinical urological practice. BJU international 95(4): 545-8	- no symptoms, fixed threshold
Nicolaiew, Nathalie, Ploussard, Guillaume, Chun, Felix K-H et al. (2013) Prediction of the risk of harboring prostate cancer by a prebiopsy nomogram based on extended biopsy protocol. Urologia internationalis 90(3): 306-11	- 2x2 diagnostic data on PSA cut off not extractable
Nowroozi, Mohammadreza, Ayati, Mohsen, Jamshidian, Hassan et al. (2015) Transition zone prostate specific antigen density improves prostate cancer detection in iranian men. Nephro-Urology Monthly 7(2): e26752	- no symptoms, fixed threshold
Oesterling, J E (1994) PSA and early prostate cancer detection: the importance of age-specific reference ranges. The Canadian journal of oncology 4suppl1: 52-6	- Exclude *Unable to retrieve item*
Ogawa, O, Shichiri, Y, Ohnishi, H et al. (1996) Usefulness of ultrasound-guided prostate biopsy in the diagnosis and treatment of localized prostate cancer. Hinyokika kiyo. Acta urologica Japonica 42(10): 805-810	- Publication not in English
Ojewola, R W, Tijani, K H, Jeje, E A et al. (2013) An evaluation of usefulness of prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer in an unscreened population:experience in a Nigerian teaching hospital. West African journal of medicine 32(1): 8-13	- no symptoms, fixed threshold
Okegawa, T, Kinjo, M, Watanabe, K et al. (2000) The significance of the free-to-complexed prostate-specific antigen (PSA) ratio	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
in prostate cancer detection in patients with a PSA level of 4.1-10.0 ng/mL. BJU international 85(6): 708-14	
Okihara, Koji, Cheli, Carol D, Partin, Alan W et al. (2002) Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. The Journal of urology 167(5): 2017-4	- no symptoms, fixed threshold
Okihara, Koji, Ukimura, Osamu, Nakamura, Terukazu et al. (2004) Can complexed prostate specific antigen enhance prostate cancer detection in Japanese men?. European urology 46(1): 57-64	- no symptoms, fixed threshold
Okihara, Koji, Ukimura, Osamu, Nakamura, Terukazu et al. (2006) Complexed PSA improves prostate cancer detection: results from a multicenter Japanese clinical trial. Urology 67(2): 328-32	- no symptoms, fixed threshold
Okpua, Nelson C., Emeh, Augusta N., Okekpa, Simon I. et al. (2021) Clinical diagnosis of prostate cancer using digital rectal examination and prostate-specific antigen tests: a systematic review and meta-analysis of sensitivity and specificity. African Journal of Urology 27(1): 32	- 2x2 diagnostic data on PSA cut off not extractable *Unclear which PSA cut off was used; unclear if population had symptoms or not*
Oremek, G M, Sapoutzis, N, Eden, F et al. (2003) Complexed PSA in routine diagnosis. Anticancer research 23(2a): 975-7	- Index test does not match protocol
Otero, Milagros, Villar, Margarita Dominguez, Penuelas, Antonio Lorenzo et al. (2007) Diagnostic methods in the detectiion of prostate cancer: Prospective observational study. Current Medical Imaging Reviews 3(1): 27-35	- Exclude *Data from study included from another paper*
Ozdal, O L, Aprikian, A G, Begin, L R et al. (2004) Comparative evaluation of various prostate specific antigen ratios for the early detection of prostate cancer. BJU international 93(7): 970-974	- no symptoms, fixed threshold
Parsons, J Kellogg, Brawer, Michael K, Cheli, Carol D et al. (2004) Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA. BJU international 94(1): 47-50	- no symptoms, fixed threshold

Study	Reason for exclusion
Partin, Alan W, Brawer, Michael K, Bartsch, Georg et al. (2003) Complexed prostate specific antigen improves specificity for prostate cancer detection: results of a prospective multicenter clinical trial. The Journal of urology 170(5): 1787-91	- no symptoms, fixed threshold
Perez-Lanzac-Lorca, A, Barco-Sanchez, A, Romero, E et al. (2013) Correlation between the complex PSA/total PSA ratio and the free PSA/total PSA ratio, sensitivity and specificity of both markers for the diagnosis of prostate cancer. Actas urologicas espanolas 37(8): 498-503	- Publication not in English
Presti, J C Jr, Hovey, R, Carroll, P R et al. (1996) Prospective evaluation of prostate specific antigen and prostate specific antigen density in the detection of nonpalpable and stage T1C carcinoma of the prostate. The Journal of urology 156(5): 1685-90	- no symptoms, fixed threshold
Puppo, P, Perachino, M, Ricciotti, G et al. (1992) Comparison between digital rectal examination, prostate-specific antigen and transrectal ultrasound in symptomatic patients. Results on 141 cases. European urology 21suppl1: 87-91	- 2x2 diagnostic data on PSA cut off not extractable *PSA cut off used to calculate sens/spec not provided*
Rais-Bahrami, Soroush, Siddiqui, M Minhaj, Vourganti, Srinivas et al. (2015) Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU international 115(3): 381-8	- no symptoms, fixed threshold
Rausch, Steffen, Hennenlotter, Joerg, Wiesenreiter, Josef et al. (2016) Assessment of a new point-of-care system for detection of prostate specific antigen. BMC urology 16: 4	- Reference standard does not match protocol
Recker, F, Kwiatkowski, M K, Piironen, T et al. (1998) Free-to-total prostate-specific antigen (PSA) ratio improves the specificity for detecting prostate cancer in patients with prostatism and intermediate PSA levels. British journal of urology 81(4): 532-8	- Population does not match the protocol
Richie, J P, Kavoussi, L R, Ho, G T et al. (1994) Prostate cancer screening: role of the digital	- no symptoms, fixed threshold

Study	Reason for exclusion
rectal examination and prostate-specific antigen. Annals of surgical oncology 1(2): 117-20	
Rohini, G. and Shyamala Devi, C.S. (2003) Relevance of age specific references of PSA and its aid in enhancing the diagnostic efficiency of PSA in prostate abnormalities (BPH and cancer), in correlation with biopsy. Biomedicine 23(12): 106-112	- Exclude *Unable to retrieve article*
Saema, Armean; Kochakarn, Wachira; Lertsithichai, Panuwat (2012) PSA density and prostate cancer detection. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 95(5): 661-6	- no symptoms, fixed threshold
Safarinejad, M R (2006) Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Iran. Annals of oncology : official journal of the European Society for Medical Oncology 17(7): 1166-71	- no symptoms, fixed threshold
Schroder, F H, Roobol-Bouts, M, Vis, A N et al. (2001) Prostate-specific antigen-based early detection of prostate cancer--validation of screening without rectal examination. Urology 57(1): 83-90	- no symptoms, fixed threshold
Segawa, Naoki, Gohji, Kazuo, Iwamoto, Yusaku et al. (2003) Prostate cancer detection by prostate-specific antigen-related parameters. Hinyokika kiyo. Acta urologica Japonica 49(7): 405-10	- Index test does not match protocol *PSAD cut off analysis, not PSA*
Semjonow, A, Hamm, M, Rathert, P et al. (1994) Prostate-specific antigen corrected for prostate volume improves differentiation of benign prostatic hyperplasia and organ-confined prostatic cancer. British journal of urology 73(5): 538-43	- Population does not match the protocol
Sheikh, M, Al-Saeed, O, Kehinde, E O et al. (2005) Utility of volume adjusted prostate specific antigen density in the diagnosis of prostate cancer in Arab men. International urology and nephrology 37(4): 721-6	- PSA thresholds outside relevant range (>10ng/ml)
Shim, Hong Bang, Lee, Sang Eun, Park, Hyoung Keun et al. (2007) Accuracy of a high prostate-specific antigen level for prostate	- PSA thresholds outside relevant range (>10ng/ml)

Study	Reason for exclusion
cancer diagnosis upon initial biopsy in Korean men. Yonsei medical journal 48(4): 678-83	
Shore, Neal D., Pieczonka, Christopher M., Henderson, R. Jonathan et al. (2020) A comparison of prostate health index, total PSA, %free PSA, and proPSA in a contemporary US population-The MiCheck-01 prospective trial. Urologic Oncology: Seminars and Original Investigations 38(8): 683	- no symptoms, fixed threshold
Smith, D S; Bullock, A D; Catalona, W J (1997) Racial differences in operating characteristics of prostate cancer screening tests. The Journal of urology 158(5): 1861-6	- no symptoms, fixed threshold
Smith, D S; Humphrey, P A; Catalona, W J (1997) The early detection of prostate carcinoma with prostate specific antigen: the Washington University experience. Cancer 80(9): 1852-6	- no symptoms, fixed threshold
Stephan, Carsten, Stroebel, Greta, Heinau, Marc et al. (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. Cancer 104(5): 993-1003	- Population does not match the protocol
Strittmatter, F, Stieber, P, Nagel, D et al. (2011) Detection of prostate cancer with complexed PSA and complexed/total PSA ratio - is there any advantage?. European journal of medical research 16(10): 445-50	- Population does not match the protocol
Tan, Lincoln Gl, Tan, Yung Khan, Tai, Bee Choo et al. (2017) Prospective validation of %p2PSA and the Prostate Health Index, in prostate cancer detection in initial prostate biopsies of Asian men, with total PSA 4-10 ng ml-1. Asian journal of andrology 19(3): 286-290	- Exclude *2*2 table not reported or calculable.*
Tanguay, S, Begin, L R, Elhilali, M M et al. (2002) Comparative evaluation of total PSA, free/total PSA, and complexed PSA in prostate cancer detection. Urology 59(2): 261-5	- no symptoms, fixed threshold
Teoh, Jeremy Yc, Yuen, Steffi Kk, Tsu, James Hl et al. (2017) The performance characteristics of prostate-specific antigen and prostate-specific	- no symptoms, fixed threshold

Study	Reason for exclusion
antigen density in Chinese men. Asian journal of andrology 19(1): 113-116	
Tokunaga, Masatoshi, Yasuda, Masanori, Miyakita, Hideshi et al. (2005) Screening program of prostate cancer at Tokai University Hospital: characterization of prostate-specific antigen measurement. The Tokai journal of experimental and clinical medicine 30(2): 103-10	- 2x2 diagnostic data on PSA cut off not extractable
Unal, D, Sedelaar, J P, Aarnink, R G et al. (2000) Three-dimensional contrast-enhanced power Doppler ultrasonography and conventional examination methods: the value of diagnostic predictors of prostate cancer. BJU international 86(1): 58-64	- Population does not match the protocol
van Gils, Martijn P M Q, Hessels, Daphne, van Hooij, Onno et al. (2007) The time-resolved fluorescence-based PCA3 test on urinary sediments after digital rectal examination; a Dutch multicenter validation of the diagnostic performance. Clinical cancer research : an official journal of the American Association for Cancer Research 13(3): 939-43	- 2x2 diagnostic data on PSA cut off not extractable
Vessella, R L, Lange, P H, Partin, A W et al. (2000) Probability of prostate cancer detection based on results of a multicenter study using the AxSYM free PSA and total PSA assays. Urology 55(6): 909-14	- 2x2 diagnostic data on PSA cut off not extractable - Index test does not match protocol *fPSA not PSA*
Vickers, Andrew J, Cronin, Angel M, Aus, Gunnar et al. (2010) Impact of recent screening on predicting the outcome of prostate cancer biopsy in men with elevated prostate-specific antigen: data from the European Randomized Study of Prostate Cancer Screening in Gothenburg, Sweden. Cancer 116(11): 2612-20	- no symptoms, fixed threshold
Vickers, Andrew, Cronin, Angel, Roobol, Monique et al. (2010) Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28(15): 2493-8	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
Wang, T Y and Kawaguchi, T P (1986) Preliminary evaluation of measurement of serum prostate-specific antigen level in detection of prostate cancer. Annals of clinical and laboratory science 16(6): 461-6	- Reference standard does not match protocol *'Clinical impression' used for diagnosis in some cases*
Wymenga, L F, Duisterwinkel, F J, Groenier, K et al. (2000) Clinical implications of free-to-total immunoreactive prostate-specific antigen ratios. Scandinavian journal of urology and nephrology 34(3): 181-7	- Study design does not match review protocol *Case-control study*
Xu, Lingyun, Lee, Jung-Rok, Hao, Shiying et al. (2019) Improved detection of prostate cancer using a magneto-nanosensor assay for serum circulating autoantibodies. PloS one 14(8): e0221051	- Study design does not match review protocol *Case control study*
Yamanaka, Kazuki, Yamada, Yuji, Kobayashi, Yasuhiro et al. (2003) The significance of prostate-specific antigen alpha-1-antichymotrypsin complex and its indices for the detection of prostate cancer. Hinyokika kiyo. Acta urologica Japonica 49(1): 5-10	- 2x2 diagnostic data on PSA cut off not extractable *Sensitivity and Specificity only given for PSA 2-6 subgroup - unclear which in this population had/didn't have pCA*
Yanai, Yoshinori, Kosaka, Takeo, Hongo, Hiroshi et al. (2018) Evaluation of prostate-specific antigen density in the diagnosis of prostate cancer combined with magnetic resonance imaging before biopsy in men aged 70 years and older with elevated PSA. Molecular and Clinical Oncology 9(6): 656-660	- 2x2 diagnostic data on PSA cut off not extractable *mpMRI is the index test*
Yang, Tian, Zhang, Limin, Jiang, Haowen et al. (2017) The predictive efficacy of hypoechoic lesion in ultrasound for prostate cancer in Chinese people: Five-year experience in a moderated 10-core transperineal prostate biopsy procedure. Oncotarget 8(45): 79433-79440	- no symptoms, fixed threshold
Yu, H J, Chie, W C, Hsieh, C H et al. (1996) Clinical efficacy of prostate-specific antigen testing in patients with prostate disease. Journal of the Formosan Medical Association = Taiwan yi zhi 95(10): 782-8	- Population does not match the protocol
Zambon, Joao Paulo, Almeida, Fernando G, Conceicao, Raquel Dilguerian O et al. (2014) Prostate-specific antigen testing in men between 40 and 70 years in Brazil: database	- 2x2 diagnostic data on PSA cut off not extractable

Study	Reason for exclusion
from a check-up program. International braz j urol : official journal of the Brazilian Society of Urology 40(6): 745-52	*Diagnostic accuracy of PSA cut off not assessed*
Zhang, W M, Finne, P, Leinonen, J et al. (2000) Determination of prostate-specific antigen complexed to alpha(2)-macroglobulin in serum increases the specificity of free to total PSA for prostate cancer. Urology 56(2): 267-72	- Study design does not match review protocol *Case-control study*

Appendix K – Research recommendations – full details

K.1.1 Research recommendation

What is the diagnostic accuracy of using age-adjusted and fixed prostate specific antigen thresholds for people with symptoms of prostate cancer, including those at high risk of developing prostate cancer (such as those with black African family origin or a family history of prostate cancer)?

K.1.2 Why this is important

Age adjusted PSA thresholds are currently recommended as a tool for primary care physicians to refer people to secondary care for further investigation into suspected prostate cancer. There was no high-quality diagnostic accuracy evidence to inform the committee of the clinical and cost effectiveness of age adjusted thresholds over fixed thresholds, but in the absence of this the committee did not want to change current practice. Further research would give primary care physicians more confidence in using age adjusted thresholds as a tool for referral. Risk of prostate cancer is also known to be higher in people from specific ethnic groups and people with a family history of prostate or breast cancer. New data stratified by ethnicity or family history would help determine if different PSA levels should be used to prompt referral in these groups. Due to the population size, a change in PSA threshold could lead to a large resource impact. The committee noted that evidence on the cost effectiveness of different PSA thresholds would help effectively manage NHS resources, and were aware that improved evidence on diagnostic accuracy could help the development of future economic models.

K.1.3 Rationale for research recommendation

Table 17:

Importance to 'patients' or the population	PSA thresholds are used to prompt referral for suspected cancer. It is important to use the right thresholds for patients to receive a timely diagnosis and treatment for prostate cancer, balanced against the risks of over treatment for clinically insignificant cancer and invasive biopsy procedures.
Relevance to NICE guidance	Future NICE guidance updates would be able to incorporate better evidence on the clinical and cost-effectiveness of using age adjusted thresholds for referral.
Relevance to the NHS	Any change in the use of age adjusted thresholds could mean more or less referrals from primary care to secondary care in people with suspected prostate cancer. Changes have the potential to have a high resource impact on the NHS.
National priorities	High
Current evidence base	Very low/low quality data
Equality considerations	Data should be stratified for different ethnic groups and people with a family history of prostate or breast cancer.

K.1.4 Modified PICO table

Table 18:

Population	People with symptoms of prostate cancer in primary care
Index test	Age-adjusted PSA thresholds
Reference Standard	Multiparametric MRI + prostate biopsy
Outcomes	Positive predictive value, sensitivity, specificity specified for: - All prostate cancer - Clinically significant cancer
Study design	Cross-sectional study design
Timeframe	Long term
Stratification	Ethnicity (people from ethnic groups at high risk of prostate cancer compared with other ethnic groups) Family history (people with family history of breast or prostate cancer compared with people without a family history of breast or prostate cancer)

Appendix L - Methods

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

This evidence review made use of the priority screening functionality within the EPPI-reviewer software. This functionality uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated if a pre-specified threshold was met for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination) and was always a minimum of 250.

As an additional check to ensure this approach did not miss relevant studies, systematic reviews (or qualitative evidence syntheses in the case of reviews of qualitative studies) were included in the review protocol and search strategy for all review questions. Relevant systematic reviews or qualitative evidence syntheses were used to identify any papers not found through the primary search. Committee members were also consulted to identify studies that were missed. If additional studies were found that were erroneously excluded during the priority screening process, the full database was subsequently screened.

The decision whether or not to use priority screening was taken by the reviewing team depending on the perceived likelihood that stopping criteria would be met, based on the size of the database, heterogeneity of studies included in the review and predicted number of includes. If it was thought that stopping criteria were unlikely to be met, priority screening was not used, and the full database was screened.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Data synthesis for diagnostic accuracy data

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 were as follows:

- **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)

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

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).

Positive predictive values were calculated by applying the sensitivity and specificity estimates from meta-analysis to prevalence estimates for the population covered by the review.

Appraising the quality of the evidence

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.

- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE for diagnostic accuracy evidence

Evidence from diagnostic accuracy studies was initially rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision, and indirectness) as detailed in table 17 below.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

For the purpose of rating risk of bias and indirectness, single studies were rated in the same way as meta-analysed studies, but with 100% of the weight in the analysis contributed by that single study.

Using positive predictive value as the primary outcome

GRADE assessments were only undertaken for positive predictive value but results for sensitivity and specificity are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the value above which a test would be recommended, and a second below which a test would be considered of no clinical use. These values were used to judge imprecision (see below). Please see 1.1.3 methods and processes for an explanation of how the decision thresholds were chosen.

Rationale for downgrading quality of evidence for diagnostic accuracy data

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

Table 18: Rationale for downgrading quality of evidence for diagnostic accuracy data

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. 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.
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.

GRADE criteria	Reasons for downgrading quality
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
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.
Imprecision	If the 95% confidence interval for the outcome crossed one of the clinical decision thresholds (0.5, 3), the outcome was downgraded one level. If the 95% confidence interval spanned both thresholds, the outcome was downgraded twice. See the sections on 'Using positive predictive value as the primary outcome' above for a description of how clinical decision thresholds were agreed.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.