Prostate Cancer: Diagnosis and management

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

NICE guideline <number>

Evidence reviews

April 2019

Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team
Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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

Review question

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

Introduction

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

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

PICO table

Table 1: PICO table

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

Methods and process

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

Declarations of interest were recorded according to NICE’s 2018 conflicts of interest policy.
Clinical evidence

Included studies

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

- MRI protocols should use at least 1.5 Tesla magnet, include diffusion weighted imaging (with the highest b value of at least 800s/mm²)
- MRI scoring should be clearly stated (using either PIRADS or LIKERT scoring system)

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

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

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

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

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion.
## Summary of clinical studies included in the evidence review

### 2 Prostate cancer antigen 3 urinary assay

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study details</th>
<th>Sample characteristics</th>
<th>Inclusion criteria</th>
<th>Index test(s)</th>
<th>Reference standard(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbera (2012)</td>
<td>Study location Italy</td>
<td>Sample size 177 participants Mean age (SD) 66.4 (5.3) years PSA ng/ml 6.8 (1.6)ng/ml</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer</td>
<td>Prostate Cancer Gene 3 Cut off of 20 and 35</td>
<td>Systematic prostate biopsy Performed transperineally</td>
</tr>
<tr>
<td></td>
<td>Study dates January 2010 and March 2012</td>
<td>Sample size 177 participants Mean age (SD) 64 (48-74) years PSA ng/ml 7.4 participants had serum PSA &gt;10ng/ml 99 between 4-10ng/ml 4 between 2.6-4ng/ml Number of previous biopsies at least one prior biopsy Time since last biopsy Not reported</td>
<td>Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination An elevated PSA &gt;10ng/ml</td>
<td>Prostate Cancer Gene 3 Cut off of 20 and 35</td>
<td>Systematic prostate biopsy Performed transperineally</td>
</tr>
<tr>
<td>Busetto (2013)</td>
<td>Study location Italy</td>
<td>Sample size 171 participants Mean age (SD) 66.4 (5.3) years PSA ng/ml 6.8 (1.6)ng/ml</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer</td>
<td>Prostate Cancer Gene 3 Cut off - 27,35 and 50</td>
<td>Systematic TRUS biopsy</td>
</tr>
<tr>
<td></td>
<td>Study dates March 2010 and July 2012</td>
<td>Sample size 171 participants Mean age (SD) 64 (48-74) years PSA ng/ml 7.4 participants had serum PSA &gt;10ng/ml 99 between 4-10ng/ml 4 between 2.6-4ng/ml Number of previous biopsies at least one prior biopsy Time since last biopsy Not reported</td>
<td>Persistent clinical suspicion of prostate cancer A persistently elevated or rising serum total PSA level Between 4-10ng/ml</td>
<td>Prostate Cancer Gene 3 Cut off - 27,35 and 50</td>
<td>Systematic TRUS biopsy</td>
</tr>
<tr>
<td>Gittelman (2013)</td>
<td>Study location USA</td>
<td>Sample size 466 participants Mean age (SD) 50 years and older PSA ng/ml to add from supplement</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer</td>
<td>Prostate Cancer Gene 3 Cut off of 50 and older</td>
<td>TRUS biopsy and MP-MRI biopsy</td>
</tr>
<tr>
<td></td>
<td>Study dates Not reported</td>
<td></td>
<td>50 years and older</td>
<td>Prostate Cancer Gene 3 Cut off of 50 and older</td>
<td>TRUS biopsy and MP-MRI biopsy</td>
</tr>
<tr>
<td>Short Title</td>
<td>Study details</td>
<td>Sample characteristics</td>
<td>Inclusion criteria</td>
<td>Index test(s)</td>
<td>Reference standard(s)</td>
</tr>
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</tr>
</tbody>
</table>
| Haese (2008) | Study location Six European centres - Germany, France, The Netherlands, Belgium and Austria  
Study dates Between August and July 2007. | PSA density, ng/ml/ml to add from supplement  
Mean prostate volume to add from supplement  
Sample size 463 participants  
Mean age (SD) 64.4 (6.6) years  
PSA ng/ml Mean 8.9 (7.5)ng/ml  
Number of previous biopsies  
331 participants had 1 biopsy 126 participants had 2 biopsies | At least one negative TRUS biopsy | Prostate Cancer Gene 3  
The PCA3 was calculated as [PCA3 mRNA]/[PSA mRNA]x1000 | TRUS biopsy |
| Kaufmann (2016) | Study location Germany  
Study dates Between 2008-2014 | Sample size 49 patients  
Mean age (SD) 65 (5.6) years  
PSA ng/ml 10 (4.4) ng/ml  
PSA density, ng/ml/ml 0.22 (0.12) ng/ml/g  
Number of previous biopsies  
1.7 (0.9) biopsies  
median interval of time between the first and last PSA assay 6 (3) months | | Prostate Cancer Gene 3 cut off of 25 and 35 | TRUS biopsy |
<p>| Marks (2007) | Study location Northern American Sites | Sample size 233 participants | At least one negative TRUS biopsy | Prostate Cancer Gene 3 | Systematic TRUS biopsy |</p>
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study details</th>
<th>Sample characteristics</th>
<th>Inclusion criteria</th>
<th>Index test (s)</th>
<th>Reference standard (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study dates</td>
<td>Mean age (SD) 64 years (7) PSA ng/ml 7.4 (4.3)ng/ml Mean prostate volume 49 (29)ml</td>
<td>An elevated PSA 2.5ng/ml or greater</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>between April 2004 and January 2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Merola</td>
<td>Study location Italy Study dates Between November 2009 and May 2011</td>
<td>Sample size 407 participants Mean age (SD) reported separately for cancer/non cancer groups cancer median 71 years (sd27) non cancer median 69 years (sd31) PSA ng/ml reported separately for cancer/non cancer groups cancer median 7.53ng/ml (sd4.88) non cancer median 7.34 ng/ml(sd5.87)</td>
<td>At least one negative TRUS biopsy An elevated PSA Suspicious DRE</td>
<td>Prostate Cancer Gene 3 Total PSA unable to calculate 2x2 for this test %PSA unable to calculate 2x2 for this test</td>
<td>Saturation prostatic biopsy</td>
</tr>
<tr>
<td>(2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pepe</td>
<td>Study location Italy Study dates From October 2009 to September 2011</td>
<td>Sample size 102 participants Mean age (SD) median age 64.5 yrs; range: 58-71 yrs</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination</td>
<td>Prostate Cancer Gene 3 PSA ratio</td>
<td>TRUS biopsy The prostate biopsy protocol included a median of 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone</td>
</tr>
<tr>
<td>Short Title</td>
<td>Study details</td>
<td>Sample characteristics</td>
<td>Inclusion criteria</td>
<td>Index test(s)</td>
<td>Reference standard(s)</td>
</tr>
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<td>-----------------------</td>
</tr>
<tr>
<td>Pepe (2012)</td>
<td>Study location Italy</td>
<td>Sample size 118 participants Mean age (SD) median 62.5 years (no range or sd) PSA ng/ml Median PSA 8.5 ng/ml (3.7-24ng/ml) Time since last biopsy 9 months</td>
<td>At least one negative TRUS biopsy Abnormal digital rectal examination All patients had a negative DRE An elevated PSA PSA&gt; 10ng/ml, PSA values between 4.1 - 10 or 2.6-4ng/ml with free/total PSA &lt;/= 25% and &lt;/= 20% respectively.</td>
<td>Prostate Cancer Gene 3 From 3-10 days prior to performing SPBx, first catch urine samples were collected following DRE, and processed to quantify PCA3 and PSA mRNA concentrations using the PROGENSA PCA3 assay</td>
<td>Systematic prostate biopsy performed transperineally using a tru-cut 18 gauge needle supplied with a biplanar transrectal probe under sedation and antibiotic prophylaxis</td>
</tr>
<tr>
<td>Porpiglia (2014)</td>
<td>Study location Italy</td>
<td>Sample size 170 participants Mean age (SD) Median age (iqr) 65 years (60-70)</td>
<td>At least one negative TRUS biopsy Positive Digital rectal examination</td>
<td>mp-MRI All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA %fPSA All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after</td>
<td>Random Biopsy under TRUS</td>
</tr>
</tbody>
</table>
### Short Title | Study details | Sample characteristics | Inclusion criteria | Index test(s) | Reference standard(s)
--- | --- | --- | --- | --- | ---
Remzi (2010) | Study location Austria  
Study dates Not reported See Haese et al | Sample size 463 participants | presence of high grade prostate intraepithelial neoplasia  
presence of atypical small acinar proliferation  
a persistently elevated or rising serum total PSA level  
Suspicious DRE  
Suspicious imaging results  
low %free PSA  
Follow up biopsy | Prostate Cancer Gene 3 | Prostate biopsy - not specified

Wu (2012) | Study location USA  
Study dates not declared | Sample size 103 participants  
Mean age (SD) 63.5 years (7.4)  
PSA ng/ml 11.0 ng/ml (8.5) | At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
presence of high grade prostate intraepithelial neoplasia  
presence of atypical small acinar proliferation  
a persistently elevated or rising serum total PSA level  
Suspicious DRE | Prostate Cancer Gene 3  
PSA density | Systematic TRUS biopsy
1 **Multiparametric MRI**

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study location</th>
<th>Study dates</th>
<th>Sample size</th>
<th>Median age (Range)</th>
<th>PSA ng/ml (median, range)</th>
<th>Number of previous biopsies</th>
<th>Inclusion criteria</th>
<th>Index test(s)</th>
<th>Reference standard(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd-Alazeez</td>
<td>UK</td>
<td>not stated</td>
<td>54 participants</td>
<td>64 years (39-75)</td>
<td>10 (2-23)</td>
<td>Between 1 and 3 biopsies Median Prostate volume 53 (19-136)</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA</td>
<td>MP-MRI MRI comprised of T2 weighted, diffusion weighted and dynamic contrast enhanced imaging with either 1.5T and 3.0T . diffusion b values - 0,150,500 and 1000. Positive MRI - PIRADS Score 3 and above Positive MRI - PIRADS score 4 and above For clinically significant disease</td>
<td>Transperineal Template Mapping Biopsy minimum number of samples was 20</td>
</tr>
<tr>
<td>Boesen</td>
<td>Denmark</td>
<td>September 2011 to September 2013</td>
<td>289 participants</td>
<td>64 years (59-67)</td>
<td>12.0 (8.3 - 19)ng/ml</td>
<td>Median (range) 0.19 (0.13-0.29)</td>
<td>Number of previous biopsies median range - 2 (1-6) (unclear if this is months or years)</td>
<td>At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer Abnormal digital rectal examination A previous abnormal TRUS image No patients had previously undergone MPMRI</td>
<td>mp-MRI PSA density Threshold - &gt;0.15ng/ml/ml MRI guided/influenced bioPSY T2 weighted, diffusion weighted image ad dynamic contrast enhanced was performed prior to rebiopsy. DWI b values - 0, 100,800,1400s/mm2</td>
</tr>
</tbody>
</table>
## RQ8: Following-up people at increased risk of prostate cancer

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

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study Details</th>
<th>Sample Characteristics</th>
<th>Inclusion Criteria</th>
<th>Index Test(s)</th>
<th>Reference Standard(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich (2012)</td>
<td>Study location USA, Study setting hospital, Study dates Between July 2008 and July 2009, Sources of funding None declared</td>
<td>Sample size 127 participants, Mean age (SD) reported as median range 63 (50-70) years, PSA ng/ml median (range) 5.3 (3.2-45.5)</td>
<td>presence of high grade prostate intraepithelial neoplasia, presence of atypical small acinar proliferation, A persistently elevated or rising serum total PSA level, Suspicious DRE, Patient aged 70 years or below</td>
<td>Total PSA %fPSA, TRUS biopsy included both 12/14 cores</td>
<td></td>
</tr>
<tr>
<td>Benecchi (2006)</td>
<td>Study location Italy, Study setting No details provided, Study dates Between January 2001 and June 2005, Sources of funding No funding details</td>
<td>Sample size 312 men, Median age (Range) 66.3 years (range 45–86), PSA ng/ml Median 7.1 (range 0.74–47.2 mg/l), median interval of time between the first and last</td>
<td>Abnormal digital rectal examination, PSA &gt;4.0ng/ml, Men with six or more cores and with at least three consecutive in 547 or more days before biopsy entered the</td>
<td>Total PSA PSAV, The PSA velocity was calculated according to the indication of Khan and Carter; for instance, with three PSA, the equation is 0.5 ((PSA2- PSA)/elapsed time in years)+((PSA3-</td>
<td>TRUS biopsy</td>
</tr>
<tr>
<td>Short Title</td>
<td>Study Details</td>
<td>Sample Characteristics</td>
<td>Inclusion Criteria</td>
<td>Index Tests</td>
<td>Reference Standard</td>
</tr>
<tr>
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<td>-------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>Bussetto</strong> (2013)</td>
<td>Study location</td>
<td>Italy</td>
<td>Study setting</td>
<td>Not reported</td>
<td>Study dates</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
<td>171 participants</td>
<td>Mean age (SD)</td>
<td>66.4 (5.3) years</td>
<td>PSA ng/ml</td>
</tr>
<tr>
<td></td>
<td>PSA assay</td>
<td>959 days (range 547–3723) Median PSA slope</td>
<td>0.403 ng/ml/year (range - 8.7 to 18.07)</td>
<td>study.</td>
<td>PSA2)/elapsed time in years), where PSA1 is the first of the three measurements, PSA2 the second and PSA3 the third; elapsed time refers to time between the two measurements</td>
</tr>
<tr>
<td><strong>Chen</strong> (2011)</td>
<td>Study location</td>
<td>China</td>
<td>Study setting</td>
<td>Hospital</td>
<td>Study dates</td>
</tr>
</tbody>
</table>
### Short Title

**Gnanapragasam (2016)**

**Study Details**
- Study location: United Kingdom
- Study dates: Between 2013 and 2015

**Sample Characteristics**
- Sample size: 279 people
- Mean age (SD): 66 years (range 45-80)

**Inclusion Criteria**
- At least one negative TRUS biopsy

**Index Tests**
- Prostate health index

**Reference Standard**
- Transperineal Template Mapping Biopsy

---

**Keetch (1996)**

**Study Details**
- Study location: USA
- Study setting: No details provided
- Study dates: Beginning July 1989
- Sources of funding: None declared

**Sample Characteristics**
- Sample size: 327 participants
- Mean age (SD): 68 (6) years
- PSA ng/ml: Median 6.8 ng/ml (SIR 1.9)

**Inclusion Criteria**
- Abnormal digital rectal examination
- An elevated PSA
- A previous abnormal TRUS image
- At least 2 prostate biopsies

**Index Tests**
- PSA density was calculated by dividing the serum PSA at initial biopsy by the TRUS determined prostate volume at initial biopsy
- PSA slope
- PSA slope was determined by subtracting the PSA value at the initial screening visit from that at the most recent biopsy divided by the years between these 2 values

**Reference Standard**
- TRUS biopsy

---

**Lazzeri (2012)**

**Study Details**
- Study location: Italy
- Study setting: Not declared
- Study dates: June 2010 and June 2011
- Sources of funding: No financial support

**Sample Characteristics**
- Sample size: 222 participants
- Mean age (SD): 63.9 years (7.1)
- PSA ng/ml: Median (range) 7.6ng/ml, (0.3-46.4)
- PSA density, ng/ml/ml

**Inclusion Criteria**
- At least one negative TRUS biopsy
- Persistent clinical suspicion of prostate cancer
- Abnormal digital rectal examination
- Presence of high grade

**Index Tests**
- Total PSA %fPSA
- Prostate health index
- Beckman-Coulter phi using the formula p2PSA/fPSA x square root of fPSA

**Reference Standard**
- TRUS biopsy
### Prostate cancer: diagnosis and management: evidence reviews for managing people at risk

#### DRAFT FOR CONSULTATION

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

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study Details</th>
<th>Sample Characteristics</th>
<th>Inclusion Criteria</th>
<th>Index Tests</th>
<th>Reference Standard</th>
</tr>
</thead>
</table>
| Lee (2012)  | Study location: Korea  
Study setting: Hospital  
Study dates: From January 2007 to December 2010  
Sources of funding: None declared | Sample size: 151 participants  
Mean age (SD): benign group - 64.82±6.59 years  
cancer group - 66.27±5.47 years  
PSA density (ng/ml/ml): 0.177±0.083 ng/ml/ml  
Time since last biopsy: 9.48±5.05 months | At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
Abnormal digital rectal examination  
An elevated PSA | PSA ratio  
The PSA change ratio was derived using the formula: \( \frac{p2PSA \text{ pg/ml}}{fPSA \text{ ng/ml}} \times 1,000 \times 100 \) | TRUS biopsy |

| Michielsen (1998) | Study location: Belgium  
Study dates: between October 1996 and September 1997  
Sources of funding: None declared | Sample size: 59 people  
Mean age (SD): 67 years (no SD)  
PSA ng/ml: 8.8 ng/ml (no SD)  
Mean prostate volume: 44 ml (no SD) | Serum PSA below 15ng/ml  
Aged 57-83 years | PSA density  
PSA transition zone | Systematic TRUS biopsy |

---

Serum PSA below 15ng/ml  
Aged 57-83 years  
PSA density  
PSA transition zone  
Systematic TRUS biopsy  
TRUS biopsy  
Lee (2012)  
Michielsen (1998)  
Prostate cancer: diagnosis and management: evidence reviews for managing people at risk  
DRAFT ([Sept 2018])
### Short Title
- **Murray (2014)**
- **Murray (2016)**
- **Ohigashi (2005)**

### Study Details
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study location</th>
<th>Study setting</th>
<th>Study dates</th>
<th>Sources of funding</th>
<th>No details provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray (2014)</td>
<td>Chile</td>
<td>No details provided</td>
<td>January 2006 and December 2010 - people without PCA were followed until Dec 2014</td>
<td>No details provided</td>
<td></td>
</tr>
<tr>
<td>Murray (2016)</td>
<td>Chile</td>
<td>Hospital</td>
<td>January 2006 to December 2014</td>
<td>No funding details provided</td>
<td></td>
</tr>
<tr>
<td>Ohigashi (2005)</td>
<td>Japan</td>
<td>No details provided</td>
<td>Between October 1997 and January 2000</td>
<td>No details provided</td>
<td></td>
</tr>
</tbody>
</table>

### Sample Characteristics

- **Sample size**: 164 participants
- **Mean age (SD)**: 65.1 (8.5) years
- **PSA ng/ml** median (range): 6.18ng/ml (4.95 - 9.26)
- **Median fPSA** 15% IQR - 11%-19%
- **Median Prostate volume**: 56ml (IQR 42-67ml)

### Inclusion Criteria
- Persistent clinical suspicion of prostate cancer
- Abnormal digital rectal examination
- An elevated PSA
- PSA > 4ng/ml
- PSA velocity of >0.75ng/ml/year

### Index Tests
- TRUS biopsy
- All biopsies were standard 12 core.
- %fPSA Chun's Normogram
- Total PSA and %free PSA were measured before the DRE using the automatic system for total PSA and %fPSA
- At least one negative TRUS biopsy
- Persistent clinical suspicion of prostate cancer
- Abnormal digital rectal examination
- PSA > 4ng/ml
- PSA between 4 and 10.0 ng/ml

### Sample size
- **Murray (2014)**: 164 participants
- **Murray (2016)**: 75 participants
- **Ohigashi (2005)**: 75 participants

### Mean age (SD)
- **Murray (2014)**: 65.1 (8.5) years
- **Murray (2016)**: 67.6 years (6.7)
- **Ohigashi (2005)**: 67.6 years (6.7)

### PSA ng/ml
- **Murray (2014)**: 6.18ng/ml (4.95 - 9.26)
- **Murray (2016)**: 7.58(1.37)
- **Ohigashi (2005)**: 0.208 (0.076) ng/ml/cm³

### Mean fPSA
- **Murray (2014)**: 0.189 (0.107)
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study Details</th>
<th>Sample Characteristics</th>
<th>Inclusion Criteria</th>
<th>Index Tests</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porpiglia (2014)</td>
<td>Study location: Italy. Study setting: Hospital. Study dates: Between March 2011 and April 2013. Sources of funding: None declared.</td>
<td>Sample size: 170 participants. Mean age (SD): Median age (iqr) 65 years (60-70).</td>
<td>At least one negative TRUS biopsy. Positive Digital rectal examination.</td>
<td>mp-MRI. All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA. %fPSA. All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after processing with a Unicel Dxi 800 Immunoassay System analyzer (Beckman Coulter). Prostate health index.</td>
<td>Random Biopsy under TRUS.</td>
</tr>
<tr>
<td>Short Title</td>
<td>Study Details</td>
<td>Sample Characteristics</td>
<td>Inclusion Criteria</td>
<td>Index Tests</td>
<td>Reference Standard</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td>-------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Shaida (2009)</td>
<td>Study location, UK - Study setting, Hospital - Study dates, between 1997 and 2002 - Sources of funding, None declared</td>
<td>Sample size, 67 participants</td>
<td>At least one negative TRUS biopsy - An elevated PSA &gt;20ng/ml</td>
<td>PSAV, PSA density</td>
<td>Trus biopsy</td>
</tr>
<tr>
<td>Shimbo (2009)</td>
<td>Study location, Japan - Study setting, Hospital - Study dates, From January 2004 to December 2005 - Sources of funding, None declared</td>
<td>Sample characteristics, Sample size, 77 cases - Mean age (SD), 72.4+6.6 years - PSA ng/ml, Initial tPSA (ng/ml), 7.2+2.7 tPSA (ng/ml) 10.2+3.8 PSA density, ng/ml/ml - Mean 0.36+0.22ng/ml</td>
<td>At least one negative TRUS biopsy - Persistent clinical suspicion of prostate cancer - An elevated PSA in a range between 4 and 20 ng/ml</td>
<td>%fPSA, %Free/tPSA was calculated from dividing free PSA by tPSA - PSA doubling time</td>
<td>TRUS biopsy</td>
</tr>
<tr>
<td>Yilmaz (2015)</td>
<td>Study location, Turkey - Study setting, Hospital - Study dates, between 2005 and 2011 - Sources of funding, None declared</td>
<td>Sample size, 605 participants - Mean age (SD), median age (IQR) - 65years (59-71) PSA ng/ml, 6.3 (5.1-7.8)ng/ml - Mean prostate volume, 49.9cm³ (36.2-69.1) Mean fPSA</td>
<td>At least one negative TRUS biopsy - tPSA between 2.5ng/ml and 10.0ng/ml - Negative digital rectal examination (defined as benign)</td>
<td>%fPSA, Different cut off points - 10%, 15%, 20%, 25%</td>
<td>Systematic TRUS biopsy, 12 core</td>
</tr>
</tbody>
</table>
RQ8: Following-up people at increased risk of prostate cancer

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Study Details</th>
<th>Sample Characteristics</th>
<th>Inclusion Criteria</th>
<th>Index Tests</th>
<th>Reference Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.1 (IQR - 0.8-1.5)ng/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1

2
1 See appendix E for full evidence tables.

**Quality assessment of clinical studies included in the evidence review**

3 See appendix G for full GRADE tables.

**Economic evidence**

**Included studies**

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

**Excluded studies**

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

**Economic model**

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

**Methods**

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

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

41 Clinically significant prostate cancer was defined as Gleason score ≥ 3+4 (i.e. any score of 7
42 or more). The terms used for health states in the model follow the cancer risk categories
1 recommended by NICE (CG175 2014). A schematic depiction of the model structure is
2 provided in Figure 1.

3 Figure 1: Schematic depiction of original health economic model

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

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

<table>
<thead>
<tr>
<th>MRI Likert score</th>
<th>Prevalence of clinically significant PCa</th>
<th>No. of previous negative biopsies</th>
<th>Baseline distribution of the modelled population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No cancer</td>
<td>Clinically non-significant</td>
</tr>
<tr>
<td>1 or 2</td>
<td>27.8%</td>
<td>0</td>
<td>50.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>68.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>78.4%</td>
</tr>
<tr>
<td>3</td>
<td>43.6%</td>
<td>1</td>
<td>61.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>68.2%</td>
</tr>
<tr>
<td>4</td>
<td>77.5%</td>
<td>1</td>
<td>36.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>46.6%</td>
</tr>
<tr>
<td>5</td>
<td>94.8%</td>
<td>1</td>
<td>39.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>61.3%</td>
</tr>
<tr>
<td>no MRI</td>
<td>58.2%</td>
<td>1</td>
<td>59.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

14 The prevalence of clinically significant prostate cancer was based on that reported in
15 PROMIS, as the committee indicated that the eligibility criteria for the study are
representative of the population of interest for this question. The prevalence of clinically non-significant prostate cancer was also obtained from PROMIS, Figure 2.

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

CnS: Clinically non-significant; CS: Clinically significant

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

The simulated follow-up strategies were formed based on screening and diagnostic tests that the committee considered clinically meaningful. They ranged from the least intensive strategies, i.e. no screening and waiting for symptoms, to the most rigorous one i.e. performing a transperineal template mapping (TPM) biopsy, assumed to be perfectly sensitive, for all people. In the base case, all follow-up strategies stopped when the modelled cohort reached 75 years, which the committee advised was a realistic upper threshold (mostly because the average person would be unlikely to be considered for radical therapy.
on diagnosis beyond this age). However, this was subject to sensitivity analysis, recognising that people can still receive radical treatment at an age more than 75 in clinical practice.

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

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

Results

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

The strategy where people receive TPM biopsy at the beginning of follow-up appeared to be the most optimal strategies in the majority of the sub-populations. However, this type of biopsy was assumed to be perfectly sensitive in the model, which may not be the case in clinical practice. In addition, it may lead to overdiagnosis, causing potential harms that the base case model may underestimate. The committee also advised that it was not feasible to adopt this strategy, as TPM was resource intensive and, although the model predicted that the resources would be justified, the healthcare system was not currently equipped to perform a large number of such procedures, mostly under general anaesthetic, resulting in an unrealistic burden for histopathology services. Thus, the model generated results with this strategy excluded and all prostate biopsies within the follow-up were TRUS.
<table>
<thead>
<tr>
<th>MRI Likert score</th>
<th>No. of negative biopsies</th>
<th>Optimal strategy</th>
<th>Optimal strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or 2</td>
<td>0</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>1 or 2</td>
<td>1</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>1 or 2</td>
<td>2</td>
<td>3-yearly %free PSA; if ≤15% (\rightarrow) mpMRI; if Likert ≥4 (\rightarrow) TPM</td>
<td>2-yearly PSA; if velocity ≥0.75 ng/ml/year (\rightarrow) mpMRI; if Likert ≥4 (\rightarrow) TPM</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>2-yearly %free PSA; if ≤15% (\rightarrow) mpMRI; if Likert ≥4 (\rightarrow) TPM</td>
<td>2-yearly PSA; if velocity ≥0.75 ng/ml/year (\rightarrow) mpMRI; if Likert ≥4 (\rightarrow) TPM</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2-yearly PSA; if density ≥0.15ng/ml/ml (\rightarrow) TRUS</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>no MRI</td>
<td>1</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
<tr>
<td>no MRI</td>
<td>2</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
<td>Immediate TPM for all; no subsequent follow-up</td>
</tr>
</tbody>
</table>

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

14 Table 4.
Table 3: Optimal follow-up strategies for different sub-populations, including the strategy where all patients are eligible to receive TPM

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

Measures derived from PSA tests, including velocity at a threshold of 0.75 ng/ml/year and density at a threshold of 0.15 ng/ml/ml, appear to be reliable indicators that trigger further diagnostics within the majority of subpopulations. However, “no screening” strategy appears optimal for the lowest-risk subpopulation who had MRI Likert scores of 1 or 2 and 2 previous negative biopsies, unless QALYs are valued at a little over £20,000 each. The model generates consistent results, as the optimal frequency of tests changes proportionally with the potential risk of disease. For example, within the population who had negative mpMRI (Likert 1 or 2), the optimal frequency of the PSA velocity test was every 6 months, every year or 2-yearly for people who had no biopsy, 1 biopsy or 2 biopsies, respectively (when QALYs are valued at £30,000). The percentage of free PSA test appears effective in directing people further diagnostics. The strategy, where people receive this test every 6 months and, if the percentage of free PSA was ≤15%, they were directed to TRUS, seems to be optimal within the population who had MRI Likert score of 5 and 1 previous negative biopsy.
### Table 4: Optimal follow-up strategies for different sub-populations, excluding TPM as part of any strategy

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

### 3 Sensitivity analysis

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

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

In a further scenario analysis, we applied both the disutility associated with the diagnosis of clinically non-significant disease and a higher cost of TPM, assuming that it required staying overnight in hospital in all cases. Under these conditions, the strategy of offering an immediate TPM to all would not be optimal in the majority of subpopulations. Optimal
strategies included PSA screening tests, using PSA velocity at a threshold of
0.75 ng/ml/year, PSA density at threshold of 0.15 ng/ml/ml and %free PSA. The frequency of
test varied based on the risk from yearly to 3-yearly based on the prostate cancer risk. For
people with negative biopsies but did not receive Mp-MRI, optimal strategies included Mp-
MRI to direct people to prostate biopsy, if Likert score ≥4.

Evidence statements

Clinical Evidence statements

Prostate cancer antigen 3 urinary assay (PCA3)

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

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

Multiparametric MRI

- Results that indicate a person suspected of prostate cancer has an increased probability
  of clinically significant disease (based on positive likelihood ratios):
  - A Likert or PIRAD score ≥3 does not alter the probability that a person
    persistently suspected of prostate cancer after an initial negative biopsy has prostate
cancer defined as either any cancer or clinically significant (high quality
    evidence from 4 cross-sectional studies comprising 967 participants; 95% confidence
    intervals range from slight increase to slight increase)
RQ8: Following-up people at increased risk of prostate cancer

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

2. Total prostate specific antigen (PSA)

- Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios):
  - A PSA ≥ 4 ng/ml could not differentiate the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Very low quality evidence from 3 cross-sectional studies comprising 1,112 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥ 5 ng/ml could not differentiate the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate quality evidence from 4 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥ 6 ng/ml could not differentiate the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Very low quality evidence from 4 cross-sectional studies comprising 509 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥ 7 ng/ml could not differentiate the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate quality evidence from 3 cross-sectional studies comprising 299 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PSA ≥ 8.5 ng/ml could not differentiate the probability that a person persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate quality evidence from 1 cross-sectional studies comprising 249 participants; 95% confidence intervals range from slight decrease to slight increase)
• Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):
  o A PSA ≥4ng/ml could not differentiate the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 1,112 participants; 95% confidence intervals range from moderate decrease to moderate increase)
  o A PSA ≥5ng/ml could not differentiate the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from large decrease to slight increase)
  o A PSA ≥6ng/ml could not differentiate the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 4 cross-sectional studies comprising 509 participants; 95% confidence intervals range from slight decrease to moderate decrease)
  o A PSA ≥7ng/ml could not differentiate the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 299 participants; 95% confidence intervals range from slight decrease to slight increase)
  o A PSA ≥8.5ng/ml could not differentiate the probability that a person Persistently suspected of prostate cancer after an initial negative biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies comprising 355 participants; 95% confidence intervals range from large decrease to slight increase)

2Prostate Specific Antigen density

• Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios):
  o A PSA ≥0.09ng/ml/ml does not alter the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight increase to slight increase)
  o A PSA density ≥0.10ng/ml/ml does not alter the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,066 participants; 95% confidence intervals range from slight increase to slight increase)
  o A PSA density ≥0.15ng/ml/ml does not alter the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,319 participants; 95% confidence intervals range from slight increase to slight increase)
  o A PSA density ≥0.30ng/ml/ml leads to a moderate increase in the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 3 cross-sectional studies comprising 267 participants; 95% confidence intervals range from slight increase to moderate increase)
  o A PSA density ≥0.36ng/ml/ml does not meaningfully alter the probability that a person Persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 1 cross-sectional studies comprising...
RQ8: Following-up people at increased risk of prostate cancer

3 Brostate Specific Antigen velocity

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

- Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):
  - A PSA density <0.09ng/ml/ml does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 7 cross-sectional studies comprising 1,319 participants; 95% confidence intervals range from moderate decrease to slight decrease)
  - A PSA density <0.30ng/ml/ml leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 3 cross-sectional studies comprising 267 participants; 95% confidence intervals range from slight decrease to moderate decrease)
  - A PSA density <0.38ng/ml/ml leads to a moderate decrease the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (low-quality evidence from 1 cross-sectional studies comprising 67 participants; 95% confidence intervals range from slight decrease to very large decrease)
RQ8: Following-up people at increased risk of prostate cancer

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

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

- **Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):**
  - A PSA-TZD <0.20ng/ml/ml leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 2 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to moderate decrease)
  - A PSA-TZD <0.25ng/ml/ml leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies comprising 978 participants; 95% confidence intervals range from slight decrease to moderate decrease)

Prostate Health Index (PHI)

- **Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios):**
  - A PHI score ≥25 has no diagnostic value in the diagnosis of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 95 participants; 95% confidence intervals range from slight decrease to slight increase)
  - A PHI score ≥30 does not alter the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 222 participants; 95% confidence intervals range from slight increase to slight increase)
  - A PHI score ≥35 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Very low-quality evidence from 1 cross-sectional studies comprising 1,000 participants; 95% confidence intervals range from slight decrease to very large decrease)
comprising 95 participants; 95% confidence intervals range from slight increase to a moderate increase)

- A PHI score ≥40 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight increase to moderate increase)

- A PHI score cut off of ≥48.9 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional studies comprising 170 participants; 95% confidence intervals range from slight increase to moderate increase)

- A PHI score cut off of ≥62 leads to a moderate increase in the probability (Moderate-quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight increase to large increase)

**Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):**

- A PHI score cut off of <25 could not differentiate the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 95 participants; 95% confidence intervals range from large decrease to moderate increase)

- A PHI score cut off of <30 leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight decrease to large decrease)

- A PHI score cut off of <35 leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 95 participants; 95% confidence intervals range from large decrease to a slight increase)

- A PHI score cut off of ≥40 leads to a moderate decrease in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional studies comprising 222 participants; 95% confidence intervals range from slight decrease to moderate increase)

- A PHI score cut off of <48.5 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Low -quality evidence from 1 cross-sectional study comprising 170 participants; 95% confidence intervals range from slight decrease to moderate decrease)

- A PHI score cut off of ≥62 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 222 participants; 95% confidence intervals range from slight decrease to slight decrease)

**Prostate Health Index (PHI) in MRI negative population**

- A PHI score ≥25 could not differentiate the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 94 participants; 95% confidence intervals range from slight decrease to slight increase)
Prostate cancer: diagnosis and management: evidence reviews for managing people at risk

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

- A PHI score ≥30 does not alter the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Moderate-quality evidence from 1 cross-sectional study comprising 94 participants; 95% confidence intervals range from slight increase to slight increase)
- A PHI score ≥35 does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Very low-quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight increase to a moderate increase)
- A PHI score ≥40 leads to a moderate increase in the probability that a person persistently suspected of prostate cancer after a negative initial mpMRI has prostate cancer (Very low-quality evidence from 1 cross-sectional studies comprising 94 participants; 95% confidence intervals range from slight increase to moderate increase)

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

Percentage Free Prostate Specific Antigen (%fPSA)

- A %fPSA ≥ 10% could not differentiate the probability that a person persistently suspected of prostate cancer after a negative initial biopsy has prostate cancer (Very low-quality evidence from 4 cross-sectional studies comprising 481 participants; 95% confidence intervals range from slight decrease to large increase)
- A %fPSA ≥ 15% does not meaningfully alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 7 cross-sectional studies comprising 1,253 participants; 95% confidence intervals range from slight increase to moderate increase)
- A %fPSA ≥ 20% does not alter in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very
low-quality evidence from 4 cross-sectional studies comprising 720 participants; 95% confidence intervals range from slight increase to slight increase)

- Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):
  - A %fPSA ≧ 25% does not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 3 cross-sectional studies comprising 1,038 participants; 95% confidence intervals range from slight increase to slight increase)
  - A %fPSA ≧ 30% does not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 5 cross-sectional studies comprising 1,290 participants; 95% confidence intervals range from slight increase to slight increase)
  - A %fPSA ≧ 35% does not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 1 cross-sectional studies comprising 820 participants; 95% confidence intervals range from slight increase to slight increase)
  - A %fPSA ≧ 38% does not alter the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Moderate -quality evidence from 1 cross-sectional studies comprising 820 participants; 95% confidence intervals range from slight increase to slight increase)

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

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

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

### Digital rectal examinations

- **Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios):**
  - A positive digital rectal examination leads to a **moderate increase** in the probability that a person persistently suspected of prostate cancer after a negative biopsy has prostate cancer (Very low-quality evidence from 5 cross-sectional studies comprising 641 participants; 95% confidence intervals range from slight increase to moderate increase)

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

### Economic evidence statements

#### TPM included in the analysis

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

#### TPM excluded from the analysis

34 One directly applicable original cost–utility model with potentially serious limitations showed that the ‘no screening’ strategy, where people are directed to prostate biopsy only if they develop symptoms, appears to be optimal for people with Likert <3 and 2 previous negative biopsies at a cost-effectiveness threshold of £20k/QALY. For people with Likert score <3 and no or 1, previous biopsy, a strategy where all candidates receive TRUS and no subsequent follow-up, seems to be optimal. The strategies including PSA velocity at a threshold of 0.75 ng/ml/year, PSA density at a threshold of 0.15 ng/ml/ml or %free PSA at a threshold of 15% that determined people who need prostate biopsy appear optimal for the majority of subpopulations. The frequency of screening tests varies based on the disease risk between 6-monthly, yearly or 2-yearly. The frequency of every 2 years seemed to be optimal for people with Likert score 3 and previous negative biopsies (either 1 or 2) and also for people with Likert 4 and Likert 5 and two previous negative biopsies. For people with Likert 4 and Likert 5 and 1 previous negative biopsy, the optimal frequency was every year and every six months, respectively.
For people with 1 or 2 previous negative biopsies and no previous mpMRI, the strategies of a yearly screening test followed by TRUS or 2-yearly screening test followed by mpMRI with a cutoff of Likert score ≥4 appear optimal, respectively. Raising the cost-effectiveness threshold from £20,000/QALY to £30,000/QALY allows strategies with greater frequency, e.g. every year instead of 2-yearly, to be optimal.

**Recommendations**

E1. For people who have a raised PSA, and MRI Likert score of 1 or 2 and have not had a prostate biopsy, repeat PSA test at 3–6 months and:
- offer prostate biopsy if there is a strong suspicion of prostate cancer (for example, PSA density greater than 0.15 ng/ml/ml or PSA velocity greater than 0.75 ng/year, or strong family history), taking into account their life expectancy and comorbidities
- discharge the person to primary care if the level of suspicion is low: advise PSA follow-up at 6 months and then every year, and set a PSA level for primary care at which to re-refer based on PSA density (0.15 ng/ml/ml) or velocity (0.75 ng/year) [2019]

E2. For people who have a raised PSA, an MRI Likert score of 1 or 2 (or a contraindication to MRI), and negative biopsy, repeat PSA at 3–6 months and:
- offer prostate biopsy if there is a strong suspicion of prostate cancer (for example, PSA density greater than 0.15 ng/ml/ml or PSA velocity greater than 0.75 ng/year, or strong family history), taking into account their life expectancy and comorbidities
- discharge the person to primary care if the level of suspicion is low: advise PSA follow-up at every 2 years, and set a PSA level for primary care at which to re-refer, based on PSA density (0.15 ng/ml/ml) or velocity (0.75 ng/year) [2019]

**Research recommendations**

What is the most suitable surveillance protocol for people who active surveillance is appropriate for, as assessed by multiparametric MRI and biopsy, when there are no clinical concerns during follow-up?

What is the performance of transperineal mapping biopsy versus transperineal non mapping biopsy in people suspected of prostate cancer?

In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?

**Rationale and impact**

Why the committee made the recommendations

There was no clinical evidence in this area, therefore the committee used evidence from economic modelling that showed people with a negative diagnosis of prostate cancer can still be at substantial risk of having prostate cancer, so follow-up is important. The evidence showed that the prevalence of initially undetected, but clinically significant, prostate cancer varies based on a person’s diagnostic history, so their diagnostic history should influence the frequency of follow-up.

The follow-up strategies recommended for primary care are based on standard PSA tests, with which primary care healthcare professionals are familiar. The committee agreed it was
important that specialist healthcare professionals should calculate thresholds for re-referral and provide these when discharging people, rather than expecting the calculations to be made in primary care.

The recommendations in NICE’s existing guidance on PCA3 assay and the prostate health index (DG17) will be updated by this guideline. The committee saw no evidence that either technique represents an effective use of NHS resources in the follow-up of people who have had a negative transrectal ultrasound guided prostate biopsy, and therefore did not make any recommendations on these technologies.

The committee identified a gap in the evidence for the performance of transperineal non-mapping biopsy and therefore made a research recommendation in this area.

The committee also noted that there is limited long-term follow-up evidence on the natural history of people whose multiparametric MRI Likert score is 1 or 2. In addition, there is limited evidence on the number of people whose multiparametric MRI is Likert score 1 or 2, who have normal PSA density and kinetics and who are found to have clinically significant cancer. Further research recommendations were made in these areas to help provide evidence across the prostate cancer treatment pathway.

How the recommendations might affect practice

Currently, there is substantial variation in clinical practice in the follow-up of people with a negative prostate biopsy. The committee’s recommendations should help to standardise practice.

Other recommendations made by the committee make it likely that more people will have a negative diagnosis on the basis of low-risk multiparametric MRI findings and no biopsy. This is a new population who will need effective follow-up strategies, and the recommendations give guidance on approaches that are likely to provide a good balance of benefits, harms and costs for this group.

The committee were confident that none of the recommendations would have a significant resource impact, as they are based on PSA measurements that are commonly used within primary care settings. In addition, if further multiparametric MRI is needed during follow-up, the evidence showed that MRI-influenced prostate biopsy may be more cost effective than systematic prostate biopsy, as it takes less time and is more efficient in identifying clinically significant cancer.

Full details of the evidence and the committee’s discussion are in evidence review E: following-up people at increased risk of prostate cancer.

The committee’s discussion of the evidence

Interpreting the evidence

The outcomes that matter most

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

The quality of the evidence

Clinical effectiveness

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

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

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

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

**Benefits and harms**

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

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

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

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

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

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

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

The committee reviewed evidence on the diagnostic accuracy of prostate health index (PHI) from 4 studies (Scattoni (2003), Lazzeri (2012), Porpiglia (2014) and Gnanapragasam (2016)). Its consideration of this evidence updates NICE’s existing guidance on PCA3 assay and the prostate health index (DG17). None of the evidence could be meta-analysed as the studies used different thresholds. The thresholds were 25, 30, 35, 40, 48.8 and 62. The evidence showed that PHI was not a useful index test to help identify prostate cancer in people with with at least one negative TRUS biopsy and MRI negative. As a result, the committee did not make any recommendations in favour of using PHI in the follow-up protocol for people who have a raised PSA, negative MRI and/or negative biopsy.
Cost effectiveness and resource use.

2 The committee reviewed the economic evidence provided by the original economic model.
3 They agreed that the analysis addressed the decision problem, in terms of the input
4 parameters, structure, assumptions and the follow-up strategies simulated. However, they
5 noted some limitations – in particular, the derivation of the sensitivity of repeat TRUS biopsy
6 in people with a previous negative biopsy. They noted that the source used to derive the
7 relation between the sensitivity of initial and subsequent TRUSs reflected practice from
8 20 years ago, when such procedures were performed somewhat differently (in particular, fewer cores were taken). However, they noted that these data were only used to estimate the
9 relative sensitivity of first and subsequent biopsies, which is then applied to a more reliable baseline (from a large, recent UK study, PROMIS), and agreed that, in the absence of contemporary, high-quality evidence, this approach was acceptable.

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

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

32 The committee noted that a follow-up strategy could be optimal for a number of
33 subpopulations, but with more intensive frequency for higher risk populations. It also agreed
34 that strategies with PSA-based screening tests, including PSA density at a threshold of
35 0.15 ng/ml/ml, PSA velocity at a threshold of 0.75 ng/ml/year and % free PSA, appeared to
36 be within the optimal strategies, were clinically meaningful in terms of thresholds. However, the committee noted that the % free PSA test required more sophisticated procedures than other PSA measurements, which may affect the uptake of this test in primary care settings.
37 They noted that the accuracy performance of PSA density and velocity tests at the
38 mentioned thresholds was sufficiently reliable compared to % free PSA test. They also noted that, if PSA kinetics were to be used, an absolute measure (PSA velocity) performed much
39 better than a relative one (PSA doubling time).
43 The committee agreed that the model’s findings were sufficient to make recommendations
44 about following up people with Likert score 1 or 2 and no previous biopsy by offering 6-
45 monthly and then yearly PSA test, with repeat biopsy indicated if density ≥0.15 ng/ml/ml or velocity ≥0.75 ng/ml/year. The same strategy was recommended to people with Likert 1 or 2 and at least 1 previous negative biopsy but, as the probability of undiagnosed disease is lower in such people, the optimal follow-up frequency may be extended to every 2 years.
### Appendix A – Review protocols

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

<table>
<thead>
<tr>
<th>ID</th>
<th>Field (based on PRISMA-P)</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Review question</td>
<td>What is the most clinically- and cost-effective follow-up protocol for people who have a raised PSA, negative MRI and/or negative biopsy?</td>
</tr>
<tr>
<td>II</td>
<td>Type of review question</td>
<td>Diagnostic</td>
</tr>
<tr>
<td>III</td>
<td>Objective of the review</td>
<td>To identify studies reporting accuracy data for PSA measures that can help simulate strategies to follow-up people who have a raised PSA, negative MRI and/or negative biopsy. No existing recommendations</td>
</tr>
</tbody>
</table>
| IV | Eligibility criteria – population/disease/condition/issue/domain | - People who have a raised PSA and negative MRI  
  - People who have a raised PSA and negative biopsy |
| V  | Index Tests               | - Individual or repeated PSA tests and calculations derived from them (including tPSA, fPSA, %fPSA, PSAD)  
  - Digital rectal examination |
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VI</strong></td>
<td><strong>Reference (gold) standard</strong></td>
</tr>
<tr>
<td></td>
<td>• MRI</td>
</tr>
<tr>
<td></td>
<td>• Biopsy (TRUS or TPM)</td>
</tr>
<tr>
<td></td>
<td>• Radical prostatectomy specimen</td>
</tr>
<tr>
<td></td>
<td>• Clinical emergence of cancer (follow up at least 10 years)</td>
</tr>
<tr>
<td><strong>VII</strong></td>
<td><strong>Outcomes and prioritisation</strong></td>
</tr>
<tr>
<td></td>
<td>Diagnostic accuracy</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity</td>
</tr>
<tr>
<td></td>
<td>• Likelihood ratios</td>
</tr>
<tr>
<td><strong>VIII</strong></td>
<td><strong>Eligibility criteria – study design</strong></td>
</tr>
<tr>
<td></td>
<td>• Diagnostic cross-sectional studies</td>
</tr>
<tr>
<td></td>
<td>• Systematic reviews of diagnostic cross-sectional studies</td>
</tr>
<tr>
<td><strong>IX</strong></td>
<td><strong>Other inclusion exclusion criteria</strong></td>
</tr>
<tr>
<td></td>
<td>• Non-English language papers</td>
</tr>
<tr>
<td></td>
<td>• Reviews</td>
</tr>
<tr>
<td></td>
<td>• Unable to calculate 2x2 tables</td>
</tr>
<tr>
<td><strong>X</strong></td>
<td><strong>Proposed sensitivity/sub-group analysis, or meta-regression</strong></td>
</tr>
<tr>
<td></td>
<td>• Negative MRI</td>
</tr>
<tr>
<td></td>
<td>• Negative biopsy</td>
</tr>
<tr>
<td></td>
<td>• Repeat biopsy</td>
</tr>
<tr>
<td></td>
<td>• Biopsy naive</td>
</tr>
<tr>
<td><strong>XI</strong></td>
<td><strong>Selection process – duplicate screening/selection/analysis</strong></td>
</tr>
<tr>
<td></td>
<td>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.</td>
</tr>
<tr>
<td>XII</td>
<td>Data management (software)</td>
</tr>
<tr>
<td>------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>XIII</td>
<td>Information sources – databases and dates</td>
</tr>
</tbody>
</table>
| XIV  | Identify if an update | This is a new clinical area, no previous question in previous updates. Committee agreed to no date limits for this question.  
**Original question**: New question, no original question in guideline.  
**Recommendations that may be affected**: No existing recommendations. |
<p>| XV   | Author contacts | Guideline updates team, National Institute for Health and Care Excellence (contact <a href="mailto:adam.okeefe@nice.org.uk">adam.okeefe@nice.org.uk</a>) |
| XVI  | Highlight if amendment to previous protocol | For details please see section 4.5 of <em>Developing NICE guidelines: the manual</em> |
| XVII | Search strategy – for one database | For details please see appendix C of relevant chapter |
| XVIII| Data collection process – forms/duplicate | A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). |
| XIX  | Data items – define all variables to be collected | For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables). |
| XX | Methods for assessing bias at outcome/study level | See Appendix B below – see section 1.4.1 |
| XXI | Criteria for quantitative synthesis (where suitable) | See Appendix B below |
| XXII | Methods for analysis – combining studies and exploring (in)consistency | See Appendix B below – see section 1.4.2 |
| XXIII | Meta-bias assessment – publication bias, selective reporting bias | See Appendix B below – see section 1.4.3 and 1.4.5 |
| XXIV | Assessment of confidence in cumulative evidence | See Appendix B below - see section 1.4.3 |
| XXV | Rationale/context – Current management | For details please see the introduction to the evidence review in the main file. |
| XXVI | Describe contributions of authors and guarantor | A multidisciplinary committee will develop the guideline update. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual. |</p>
<table>
<thead>
<tr>
<th>XXVI</th>
<th>Sources of funding/support</th>
<th>The NICE Guideline Updates Team is an internal team within NICE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXVI</td>
<td>Name of sponsor</td>
<td>The NICE Guideline Updates Team is an internal team within NICE.</td>
</tr>
<tr>
<td>XXIX</td>
<td>Roles of sponsor</td>
<td>The NICE Guideline Updates Team is an internal team within NICE.</td>
</tr>
</tbody>
</table>
Appendix B – Methods

Diagnostic test accuracy evidence

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

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

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.

\[ \text{LR}^+ = (\text{TP}/(\text{TP}+\text{FN}))/\text{(FP}/\text{(FP}+\text{TN})} \]

- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.

\[ \text{LR}^- = (\text{FN}/(\text{TP}+\text{FN}))/\text{(TN}/\text{(FP}+\text{TN})} \]

- **Sensitivity** is the probability that the feature will be positive in a person with the condition.

\[ \text{sensitivity} = \text{TP}/(\text{TP}+\text{FN}) \]

- **Specificity** is the probability that the feature will be negative in a person without the condition.

\[ \text{specificity} = \text{TN}/(\text{FP}+\text{TN}) \]

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

<table>
<thead>
<tr>
<th>Value of likelihood ratio</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{LR} \leq 0.1 )</td>
<td>Very large decrease in probability of disease</td>
</tr>
<tr>
<td>( 0.1 &lt; \text{LR} \leq 0.2 )</td>
<td>Large decrease in probability of disease</td>
</tr>
<tr>
<td>( 0.2 &lt; \text{LR} \leq 0.5 )</td>
<td>Moderate decrease in probability of disease</td>
</tr>
<tr>
<td>( 0.5 &lt; \text{LR} \leq 1.0 )</td>
<td>Slight decrease in probability of disease</td>
</tr>
<tr>
<td>( 1.0 &lt; \text{LR} &lt; 2.0 )</td>
<td>Slight increase in probability of disease</td>
</tr>
<tr>
<td>( 2.0 \leq \text{LR} &lt; 5.0 )</td>
<td>Moderate increase in probability of disease</td>
</tr>
<tr>
<td>( 5.0 \leq \text{LR} &lt; 10.0 )</td>
<td>Large increase in probability of disease</td>
</tr>
<tr>
<td>( \text{LR} \geq 10.0 )</td>
<td>Very large increase in probability of disease</td>
</tr>
</tbody>
</table>

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

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

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the index test lead to a moderate, large and very large increase/decrease in probability of disease.

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the index test could not meaningfully alter the probability of disease.

- In all other cases, we state that the index test could not alter the probability between the comparators.

- When the likelihood ratios were reversed for example – positive likelihood ratio of 0.1 and negative likelihood ratio of 3, we state that the index test has no diagnostic value.

19 Methods for combining diagnostic test accuracy evidence

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

Where applicable, diagnostic syntheses were stratified by:

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

- The reference standard used for true diagnosis.

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

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

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

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

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

7 Prostate cancer antigen 3 urinary assay

• Thresholds were pooled using the following ranges, these were adapted from some of the included articles that defined the cutoff points in a similar way -:
  o cutoff of 20 – any values between 0-20
  o cutoff of 35 any values between 21-35
  o cut off 50 any values between 36-50
• If the same study provided studies within the same range, the value closest to the top of the range was used.

17 Percent free Prostate specific antigen

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

25 Publication bias

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

31 Modified GRADE for diagnostic test accuracy evidence

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

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

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

<table>
<thead>
<tr>
<th>GRADE criteria</th>
<th>Reasons for downgrading quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bias</td>
<td>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.</td>
</tr>
<tr>
<td>GRADE criteria</td>
<td>Reasons for downgrading quality</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.</td>
</tr>
<tr>
<td></td>
<td>Indirectness</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.</td>
</tr>
<tr>
<td></td>
<td>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.</td>
</tr>
<tr>
<td></td>
<td>Inconsistency</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.</td>
</tr>
<tr>
<td></td>
<td>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.</td>
</tr>
<tr>
<td></td>
<td>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.</td>
</tr>
<tr>
<td></td>
<td>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels.</td>
</tr>
<tr>
<td></td>
<td>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.</td>
</tr>
<tr>
<td></td>
<td>Imprecision</td>
</tr>
<tr>
<td></td>
<td>If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratios that spanned both 0.5 and 2 were downgraded twice, as suffering from very serious imprecision.</td>
</tr>
<tr>
<td></td>
<td>Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.</td>
</tr>
</tbody>
</table>

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

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

Search summary

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

Clinical searches

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

The clinical searches were conducted in April 2018.

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

<table>
<thead>
<tr>
<th>Database: Ovid MEDLINE(R) 1946 to Present with Daily Update</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Prostate-Specific Antigen/</td>
</tr>
<tr>
<td>2. (Prostate* specific antigen adj2 (rais* or high* or elevate* or rise* or increase*)).tw.</td>
</tr>
<tr>
<td>3. (PSA adj2 (rais* or high* or elevate* or rise* or increase*)).tw.</td>
</tr>
<tr>
<td>4. (Kallikrein or semenogelase or seminin or gamma seminoprotein or gamma-seminoprotein or HK3).tw.</td>
</tr>
<tr>
<td>5. Prostate Health Index.tw.</td>
</tr>
<tr>
<td>6. PHI.tw.</td>
</tr>
<tr>
<td>7. or/1-6</td>
</tr>
<tr>
<td>8. *Magnetic Resonance Imaging/</td>
</tr>
<tr>
<td>9. (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw.</td>
</tr>
<tr>
<td>10. (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw.</td>
</tr>
<tr>
<td>11. (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw.</td>
</tr>
<tr>
<td>12. (contrast* adj2 (imag* or scan*)).tw.</td>
</tr>
<tr>
<td>13. ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostate*).tw.</td>
</tr>
<tr>
<td>14. turbo spin echo*.tw.</td>
</tr>
<tr>
<td>15. ((diffusio* or weight*) adj2 imag*).tw.</td>
</tr>
<tr>
<td>16. ((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI*) adj4 prostate*).tw.</td>
</tr>
<tr>
<td>17. (Multi-parametric or multiparametric* or biparametric* or bi-parametric*).tw.</td>
</tr>
<tr>
<td>18. or/8-17</td>
</tr>
<tr>
<td>19. *biopsy/ or *image-guided biopsy/</td>
</tr>
</tbody>
</table>
20 \(((\text{transrectal* or trans-rectal* or transperineal* or trans-perineal*) \text{ adj2} (\text{ultrasound* or biops*})\).tw.
21 \(((\text{saturat* or extend* or templat* or negative*}) \text{ adj2} (\text{ultrasound* or biops*})\).tw.
22 \(((\text{TRUS or TRUSB}) \text{ adj4} \text{ prostat*})\).tw.
23 or/19-22
24 7 and 18
25 7 and 23
26 or/24-25

1 **Study design filters and limit**

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

3 **Filters presented below.**

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

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

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

7 **Health Economics search strategy**

8 Economic evaluations and quality of life data.

9 **Sources searched:**

10 • NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
11 • Health Technology Assessment (HTA Database)
12 • EconLit (Ovid)
13 • Embase (Ovid)
14 • MEDLINE (Ovid)
15 • MEDLINE In-Process (Ovid)

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

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

18 The economic searches were conducted in April 2018.
1 Health Economics filters

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

### Economic evaluations

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

### Quality of life

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

The search strategies were based on the review protocol provided. The prostate cancer population terms have been removed from this strategy as the focus of this question is patients who haven’t been diagnosed with prostate cancer. The population was as follows:

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

Clinical searches

Sources searched for this review question:

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

The clinical searches were conducted in April 2018

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

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

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<th>Search Strategy:</th>
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<td>4 (Kallikrein or semenogelase or seminin or gamma seminoprotein or gamma-seminoprotein or HK3).tw.</td>
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<tr>
<td>5 Prostate Health Index.tw.</td>
</tr>
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<td>6 PHI.tw.</td>
</tr>
<tr>
<td>7 or/1-6</td>
</tr>
<tr>
<td>8 Magnetic Resonance Imaging/</td>
</tr>
<tr>
<td>9 (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw.</td>
</tr>
<tr>
<td>10 (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw.</td>
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<tr>
<td>11 (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw.</td>
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<td>12 (contrast* adj2 (imag* or scan*)).tw.</td>
</tr>
<tr>
<td>13 ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostat*).tw.</td>
</tr>
<tr>
<td>14 turbo spin echo*.tw.</td>
</tr>
<tr>
<td>15 ((diffusion* or weight*) adj2 imag*).tw.</td>
</tr>
</tbody>
</table>
Study design filters and limit

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

**MEDLINE McMaster Diagnosis filter.**

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

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

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

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

The economic searches were conducted in April 2018.

**Health Economics filters**

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

**Economic evaluations**

1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Dental/
4. exp Economics, Hospital/
5. exp Economics, Medical/
6. Economics, Nursing/
7. Economics, Pharmaceutical/
8. Budgets/
9. exp Models, Economic/
10. Markov Chains/
11. Monte Carlo Method/
12. Decision Trees/
13. econom$.tw.
14. cba.tw.
15. cea.tw.
16. cua.tw.
17. markov$.tw.
18. (monte adj carlo).tw.
19. (decision adj3 (tree$ or analys$)).tw.
20. (cost or costs or costing$ or costly or costed).tw.
21. (price$ or pricing$).tw.
22. budget$.tw.
23. expenditure$.tw.
24. (value adj3 (money or monetary)).tw.
25. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26. or/1-25
<table>
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<th>Quality of life</th>
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<td>31</td>
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</tbody>
</table>
Appendix D – Study selection

2 Clinical evidence

- All data
  - No date limit
  - 5032 Citation(s)

- Re-run search
  - May - August 2018
  - 212 Citation(s)

- 5244 Non-Duplicate Citations Screened

- Inclusion/Exclusion Criteria Applied
  - 4848 Articles Excluded After Title/Abstract Screen

- 396 Articles Retrieved

- Inclusion/Exclusion Criteria Applied
  - 318 Articles Excluded After Full Text Screen
  - 39 Articles Excluded During Data Extraction

- 39 Articles Included
1 Economic evidence

2

All databases
667 Citation(s)

667 Non-Duplicate Citations Screened

Inclusion/Exclusion Criteria Applied
666 Articles Excluded After Title/Abstract Screen

1 Articles Retrieved

Inclusion/Exclusion Criteria Applied
1 Articles Excluded After Full Text Screen
- Articles Excluded During Data Extraction

No Articles Included
## Appendix E – Clinical evidence tables

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
</table>
| Abd-Alazeez (2014)| The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level–can it rule out clinically significant prostate cancer? | Study type: Cross-sectional study  
Study details:  
Study location: UK  
Study dates: not stated  
Sources of funding: UK National Institute of Health Research Council, UCL Comprehensive Biomedical Research Centre London UK  
Inclusion criteria: At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
An elevated PSA  
Exclusion criteria: Anyone who received less than 20 cores of template biopsy  
Sample characteristics:  
Sample size: 54 participants  
Median age (Range): 64 years (39-75) | Patient selection: Unclear risk of bias  
Patient selection strategy was not provided  
Index test: Low risk of bias  
Mp MRI was performed in a blinded manner to the template biopsy as all imaging reports were committed to the electronic medical record before the biopsy result became available  
Reference standard: Low risk of bias  
The reference standard matched the protocol and was regarded as the gold standard. It is unclear if the template biopsy was carried out in a blinded manner  
Flow and timing: Unclear risk of bias  
The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis  
Overall risk of bias: Moderate  
Moderate – as a result of the uncertainties surrounding
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml median, range - 10 (2-23) Number of previous biopsies Between 1 and 3 biopsies Median Prostate volume 53 (19-136)</td>
<td>patients selection and flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s) mp-MRI MRI comprised of T2 weighted, diffusion weighted and dynamic contrast enhanced imaging with either 1.5T and 3.0T. Diffusion b values - 0,150,500 and 1000. Positive MRI - PIRADS Score 3 and above Positive MRI - PIRADS score 4 and above For clinically significant disease</td>
<td>Directness Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference standard(s) Transperineal Template Mapping Biopsy minimum number of samples was 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition for clinically significant cancer Several definitions were used for multiple analyses UCL definition 1 UCL definition 2 Primary definition used by the study Gleason score 4+3 Gleason score 3+4</td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Aubin (2010)</td>
<td>PCA3 molecular urine test for predicting repeat prostate biopsy outcome in populations at risk: validation in the placebo arm of the dutasteride REDUCE trial</td>
<td>Study type&lt;br&gt;Cross-sectional study&lt;br&gt;Study details&lt;br&gt;Study location&lt;br&gt;USA&lt;br&gt;Study setting&lt;br&gt;Study dates&lt;br&gt;No details provided&lt;br&gt;Sources of funding&lt;br&gt;None declared&lt;br&gt;Inclusion criteria&lt;br&gt;At least one negative TRUS biopsy&lt;br&gt;Within 6 months of enrollment&lt;br&gt;tPSA between 2.5ng/ml and 10.0ng/ml&lt;br&gt;Exclusion criteria&lt;br&gt;None reported&lt;br&gt;Sample characteristics&lt;br&gt;Sample size&lt;br&gt;1,072 participants&lt;br&gt;Mean age (SD)&lt;br&gt;Not provided - ranged 50-70 years&lt;br&gt;Index test(s)&lt;br&gt;Prostate Cancer Gene 3</td>
<td>Patient selection&lt;br&gt;Unclear risk of bias&lt;br&gt;No details provided on patient selection strategy - only they were the control arm of another study&lt;br&gt;Index test&lt;br&gt;Unclear risk of bias&lt;br&gt;Thresholds similar to that from other published studies&lt;br&gt;Reference standard&lt;br&gt;Low risk of bias&lt;br&gt;Matched the protocol and deemed to be best at classifying prostate cancer&lt;br&gt;Flow and timing&lt;br&gt;Unclear risk of bias&lt;br&gt;All participants received the both tests&lt;br&gt;Overall risk of bias&lt;br&gt;Moderate&lt;br&gt;Directness&lt;br&gt;Directly applicable</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
</tbody>
</table>
Prostate biopsy - not specified  
Definition for clinically significant cancer  
Any cancer | Patient selection  
Unclear risk of bias  
No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria |

| Study type | Associated Study  
2x2 tables obtained from this systematic review -  
Cross-sectional study | Index test  
Unclear risk of bias  
It is not clear whether the index test were interpreted without the knowledge of the reference standard results. The thresholds were defined by the predefined sensitivity levels. | |
| Study details | Study location  
USA  
Study setting  
hospital  
Study dates  
Between July 2008 and July 2009  
Sources of funding  
None declared | Reference standard  
Unclear risk of bias  
The reference standard was chosen by the committee and was regarded as gold standard | |
| Inclusion criteria | presence of high grade prostate intraepithelial neoplasia  
presence of atypical small acinar proliferation  
A persistently elevated or rising serum total PSA level  
Suspicious DRE  
Patient aged 70 years or below | Flow and timing  
Unclear risk of bias  
No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria | |
### Study 1: Barbera (2012)

#### Title
PCA3 score accuracy in diagnosing prostate cancer at repeat biopsy: our experience in 177 patients

#### Study Details
- **Study Type**: Prospective cohort study
- **Study Location**: Italy
- **Study Setting**: Not reported
- **Study Dates**: January 2010 and March 2012
- **Sources of Funding**: Not reported

#### Quality Assurance
- **Overall Risk of Bias**: Moderate
- **Due to uncertainties surrounding patient section and time lapse between the index test and reference standard**
- **Directness**: Directly applicable

#### Exclusion Criteria
- tPSA >50ng/ml

#### Sample Characteristics
- **Sample size**: 127 participants
- **Mean age (SD)**: reported as median range 63 (50-70) years
- **PSA ng/ml**: median (range) 5.3 (3.2-45.5)

#### Index Test(s)
- Total PSA
- %fPSA

#### Reference Standard(s)
- Systematic TRUS biopsy
- included both 12/14 cores

#### Summary
- Unclear risk of bias
- No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria
- Unclear risk of bias
- It is unclear if the index test was interpreted without the knowledge of the reference standard. It is unclear how the thresholds were determined, however the cutoffs are similar.
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
</table>
| None declared |  | Inclusion criteria  
At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
Abnormal digital rectal examination  
An elevated PSA >10ng/ml |  | to other papers in the review  
Reference standard  
Low risk of bias  
The reference standard was chosen by the committee and was regarded as gold standard  
Flow and timing  
Unclear risk of bias  
The index test was carried out before the reference standard, however the authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis  
Overall risk of bias  
Moderate  
Due to uncertainties surrounding patient section and time lapse between the index test and reference standard  
Directness  
Directly applicable |
|  |  | Sample characteristics  
Sample size  
177 participants  
Mean age (SD)  
Median (range) 64 (48-74) years  
PSA ng/ml  
74 participants had serum PSA >10ng/ml  
99 between 4-10ng/ml  
4 between 2.6-4ng/ml  
Number of previous biopsies  
at least one prior biopsy  
Time since last biopsy  
Not reported |  |  |
|  |  | Index test(s)  
Prostate Cancer Gene 3  
Cut off of 20 and 35 |  |  |
|  |  | Reference standard(s)  
Systematic prostate biopsy  
Performed transperineally |  |  |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
</table>
| Boesen (2018) | Multiparametric MRI in men with clinical suspicion of prostate cancer undergoing repeat biopsy: a prospective comparison with clinical findings and histopathology | Study type  
Cross-sectional study  
Study details  
Study location: Denmark  
Study setting: No details provided  
Study dates: Between September 2011 to September 2013  
Sources of funding: No financial support  
Inclusion criteria: At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
Abnormal digital rectal examination  
A previous abnormal TRUS image  
No patients had previously undergone MPMRI  
Exclusion criteria: Prostate cancer diagnosis  
contraindications for undergoing prostate biopsy or mpMRI  
Sample characteristics: Sample size  
289 participants  
%female: n/a  
Median age (Range): 64 years (59-67) | Patient selection  
Unclear risk of bias  
A database was used to enrol participants, however the selection strategy was not detailed  
Index test  
Low risk of bias  
"... All mpMRI underwent blinded evaluation by the same physicia who registered and scored all suspicious lesions..." using PIRADS V1  
Reference standard  
Low risk of bias  
The reference standard matches protocol and is regarded as the "gold standard" "... cores were obtained systematically blinded to mpMRI findings."  
Flow and timing  
Low risk of bias  
The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis  
Overall risk of bias  
Low  
Directness  
Directly applicable |
<table>
<thead>
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<th>Study Characteristics</th>
<th>Quality Assurance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Median Range - 12.0 (8.3 - 19)ng/ml</td>
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<tr>
<td></td>
<td></td>
<td>PSA density, ng/ml/ml</td>
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<td></td>
<td>Median (range) - 0.19 (0.13-0.29)</td>
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<td></td>
<td></td>
<td>Number of previous biopsies</td>
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<td></td>
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<td>median range - 2 (1-6) (unclear if this is months or years)</td>
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<td>Index test(s)</td>
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<td>mp-MRI</td>
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<td></td>
<td>PSA density</td>
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<td></td>
<td>Threshold - &gt;0.15ng/ml/ml</td>
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<td>MRI guided/influenced bioPSY</td>
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<td></td>
<td>T2 weighted, diffusion weighted image ad dynamic contrast enhanced was performed prior to rebiopsy. DWI b values - 0, 100,800,1400s/mm²</td>
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<tr>
<td></td>
<td></td>
<td>Reference standard(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRUS guided biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition for clinically significant cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any biopsy core with Gleason score &gt;6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum cancer core length of at least 50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>For Trus biopsy only - presence of at least 3 prostate cancer positive cores</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Busetto (2013)</th>
<th>Prostate cancer gene 3 and multiparametric magnetic resonance can reduce unnecessary biopsies:</th>
<th>Study type</th>
<th>Prospective cohort study</th>
<th>Patient selection</th>
<th>Low risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study type</td>
<td></td>
<td>Patient selection</td>
<td>Low risk of bias</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The study participants were consecutively enrolled to the study. The study was not of a case control design, all patients had both tests done. The authors did not state any</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
<td></td>
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<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>decision curve analysis to evaluate predictive models</td>
<td>Study details</td>
<td>Study location Italy</td>
<td>inappropriate exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study setting Not reported</td>
<td></td>
<td>Index test</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study dates March 2010 and July 2012</td>
<td></td>
<td>Low risk of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sources of funding None disclosed</td>
<td></td>
<td>It is unclear if the index test was interpreted without the knowledge of the reference standard</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review</td>
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</tr>
<tr>
<td></td>
<td>Inclusion criteria</td>
<td></td>
<td>Reference standard</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least one negative TRUS biopsy</td>
<td></td>
<td>Low risk of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persistent clinical suspicion of prostate cancer</td>
<td></td>
<td>The reference standard was chosen by the committee and was regarded as gold standard</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A persistently elevated or rising serum total PSA level</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Between 4-10ng/ml</td>
<td></td>
<td>Flow and timing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria</td>
<td></td>
<td>Unclear risk of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate cancer diagnosis patients with missing data</td>
<td></td>
<td>The authors did not state the time lapse between the 2 tests.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment</td>
<td></td>
<td>All the patients received the reference standard and all patients were included in the final analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>An inadequate proste biopsy with &lt;10 cores</td>
<td></td>
<td>Overall risk of bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample characteristics</td>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample size 171 participants</td>
<td></td>
<td>Directness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean age (SD) 66.4 (5.3) years</td>
<td></td>
<td>Directly applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PSA ng/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<td>-------------</td>
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</tbody>
</table>
|             | PSA density as a better predictor of prostate cancer than percent-free PSA in a repeat biopsy | Study type: Cross-sectional study | Patient selection: Unclear risk of bias
| Chen (2011) | | Study details: Study location China, Study setting: Hospital, Study dates: From April 1999 to February 2008 | Patient selection strategy was not detailed |
|             | | Inclusion criteria: At least one negative TRUS biopsy, Abnormal digital rectal examination, An elevated PSA, PSA between 4 and 10.0 ng/ml | Index test: Unclear risk of bias
|             | | Exclusion criteria: Abnormal DRE | Reference standard: Low risk of bias
|             | | | The reference standard matched the protocol. All the participants had the same reference standard. It is unclear if the results were interpreted without the knowledge of index test results |
|             | | | Flow and timing: Unclear risk of bias
<p>|             | | | The authors did not provide the time lapse between the... |</p>
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>And PSA levels &gt;10ng/ml</td>
<td>reference standard and index tests. All the patients received the same reference standard and all patients were included in the analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample size 212 men</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD) 66.59 (9.92) years</td>
<td>Due to uncertainties surrounding threshold setting, patient selection and blinding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml 6.34 (1.66) ng/ml</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA density, ng/ml/ml 0.182 (0.203) ng/ml/ml</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s) Total PSA Serum tPSA and free PSA (fPSA) were measured using TPSA-RIACT and FPSA-RIACT kits (CIS-Bio International, France), respectively</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>%fPSA PSAV For the determination of PSAV, the latest three values of tPSA were obtained, and PSAV was calculated using linear regression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA density</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference standard(s) TRUS biopsy TRUS-guided prostate biopsy was performed using an 18-G needle. The number of core biopsy specimens in the first and second TRUS-guided prostate biopsy was the same.</td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>-------------</td>
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<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Ciatto (2008)</td>
<td>PSA doubling time as a predictor of the outcome of random prostate biopsies prompted by isolated PSA elevation in subjects referred to an outpatient biopsy facility in a routine clinical scenario</td>
<td>The number was between 8 and 14. Definition for clinically significant cancer Definition was not provided</td>
<td>Patient selection Low risk of bias Consecutive patients were selected .. Index test Unclear risk of bias it is unclear how thresholds were determined but these were adopted apriori Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard Flow and timing Low risk of bias total and f/t psa were tested immediately prior to biopsy using the Hybritech Tandem MP PSA Overall risk of bias Low Directness Directly applicable</td>
</tr>
</tbody>
</table>

Ciatto (2008) is a study that evaluated the role of PSA doubling time as a predictor of clinical outcome in the context of random prostate biopsies. The study, conducted in Italy at a hospital setting from January 2001 to August 2007, included 355 participants with at least one negative TRUS biopsy and a negative digital rectal examination, defined as benign. The inclusion criteria were a PSA level between 4 and 10.0 ng/ml. The study type was a cross-sectional design. The study did not report any sources of funding and had no reported exclusion criteria. The patient selection was low risk of bias, and the study details included the adoption of thresholds determined a priori. The reference standard was chosen by the committee and was regarded as gold standard. The PSA values were tested immediately prior to biopsy. The study was considered to have an overall risk of bias of low and was directly applicable.
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>68 years (49-85 years)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total PSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSAV</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PSA density</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Free/Total PSA ratio</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference standard(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TRUS biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition for clinically significant cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition was not provided</td>
<td></td>
</tr>
<tr>
<td>Gittelman (2013)</td>
<td>PCA3 molecular urine test as a predictor of repeat prostate biopsy outcome in men with previous negative biopsies: a prospective multicenter clinical study</td>
<td>Study type</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study details</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study location</td>
<td>USA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study setting</td>
<td>Community clinic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study dates</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sources of funding</td>
<td>Genprobe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria</td>
<td>At least one negative TRUS biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 years and older</td>
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</table>
### Study Characteristics

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer diagnosis</td>
<td>Flow and timing</td>
</tr>
<tr>
<td>Any medication which can lower PSA levels</td>
<td>Low risk of bias samples were collected 24 hrs of each other, if not possible within 7 days. The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis</td>
</tr>
<tr>
<td>Clinical symptoms of urinary tract infection</td>
<td>Overall risk of bias Moderate Due to uncertainties surrounding patient section and time lapse between the index test and reference standard</td>
</tr>
<tr>
<td>History of invasive therapy for benign prostatic hyperplasia</td>
<td>Directness Directly applicable</td>
</tr>
<tr>
<td>Participation in treatment studies within 6 months</td>
<td></td>
</tr>
</tbody>
</table>

### Quality Assurance

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Patient selection Patient selection strategy was not detailed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td>466 participants</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td></td>
</tr>
<tr>
<td>to add from supplement</td>
<td></td>
</tr>
<tr>
<td>PSA ng/ml</td>
<td></td>
</tr>
<tr>
<td>to add from supplement</td>
<td></td>
</tr>
<tr>
<td>PSA density, ng/ml/ml</td>
<td></td>
</tr>
<tr>
<td>to add from supplement</td>
<td></td>
</tr>
<tr>
<td>Mean prostate volume</td>
<td></td>
</tr>
<tr>
<td>to add from supplement</td>
<td></td>
</tr>
<tr>
<td>Index test(s)</td>
<td></td>
</tr>
<tr>
<td>Prostate Cancer Gene 3</td>
<td></td>
</tr>
<tr>
<td>Reference standard(s)</td>
<td></td>
</tr>
<tr>
<td>TRUS biopsy and MP-MRI biopsy</td>
<td></td>
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</table>

### Study Characteristics

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gnanapragasam (2016)</td>
<td>The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant</td>
</tr>
</tbody>
</table>

### Study type

<table>
<thead>
<tr>
<th>Retrospective cohort study</th>
<th>Study type</th>
</tr>
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</table>

### Flow and timing

| Low risk of bias samples were collected 24 hrs of each other, if not possible within 7 days. The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis | Overall risk of bias Moderate Due to uncertainties surrounding patient section and time lapse between the index test and reference standard |

### Directness

<table>
<thead>
<tr>
<th>Directly applicable</th>
<th>Directness</th>
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<tbody>
<tr>
<td>Directly applicable</td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
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<tr>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td>prostate cancers in a repeat biopsy population</td>
<td>Study details</td>
</tr>
<tr>
<td></td>
<td>Study location</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
<tr>
<td></td>
<td>Study dates</td>
</tr>
<tr>
<td></td>
<td>Between 2013 and 2015</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria</td>
</tr>
<tr>
<td></td>
<td>At least one negative TRUS biopsy</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Presence of general contraindications for MRI patients with any suspicion of extracapsular extension</td>
</tr>
<tr>
<td></td>
<td>any infection, prostatitis or previous prostate surgery</td>
</tr>
<tr>
<td></td>
<td>Sample characteristics</td>
</tr>
<tr>
<td></td>
<td>Sample size</td>
</tr>
<tr>
<td></td>
<td>279 people</td>
</tr>
<tr>
<td></td>
<td>Mean age (SD)</td>
</tr>
<tr>
<td></td>
<td>66 years (range 45-80)</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
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<tr>
<td>-------------</td>
<td>-----------------------------------------------------------------------</td>
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</tbody>
</table>
| Goode (2013)| Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients | Study type  
Associated Study  
Obtained the 2x2 tables from this paper  
Retrospective cohort study  
Study details  
Study location  
USA  
Study setting  
Not reported  
Study dates  
Not reported  
Sources of funding  
None disclosed  
Inclusion criteria  
At least one negative TRUS biopsy  
Abnormal digital rectal examination  
An elevated PSA  
presence of high grade prostate intraepithelial neoplasia  
presence of atypical small acinar proliferation  
Exclusion criteria  
Prostate cancer diagnosis  
Sample characteristics  
Sample size  
456 participants  
Mean age (SD) reported as median (range) 66(41-90) years  
PSA ng/ml | Patient selection  
Unclear risk of bias  
No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria  
Index test  
Unclear risk of bias  
It is unclear if the index test was interpreted without the knowledge of the reference standard It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review  
Reference standard  
Low risk of bias  
The reference standard was chosen by the committee and was regarded as gold standard  
Flow and timing  
Unclear risk of bias  
The index test was collected prior to the reference standard, however it is unclear what the time lapse was between the two tests. All the patients received the reference standard and all patients were included in the final analysis  
Overall risk of bias  
Moderate  
Due to uncertainties surrounding patient section and time lapse between the index test and reference standard |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haese (2008)</td>
<td>Study type: Prospective cohort study</td>
<td>Patient selection</td>
</tr>
</tbody>
</table>
|                  | Clinical Utility of the PCA3 Urine Assay in European Men Scheduled for Repeat Biopsy | Study details: Study location - Six European centres - Germany, France, The Netherlands, Belgium and Austria  
Study setting - Hospitals  
Study dates - Between August and July 2007  
Sources of funding - Gen Probe Inc.  

Inclusion criteria - At least one negative TRUS biopsy  

Exclusion criteria - Any medication which can lower PSA levels  

Reference standard(s) - Systematic TRUS biopsy  

Directness: Directly applicable | Patient selection: Unclear risk of bias  
Patient selection was not detailed in terms of sampling strategy  
Index test: Low risk of bias  
Specimens for the index tests were collected before the biopsies, The authors used three different thresholds for PCA3 and one for %fPSA. The thresholds were predetermined and in line with those from similar studies  
Reference standard: Low risk of bias  
The reference standard matched the protocol and regarded as the gold standard. It is not clear if the results were interpreted in a blinded fashion |
### Prostate cancer: diagnosis and management

**Clinical symptoms of urinary tract infection**
- Patients with atypia or prostatic intraepithelia neoplasia at any biopsy were excluded.
- Men with more than 2 previous negative biopsies.

**Sample characteristics**
- **Sample size**: 463 participants.
- **Mean age (SD)**: 64.4 (6.6) years.
- **PSA ng/ml**: Mean 8.9 (7.5)ng/ml.
- **Number of previous biopsies**: 331 participants had 1 biopsy, 126 participants had 2 biopsies.

**Index test(s)**
- **Prostate Cancer Gene 3**
  - The PCA3 was calculated as \([\text{PCA3 mRNA}] / [\text{PSA mRNA}] \times 1000\).

**Reference standard(s)**
- **TRUS biopsy**

**Definition for clinically significant cancer**
- Definition was not provided.

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical symptoms of urinary tract infection</td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients with atypia or prostatic intraepithelia neoplasia at any biopsy were excluded</td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men with more than 2 previous negative biopsies</td>
<td>The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample size</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>463 participants</td>
<td>Moderate – as a result of the uncertainties surrounding patients selection and index test results interpretation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD)</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64.4 (6.6) years</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean 8.9 (7.5)ng/ml</td>
<td></td>
</tr>
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<td></td>
<td>Number of previous biopsies</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>331 participants had 1 biopsy, 126 participants had 2 biopsies</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate Cancer Gene 3</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>The PCA3 was calculated as ([\text{PCA3 mRNA}] / [\text{PSA mRNA}] \times 1000)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reference standard(s)</td>
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<tr>
<td></td>
<td></td>
<td>TRUS biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition for clinically significant cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition was not provided</td>
<td></td>
</tr>
</tbody>
</table>

**Kaufmann (2016)**

**Prostate cancer gene 3 (PCA3) is of additional predictive**

**Study type**
- Retrospective cohort study

**Patient selection**
- Unclear risk of bias
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
</table>
|             | value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. | Study details  
Study location  
Germany  
Study dates  
Between 2008-2014  
Sample characteristics  
Sample size  
49 patients  
Mean age (SD)  
65 (5.6) years  
PSA ng/ml  
10 (4.4) ng/ml  
PSA density, ng/ml/ml  
0.22 (0.12) ng/ml/g  
Number of previous biopsies  
1.7 (0.9) biopsies  
median interval of time between the first and last PSA assay  
6 (3) months  
Index test(s)  
Prostate Cancer Gene 3  
cut off of 25 and 35  
Reference standard(s)  
TRUS biopsy  
Definition for clinically significant cancer  
Definition was not provided  
Any cancer | the patient selection strategy was not detailed  
Index test  
Low risk of bias  
the threshold was chosen based on evidence from similar studies. operators performing the PCA3 assay assessment were blinded to the patient's status  
Reference standard  
Low risk of bias  
the reference standard was the one chosen by the committee as a gold standard  
Flow and timing  
Unclear risk of bias  
the time between treatments was not detailed.  
Overall risk of bias  
Moderate  
as result of the lack of detail regarding patient selection  
Directness  
Directly applicable |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keetch (1996)</td>
<td>Prostate specific antigen density versus prostate specific antigen slope as predictors of prostate cancer in men with initially negative prostatic biopsies</td>
<td><strong>Study type</strong>&lt;br&gt;Cross-sectional study</td>
<td>Patient selection&lt;br&gt;Unclear risk of bias&lt;br&gt;The study population was via a newspaper article and only men who responded were included in the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Study details</strong>&lt;br&gt;Study location&lt;br&gt;USA&lt;br&gt;Study setting&lt;br&gt;No details provided&lt;br&gt;Study dates&lt;br&gt;Beginning July 1989&lt;br&gt;Sources of funding&lt;br&gt;None declared</td>
<td><strong>Index test</strong>&lt;br&gt;Low risk of bias&lt;br&gt;The index test were obtained prior to the reference standard. The thresholds were predetermined and were similar to those from similar studies</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Inclusion criteria</strong>&lt;br&gt;Abnormal digital rectal examination&lt;br&gt;An elevated PSA&lt;br&gt;A previous abnormal TRUS image&lt;br&gt;At least 2 prostate biopsies</td>
<td><strong>Reference standard</strong>&lt;br&gt;Low risk of bias&lt;br&gt;The reference standard matched the protocol, it was carried out after the index tests, it is not clear is the results from the index tests were blinded when interpreting reference standard results.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Exclusion criteria</strong>&lt;br&gt;Patients with atypia or prostatic intraepithelial neoplasia at any biopsy were excluded</td>
<td><strong>Flow and timing</strong>&lt;br&gt;Unclear risk of bias&lt;br&gt;The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Sample characteristics</strong>&lt;br&gt;Sample size&lt;br&gt;327 participants&lt;br&gt;Mean age (SD)&lt;br&gt;68 (6) years&lt;br&gt;PSA ng/ml&lt;br&gt;Median 6.8 ng/ml (SIR 1.9)</td>
<td><strong>Overall risk of bias</strong>&lt;br&gt;Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Directness</strong>&lt;br&gt;Directly applicable</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<tr>
<td></td>
<td>Serum index test %[-2]proPSA and Prostate Health Index are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy</td>
<td>Index test(s) PSA density was calculated by dividing the serum PSA at initial biopsy by the TRUS determined prostate volume at initial biopsy PSA slope was determined by subtracting the PSA value at the initial screening visit from that at the most recent biopsy divided by the years between these 2 values Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided</td>
<td>Patient selection Unclear risk of bias Men who were scheduled for repeat biopsy, no specific patient selection was detailed Index test Unclear risk of bias The thresholds were not chosen apriori Reference standard Low risk of bias the reference standard was similar to the one identified in the protocol as the gold standard</td>
</tr>
<tr>
<td>Lazzeri (2012)</td>
<td>Study type Cross-sectional study Study details Study location Italy Study setting Not declared Study dates June 2010 and June 2011 Sources of funding No financial support declared, however Unicel Dxl 800 Immuniasys System analyzer p2PSA ([2]proPSA) reagents were provided by Beckman Coulter Inc and Beckman Coulter</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lazzeri (2012) is credited for the study. The study was a cross-sectional study conducted in Italy from June 2010 to June 2011. The serum index test was %[-2]proPSA and Prostate Health Index, which are more accurate than prostate specific antigen and %fPSA in predicting a positive repeat prostate biopsy. The study details include the study location in Italy, and the study dates. The sources of funding include Unicel Dxl 800 Immuniasys System analyzer p2PSA ([2]proPSA) reagents provided by Beckman Coulter Inc and Beckman Coulter. The patient selection was unclear, and the reference standard was similar to the one identified in the protocol as the gold standard.
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
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</thead>
<tbody>
<tr>
<td>Italy</td>
<td></td>
<td>Inclusion criteria</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>At least one negative TRUS biopsy</td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent clinical suspicion of prostate cancer</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal digital rectal examination</td>
<td>Index test measurements were taken at the same time as</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presence of high grade prostate intraepithelial neoplasia</td>
<td>the prepeat biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presence of atypical small acinar proliferation</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exclusion criteria</td>
<td>Moderate due to unclear patient selection and no apriori determination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment</td>
<td>of index test thresholds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previous prostate treatment (i.e. transurethral prostate resection)</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostatits and underwent urethral catheterisation</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Sample size</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>222 participants</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>63.9 years (7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (range) 7.6ng/ml, (0.3-46.4)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PSA density, ng/ml/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median (range) 0.11 (0.02-0.91) ng/ml/ml</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Total PSA</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>%fPSA</td>
<td></td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<td></td>
<td>Prostate health index Beckman-Coulter phi using the formula p2PSA/fPSA x square root of tPSA p2PSA,%p2PSA derived using the formula (p2PSA pg/ml/fPSA ng/ml x 1,000)x100</td>
<td>Reference standard(s) TRUS biopsy Definition for clinically significant cancer Definition was not provided</td>
<td></td>
</tr>
<tr>
<td>Lista (2015)</td>
<td>Multiparametric magnetic resonance imaging predicts the presence of prostate cancer in patients with negative prostate biopsy</td>
<td>Study type Prospective cohort study Study details Study location Spain Sources of funding FIS grant Inclusion criteria At least one negative TRUS biopsy An elevated PSA &gt;4 ng/ml</td>
<td>Patient selection Unclear risk of bias Unclear how the patients were selected. All patients underwent both trials to avoid a case-control design. The authors did not state any inappropriate exclusion criteria. Index test Unclear risk of bias It is unclear if the index test was interpreted without the knowledge of the reference standard. The thresholds were pre-specified. Reference standard Low risk of bias The reference standard was chosen by the committee and was regarded as gold standard</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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</tr>
<tr>
<td></td>
<td>66.2 (5) PSA ng/ml 11.3 (9.6) Time since last biopsy 3 - 6 months</td>
<td></td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td>Index test(s) mp-MRI</td>
<td></td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td>Reference standard(s) TRUS biopsy</td>
<td></td>
<td>The authors did not state the time lapse between the 2 tests.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All the patients received the reference standard and all patients were included</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>in the final analysis</td>
</tr>
<tr>
<td>Marks (2007)</td>
<td>PCA3 Molecular Urine Assay for Prostate Cancer in Men Undergoing</td>
<td>Study type</td>
<td>Patient selection</td>
</tr>
<tr>
<td></td>
<td>Repeat Biopsy</td>
<td>Cross-sectional study</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td></td>
<td>Study details</td>
<td></td>
<td>Consecutive men,</td>
</tr>
<tr>
<td></td>
<td>Study location Nothern American Sites</td>
<td></td>
<td>Index test</td>
</tr>
<tr>
<td></td>
<td>Study setting Not reported</td>
<td></td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td>Study dates between April 2004 and January 2006</td>
<td></td>
<td>It is unclear if the index test was interpreted without the knowledge of the</td>
</tr>
<tr>
<td></td>
<td>Sources of funding None disclosed</td>
<td></td>
<td>reference standard It is unclear how the thresholds were determined, however the</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>cutoffs are similar to other papers in the review</td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria At least one negative TRUS biopsy An elevated PSA</td>
<td></td>
<td>Reference standard</td>
</tr>
<tr>
<td></td>
<td>2.5ng/ml or greater</td>
<td></td>
<td>Low risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The reference standard was chosen by the committee and was regarded as gold</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>The authors did not state the time lapse between the 2 tests.</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria</td>
<td>None reported</td>
<td>All the patients received the reference standard and all patients were included in the final analysis</td>
</tr>
<tr>
<td></td>
<td>Sample characteristics</td>
<td>Sample size 233 participants</td>
<td>Overall risk of bias: Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD) 64 years (7)</td>
<td>Due to uncertainties surrounding patient section and time lapse between the index test and reference standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml 7.4 (4.3)ng/ml</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean prostate volume 49 (29)ml</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td>Index test(s)</td>
<td>Prostate Cancer Gene 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference standard(s)</td>
<td>Systematic TRUS biopsy</td>
<td></td>
</tr>
</tbody>
</table>
| Merola (2015) | PCA3 in prostate cancer and tumor aggressiveness detection on 407 high-risk patients: a National Cancer Institute experience | Study details Study location Italy Study dates Between November 2009 and May 2011 Inclusion criteria At least one negative TRUS biopsy An elevated PSA Suspicious DRE | Patient selection Low risk of bias 407 consecutive men with 2 or more risk factors for prostate cancer and at least one negative biopsy were included in the study. The study was not of a case control design and no inappropriate exclusions were identified Index test Unclear risk of bias The sample tests were carried prior to biopsies however, it is not clear whether the interpretations were carried out prior to reference standard test. is is unclear if the thresholds were
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Exclusion criteria</td>
<td>prespecified, however the thresholds are similar to other studies apart from threshold 5 for PCA3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate cancer diagnosis</td>
<td>Reference standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Any medication which can lower PSA levels</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
<td>The reference standard was chosen by the committee and was regarded as gold standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample size</td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>407 participants</td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD)</td>
<td>The authors did not state the time lapse between the 2 tests. All the patients received the reference standard and all patients were included in the final analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reported separately for cancer/non cancer groups cancer median 71 years (sd27) non cancer median 69 years (sd31) PSA ng/ml reported separately for cancer/non cancer groups cancer median 7.53ng/ml (sd4.88) non cancer median 7.34 ng/ml(sd5.87)</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate Cancer Gene 3</td>
<td>Due to uncertainties surrounding index tests thresholds and time lapse between the index test and reference standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total PSA</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unable to calculate 2x2 for this test</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%fPSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>unable to calculate 2x2 for this test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference standard(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saturation prostatic biopsy</td>
<td></td>
</tr>
<tr>
<td>Michielsen (1998)</td>
<td>Specificity and accuracy of TRUS-measured PSA-density and transition zone-</td>
<td>Study details</td>
<td>Patient selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study location</td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Belgium</td>
<td>no details provided - however these were individuals refereed to the department for eurological evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study dates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>between October 1996 and September 1997</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sources of funding</td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<td>-------------------</td>
</tr>
<tr>
<td>PSA in the diagnosis of prostate cancer</td>
<td>None declared</td>
<td>Index test&lt;br&gt;Unclear risk of bias&lt;br&gt;it is unclear if the index test were interpreted prior to the reference standard The threshold were based on evidence from previous studies</td>
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</tr>
<tr>
<td></td>
<td>Inclusion criteria&lt;br&gt;Serum PSA below 15ng/ml&lt;br&gt;Aged 57-83 years</td>
<td>Reference standard&lt;br&gt;Low risk of bias&lt;br&gt;The reference standard was chosen by the committee and was regarded as gold standard</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria&lt;br&gt;None reported</td>
<td>Flow and timing&lt;br&gt;Unclear risk of bias&lt;br&gt;Unclear no details provided</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sample characteristics&lt;br&gt;Sample size&lt;br&gt;59 people&lt;br&gt;Mean age (SD)&lt;br&gt;67 years (no SD)&lt;br&gt;PSA ng/ml&lt;br&gt;8.8 ng/ml (no SD)&lt;br&gt;Mean prostate volume&lt;br&gt;44 ml (no SD)</td>
<td>Overall risk of bias&lt;br&gt;Moderate&lt;br&gt;Due to the uncertainties surrounding patient selection, index test and flow and timing</td>
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<tr>
<td></td>
<td>Index test(s)&lt;br&gt;PSA density&lt;br&gt;PSA transition zone</td>
<td>Directness&lt;br&gt;Directly applicable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference standard(s)&lt;br&gt;Systematic TRUS biopsy</td>
<td></td>
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</tr>
<tr>
<td>Murray (2016)</td>
<td>Head to Head Comparison of the Chun Nomogram, Percentage Free PSA and Primary</td>
<td>Study type&lt;br&gt;Retrospective cohort study</td>
<td>Patient selection&lt;br&gt;Unclear risk of bias&lt;br&gt;Patient selection strategy was not detailed. The participants were followed up following initial negative biopsies. The exclusion criteria was appropriate and we could</td>
</tr>
<tr>
<td></td>
<td>Study details</td>
<td></td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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</tbody>
</table>
|             | Circulating Prostate Cells to Predict the Presence of Prostate Cancer at Repeat Biopsy | Chile  
Study setting  
Hospital  
Study dates  
January 2006 to December 2014  
Sources of funding  
No funding details provided | not identify inappropriate exclusions  
Index test  
Low risk of bias  
Index tests were carried out soon after biopsy. The thresholds were predetermined and were similar to those from previous studies  
Reference standard  
Low risk of bias  
All participants had the same reference standard. The reference standard matches protocol and is regarded as the "gold standard"  
Flow and timing  
Low risk of bias  
"Repeat blood samples were taken immediately prior to the second prostate biopsy for the detection of circulating prostate cells..."  
Overall risk of bias  
Low  
Directness  
Directly applicable |
|             | Prostate specific antigen adjusted for transition zone epithelial volume: the powerful predictor for | Study type  
Associated Study  
Low risk of bias  
"consecutive patients undergoing initial biopsies were enrolled.." |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td>the detection of prostate cancer on repeat biopsy</td>
<td>Clinical value of prostate specific antigen based parameters for the detection of prostate cancer on repeat biopsy: the usefulness of complexed prostate specific antigen adjusted for transition zone volume. The Journal of urology 168(3), 986-90 Cross-sectional study</td>
<td>Index test&lt;br&gt;Low risk of bias&lt;br&gt;&quot;serum specimens for determining total PSA and free Psa were obtained prior to reference standards&quot;, thresholds were set using evidence from previous studies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study details&lt;br&gt;Study location&lt;br&gt;Japan&lt;br&gt;Study setting&lt;br&gt;No details provided&lt;br&gt;Study dates&lt;br&gt;Between October 1997 and January 2000&lt;br&gt;Sources of funding&lt;br&gt;No details provided</td>
<td>Reference standard&lt;br&gt;Low risk of bias&lt;br&gt;The reference standard matched the protocol, the reference standard was carried out after the index test, however it is unclear if interpretation was blinded</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inclusion criteria&lt;br&gt;At least one negative TRUS biopsy&lt;br&gt;Persistent clinical suspicion of prostate cancer&lt;br&gt;Abnormal digital rectal examination&lt;br&gt;PSA &gt; 4ng/ml&lt;br&gt;PSA between 4 and 10.0 ng/ml</td>
<td>Flow and timing&lt;br&gt;Unclear risk of bias&lt;br&gt;The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis</td>
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<tr>
<td></td>
<td>Exclusion criteria&lt;br&gt;Prostatitis and underwent urethral catheterisation</td>
<td>Overall risk of bias&lt;br&gt;Low</td>
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<td>Directness&lt;br&gt;Directly applicable</td>
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<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<tr>
<td></td>
<td></td>
<td>Mean age (SD) 67.6 years (6.7)</td>
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<td>PSA ng/ml Mean (sd) - 7.58(1.37)</td>
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<td></td>
<td></td>
<td>PSA density, ng/ml/ml 0.208 (0.076) ng/ml/cm3</td>
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<td>Mean fPSA 0.189 (0.107)</td>
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<td></td>
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<td>Index test(s) Total PSA PSA density Free/Total PSA ratio</td>
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<td></td>
<td>Reference standard(s) TRUS biopsy</td>
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<td></td>
<td></td>
<td>Definition for clinically significant cancer Definition was not provided</td>
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Okada (2010) Community-based prostate cancer screening in Japan: Predicting factors for positive repeat biopsy

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<tr>
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<th>Retrospective cohort study</th>
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<td>Study location Japan Study setting Hospital Study dates 1995 and 2006 Sources of funding</td>
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<td></td>
<td>Patient selection Unclear risk of bias Participants were selected from a screening program and had to meet specific inclusion criteria. The authors did not mention the exact patient selection strategy - i.e. whether or not random or consecutive patients were enrolled</td>
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<td></td>
<td>Index test Unclear risk of bias it is unclear if the index tests were interpreted without the knowledge of the reference standard. The thresholds were</td>
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<td>Okegawa (2003)</td>
<td>Predictors of prostate cancer on repeat prostatic biopsy in men with serum total prostate-specific antigen between 4.1 and 10 ng/mL</td>
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### Study Characteristics

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<td>Sources of funding</td>
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**Loss to follow-up**

None mentioned

**Sources of funding**

None declared

**Inclusion criteria**

At least one negative TRUS biopsy

PSA > 4ng/ml

**Exclusion criteria**

None reported

### Quality Assurance

**The index tests thresholds were not pre-specified. It is unclear if interpretations were carried without knowledge of the reference standard**

Reference standard

Low risk of bias

The reference matched the protocol and was thought to be able to classify prostate cancer as accurately as possible by the committee

Flow and timing

Unclear risk of bias

All the participants received both the index tests and reference standard. All the participants were included in the analysis

**Overall risk of bias**

Moderate

due to lacking details on patient selection strategy

**Directness**

Directly applicable

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<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
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<td>The index tests thresholds were not pre-specified. It is unclear if interpretations were carried without knowledge of the reference standard</td>
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<td>Study dates</td>
<td>Reference standard</td>
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<td>PSA &gt; 4ng/ml</td>
<td>due to lacking details on patient selection strategy</td>
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<td>Panebianco (2011)</td>
<td>PCA3 urinary test versus 1H-MRSI and DCEMR in the detection of prostate cancer foci in patients with biochemical alterations</td>
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<td>Persistent clinical suspicion of prostate cancer</td>
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<td>Negative digital rectal examination (defined as benign)</td>
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<td>PSA between 4 and 10.0 ng/ml</td>
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<td>Exclusion criteria</td>
<td>patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment</td>
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<td>Patient selection details were not provided</td>
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<td>Index test</td>
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<td>It is unclear if the index test was carried out before the biopsy. The threshold was predetermined and was similar to that from other papers investigating the same index test</td>
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<td></td>
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<td>Flow and timing</td>
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<td>The authors did not provide the time lapse between the reference standard and index tests. All the patients received the same reference standard and all patients were included in the analysis</td>
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<td>Study Characteristics</td>
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<td>Sample characteristics</td>
<td>Due to uncertainties surrounding patient selection, blinding of results and time lapse between the index test and reference standard</td>
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<td>41 participants</td>
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<td>60.3 years (48-69 years)</td>
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<td>Mean 6.37ng/ml</td>
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<td>Index test(s)</td>
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<td></td>
<td>Prostate Cancer Gene 3</td>
<td>Directness Directly applicable</td>
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<td>Reference standard(s)</td>
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<tr>
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<td>TRUS biopsy</td>
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<tr>
<td>Pepe (2011)</td>
<td>PCA3 score vs PSA free/total accuracy in prostate cancer diagnosis at repeat saturation biopsy</td>
<td>Study type Cross-sectional study</td>
<td>Patient selection Low risk of bias &quot;...74 consecutive Caucasian men aged between 48 and 74 years..&quot;</td>
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<tr>
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<td>Reference standard Unclear risk of bias</td>
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<td>At least one negative TRUS biopsy</td>
<td>The reference standard matched protocol and regarded as the gold standard.</td>
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<td>Persistent clinical suspicion of prostate cancer</td>
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<td>Abnormal digital rectal examination</td>
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<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
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</table>
| Pepe (2012) | PCA3 score and prostate cancer diagnosis at repeated saturation biopsy. Which cut-off: 20 or 35? | Sample characteristics  
Sample size  
102 participants  
Mean age (SD)  
median age 64.5 yrs; range: 58-71 yrs  
Index test(s)  
Prostate Cancer Gene 3  
PSA ratio  
Reference standard(s)  
TRUS biopsy  
The prostate biopsy protocol included a median of 12 cores in the posterior zone of each lobe (apex, median zone and base of the gland) beginning parasagittally to reach the outer edges of the gland (lateral margins) and 2-3 cores in the transition zone | Flow and timing  
Low risk of bias  
Three-ten days before performing the SPBx, first-catch urine samples were collected following DRE (three strokes per lobe) and processed to quantify PCA3 and PSA mRNA concentrations using the Progensa PCA3 assay  
Overall risk of bias  
Moderate  
Directness  
Directly applicable |
|             |       | Study type  
Prospective cohort study  
Study details  
Study location  
Italy  
Study setting  
Hospital  
Study dates  
January 2010 to May 2011  
Sources of funding | Patient selection  
Low risk of bias  
the patients were consecutive patients meeting the protocol. the study was not of a case-control design or patients had biomarkers taken and had biopsies  
Index test  
Unclear risk of bias  
First catch samples of urine were caught following digital rectal examination, 3-10 days prior to biopsy, it is unclear if the results were interpreted prior to biopsy |
<table>
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<th>Study Characteristics</th>
<th>Quality Assurance</th>
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<td>All patients had a negative DRE</td>
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<td>An elevated PSA</td>
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<td>PSA &gt; 10ng/ml, PSA values between 4.1 - 10 or 2.6-4ng/ml with free/total PSA &lt;= 25% and &lt;= 20% respectively.</td>
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<td>Mean age (SD)</td>
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<td>median 62.5 years (no range or sd)</td>
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<td>Median PSA 8.5 ng/ml (3.7-24ng/ml)</td>
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<td>Time since last biopsy</td>
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<td>9 months</td>
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<td>Prostate Cancer Gene 3</td>
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<td>From 3-10 days prior to performing SPBx, first catch urine samples were collected following DRE, and processed to quantify PCA3 and PSA mRNA concentrations using the PROGENSA PCA3 assay</td>
<td>Reference standard</td>
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<td>The reference standard was chosen by the committee and was regarded as gold standard</td>
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<td>Flow and timing</td>
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<td>Low risk of bias</td>
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<td>First catch samples of urine were caught following digital rectal examination, 3-10 days prior to biopsy All patients received the same reference standard All patients were included in the analysis</td>
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<td>Overall risk of bias</td>
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<td>Reference standard(s) Systematic prostate biopsy performed transperineally using a tru-cut 18 gauge needle supplied with a biplanar transrectal probe under sedation and antibiotic prophylaxis</td>
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<td>Pepe (2013)</td>
<td>Prostate cancer detection rate at repeat saturation biopsy: PCPT risk calculator versus PCA3 score versus case-finding protocol</td>
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<td>Index test</td>
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<td>Study details</td>
<td>All patients underwent pca3 testing before random biopsy</td>
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<td>Single experienced radiologist analyzed the mp-MRI</td>
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<td>Study setting</td>
<td>findings. The radiologist was blinded to the pathologist</td>
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<td>Study dates</td>
<td>biopsy reports and to the biomarker results. The cutoffs</td>
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<td>Between March 2011 and April 2013</td>
<td>for PCA3 and PHI in our cohort were obtained using ROC</td>
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<td>Sources of funding</td>
<td>analysis - therefore not predetermined</td>
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<td>Reference standard</td>
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<td>At least one negative TRUS biopsy</td>
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<td>Positive Digital rectal examination</td>
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<td>Porpiglia (2014)</td>
<td>The roles of multiparametric magnetic resonance imaging, PCA3 and prostate health index which is the best predictor of prostate cancer after a negative biopsy?</td>
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<td>Italy</td>
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<td></td>
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<td>Study setting</td>
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<td>Hospital</td>
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<td></td>
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<td>Study dates</td>
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<tr>
<td></td>
<td></td>
<td>Between March 2011 and April 2013</td>
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<tr>
<td></td>
<td></td>
<td>Sources of funding</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>None declared</td>
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<tr>
<td></td>
<td></td>
<td>Inclusion criteria</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>At least one negative TRUS biopsy</td>
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<tr>
<td></td>
<td></td>
<td>Positive Digital rectal examination</td>
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<tr>
<td></td>
<td></td>
<td>Reference standard</td>
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<td></td>
<td></td>
<td>Low risk of bias</td>
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<tr>
<td></td>
<td></td>
<td>The reference standard was chosen by the committee and</td>
<td></td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<tr>
<td></td>
<td></td>
<td>Exclusion criteria</td>
<td>was regarded as gold standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>contraindications for undergoing prostate biopsy or mpMRI</td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previous prostate treatment (i.e. transurethral prostate resection)</td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients suspected to have anterioly located PCA</td>
<td>No details provided</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample size</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>170 participants</td>
<td>No details provided on patient selection and the thresholds dor biomarkers was determined by the ROC curve and not prior analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD)</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median age (iqr) 65 years (60-70)</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>mp-MRI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All patients underwent mp-MRI with a 1.5-T scanner (Signa Excite HD, GE Healthcare, Wauwatosa, Wisconsin) using a 4-channel phase array coil combined with an endorectal coil. Functional information was obtained by DWI and dynamic contrast enhanced MRI. Total PSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>%fPSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All patients underwent serum measurements of tPSA, %fPSA and PHI before repeat biopsy. The PHI analyses were performed using Hybritech Calibrated Access assays (Beckman Coulter, Brea, California)16 after processing with a Unicel Dxi 800 Immunoassay System analyzer (Beckman Coulter).</td>
<td></td>
</tr>
</tbody>
</table>
### Remzi (2003)

**Short Title**
An artificial neural network to predict the outcome of repeat prostate biopsies

<table>
<thead>
<tr>
<th>Study Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate health index</td>
</tr>
<tr>
<td>Reference standard(s)</td>
</tr>
<tr>
<td>Random Biopsy under TRUS</td>
</tr>
</tbody>
</table>

**Study Details**
- **Study type**: Cross-sectional study
- **Study location**: Austria
- **Study setting**: Not detailed
- **Study dates**: January 1997 to January 2001
- **Sources of funding**: Not declared

**Inclusion criteria**
- At least one negative TRUS biopsy
- PSA between 4 and 10.0 ng/ml

**Sample characteristics**
- **Sample size**: 820 patients
- **Mean age (SD)**: 68 years (8.5)
- **PSA ng/ml**
  - Mean: 6.4 ng/ml (1.8)
  - PSA density, ng/ml/ml: 0.156 ng/ml/ml (0.007)

**Quality Assurance**
- **Patient selection**: Low risk of bias
  - The patients were enrolled as consecutive referrals for early prostate cancer detection
- **Index test**: Unclear risk of bias
  - Thresholds were not prespecified, however were determined using the 95% sensitivity threshold
- **Reference standard**: Low risk of bias
  - The reference standard matched protocol and was deemed to be the optimal to correctly classify the target condition
- **Flow and timing**: Low risk of bias
  - All the included participants received both tests. The tests were taken within the same time scale
- **Overall risk of bias**: Low
- **Directness**: Directly applicable
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
</table>
| Remzi (2010) | Follow-up of men with an elevated PCA3 score and a negative biopsy: does an elevated PCA3 score indeed predict the presence of prostate cancer? | Study type
Associated Study
Low risk of bias
No details were provided for this study. It is linked to the Haese study. See QA for Haese |
| Time since last biopsy
6 weeks | | 
| Index test(s)
Total PSA
PSA density
PSA transition zone
Free/Total PSA ratio | 
| Reference standard(s)
TRUS biopsy | 
| Definition for clinically significant cancer
Definition was not provided | 
| Study details
Study location
Austria | |

Patient selection
Low risk of bias
No details were provided for this study. It is linked to the Haese study. See QA for Haese

Index test
Unclear risk of bias
It is unclear if the index test was interpreted without the knowledge of the reference standard. It is unclear how the thresholds were determined, however the cutoffs are similar to other papers in the review.

Reference standard
Low risk of bias
The reference standard was chosen by the committee and
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study setting</td>
<td>was regarded as gold standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital</td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study dates</td>
<td>Low risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not reportee See Haese et al</td>
<td>The authors did not state the time lapse between the 2 tests.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sources of funding</td>
<td>All the patients received the reference standard and all patients were included in the final analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None disclosed</td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inclusion criteria</td>
<td>Details of the study not fully explained, study linked to Haese 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presence of high grade prostate intraepithelial neoplasia</td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>presence of atypical small acinar proliferation</td>
<td>Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A persistently elevated or rising serum total PSA level</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Suspicious DRE</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Suspicious imaging results</td>
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<tr>
<td></td>
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<td>low %free PSA</td>
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<td>Follow up biopsy</td>
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<td>Exclusion criteria</td>
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<td>None reported</td>
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<td></td>
<td></td>
<td>Sample characteristics</td>
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<td></td>
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<td>Sample size</td>
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<tr>
<td></td>
<td></td>
<td>463 participants</td>
<td></td>
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<td></td>
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<td>Index test(s)</td>
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<tr>
<td></td>
<td></td>
<td>Prostate Cancer Gene 3</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reference standard(s)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate biopsy - not specified</td>
<td></td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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</tbody>
</table>
| Scattoni (2013) | Head-to-head comparison of prostate health index and urinary PCA3 for predicting cancer at initial or repeat biopsy | Study type  
Prospective cohort study  
Study details  
Study location  
Italy  
Study setting  
Not disclosed  
Study dates  
December 2011 and May 2012  
Sources of funding  
Beckman Coulter provided access Hybritech p2PSA reagents and the Access 2 immunoassay system. No financial support declared  
Inclusion criteria  
presence of high grade prostate intraepithelial neoplasia  
presence of atypical small acinar proliferation  
PSA between 4 and 15 ng/ml  
Exclusion criteria  
None reported  
Sample characteristics  
Sample size  
95 participants  
Mean age (SD)  
67.7 years (7.3)  
PSA ng/ml | Patient selection  
Low risk of bias  
"Consecutive cohort of European men scheduled for repeat biopsy"  
Index test  
Unclear risk of bias  
it is not clear whether the index test were interpreted without the knowledge of the reference standard results.  
Reference standard  
Low risk of bias  
The reference standard was matched the one chosen by the committee and was regarded as gold standard  
Flow and timing  
Unclear risk of bias  
The blood sample was drown at biopdt just before prostatic manipulations  
Overall risk of bias  
Moderate  
Due to uncertainties surrounding patient section and time lapse between the index test and reference standard  
Directness  
Directly applicable |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.8 ng/ml (3.9)</td>
<td>Index test(s)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Prostate Cancer Gene 3</td>
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<td></td>
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<td>%fPSA</td>
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<td></td>
<td></td>
<td>PSAV</td>
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<tr>
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<td></td>
<td>Prostate health index</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference standard(s)</td>
<td>TRUS biopsy</td>
<td></td>
</tr>
<tr>
<td>Shaida (2009)</td>
<td>The chances of subsequent cancer detection in patients with a PSA &gt; 20 ng/ml and an initial negative biopsy</td>
<td>Study type</td>
<td>Patient selection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross-sectional study</td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study details</td>
<td>No details were provided regarding patient selection strategy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study location</td>
<td></td>
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<tr>
<td></td>
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<td>UK</td>
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<tr>
<td></td>
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<td></td>
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<td>Hospital</td>
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<td></td>
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<td>Study dates between 1997 and 2002</td>
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<td></td>
<td></td>
<td>Sources of funding</td>
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</tr>
<tr>
<td></td>
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<td>None declared</td>
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<tr>
<td></td>
<td>Inclusion criteria</td>
<td>At least one negative TRUS biopsy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>An elevated PSA</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>&gt;20ng/ml</td>
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<td></td>
<td>Sample characteristics</td>
<td>Sample size</td>
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<tr>
<td></td>
<td>Study size</td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<tr>
<td></td>
<td></td>
<td>67 participants</td>
<td>frame</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
<td>Overall risk of bias Moderate Due to lack of patient strategy and index thresholds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSAV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA density</td>
<td></td>
</tr>
<tr>
<td>Shimbo (2009)</td>
<td>PSA doubling time as a predictive factor on repeat biopsy for detection of prostate cancer</td>
<td>Study type Cross-sectional study</td>
<td>Patient selection Unclear risk of bias Sampling strategy was not detailed in terms of randomisation or consecutive participants Index test Unclear risk of bias It is unclear when and how the index test was carried out.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study details</td>
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<tr>
<td></td>
<td></td>
<td>Study location Japan</td>
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<td></td>
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<td>Study setting Hospital</td>
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<td></td>
<td></td>
<td>Study dates</td>
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<td></td>
<td></td>
<td>From January 2004 to December 2005</td>
<td></td>
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<td>Sources of funding None declared</td>
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<tr>
<td></td>
<td></td>
<td>Inclusion criteria At least one negative TRUS biopsy Persistent clinical suspicion of prostate cancer An elevated PSA in a range between 4 and 20 ng/ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics Sample size 77 cases</td>
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<tr>
<td></td>
<td></td>
<td>Sample size 77 cases</td>
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</tr>
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<td></td>
<td></td>
<td>Overall risk of bias Moderate</td>
<td></td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
<td>Quality Assurance</td>
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<tr>
<td></td>
<td></td>
<td>Mean age (SD) 72.4+6.6 years</td>
<td>as a result of the uncertainties surrounding patients selection and index test results interpretation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml Initial tPSA (ng/ml) 7.2+2.7 tPSA (ng/ml) 10.2+3.8</td>
<td>Directness Directly applicable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA density, ng/ml 0.36+0.22ng/ml</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Index test(s) %fPSA</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>%Free/tPSA was calculated from dividing free PSA by tPSA</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>PSA doubling time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reference standard(s) TRUS biopsy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Definition for clinically significant cancer Definition was not provided</td>
<td></td>
</tr>
<tr>
<td>Simmons (2017)</td>
<td>The PICTURE study: diagnostic accuracy of multiparametric MRI in men requiring a repeat prostate biopsy</td>
<td>Study type Cross-sectional study</td>
<td>Patient selection Unclear risk of bias the patient selection strategy was not defined</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Study details Study location UK Study dates 11 January 2012 to 29 January 2014</td>
<td>Index test Low risk of bias The radiologist was blinded to previous TRUS-biopsy results, but given the PSA level and any other risk factors The thresholds were predetermined, the authors used PIRADS scoring system and MPMRI greater than 3 were</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sources of funding United Kingdom’s National Institute of Health Research (NIHR) UCLH/UCL Biomedical</td>
<td></td>
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</table>

Prostate cancer: diagnosis and management: evidence reviews for managing people at risk DRAFT [(Sept 2018)]
## Study Characteristics

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<th>Title</th>
<th>Research Centre.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>At least one negative TRUS biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample characteristics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sample size</td>
</tr>
<tr>
<td></td>
<td></td>
<td>249 completing both mpMRI and TTPM biopsies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age (SD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62 (7) years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.8 (4.8–9.8) ng/ml/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of previous biopsies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (1–2)</td>
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<tr>
<td></td>
<td></td>
<td>Median Prostate volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37.0 (26.8–50.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Index test(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mp-MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Using a 3 T magnetic field strength scanner with a pelvic-phased array coil. Magnetic resonance imaging sequences included T1-weighted, T2-weighted, diffusion weighting with high b-value (b¼2000) sequence and apparent diffusion coefficient map using multiple b-values (b¼0, 150, 500, 1000) and dynamic contrast enhancement with gadolinium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive MRI - PIRADS Score 3 and above</td>
</tr>
</tbody>
</table>

## Quality Assurance

<table>
<thead>
<tr>
<th></th>
<th>Low risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference standard</td>
</tr>
<tr>
<td></td>
<td>Patients were blinded to the mpMRI results to minimise non-compliance and selection bias. All biopsies were reported by one of two expert uropathologists of 420 years of experience each who were blinded to the mpMRI reports</td>
</tr>
<tr>
<td></td>
<td>Flow and timing</td>
</tr>
<tr>
<td></td>
<td>Unclear risk of bias</td>
</tr>
<tr>
<td></td>
<td>The authors did not mention any time lapses between the index test and the reference standard</td>
</tr>
<tr>
<td></td>
<td>Overall risk of bias</td>
</tr>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Directness</td>
</tr>
<tr>
<td></td>
<td>Directly applicable</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
</tr>
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</tbody>
</table>
| Tsivian (2017) | Assessing clinically significant prostate cancer: Diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology | Study type: Retrospective cohort study  
Study details:  
Study location: USA  
Study setting: No details provided  
Study dates: 3 year period beginning in 2011  
Sources of funding: None declared  
Inclusion criteria: At least one negative TRUS biopsy  
Persistent clinical suspicion of prostate cancer  
An elevated PSA  
Exclusion criteria: Prostate cancer diagnosis  
Sample characteristics: Sample size | Patient selection: Low risk of bias  
Authors state "...consecutive patients who underwent mpMRI followed by 3Dttmb"  
Index test: Low risk of bias  
The index test was carried out before the reference standard. All image interpretation was carried out on a picture archiving and communication system by a single board -certified fellowship-trained radiologist with 5 years experience Authors state "Interpretation was carried out in a blinded fashion" mpMRI scores of 3-5 were considered positive - additional analysis of scores 3 and 4-5 were also included  
Reference standard: Low risk of bias  
The reference standard matches protocol and is regarded as the "gold standard"  
Flow and timing: Low risk of bias |
<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Study Characteristics</th>
<th>Quality Assurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 patients</td>
<td>%female n/a</td>
<td>The authors did not provide the time lapse between the 2 tests. All the patients received the same reference standard and all patients were included in the analysis</td>
</tr>
<tr>
<td></td>
<td>Median age (Range) 65 (61-69) years</td>
<td>PSA ng/ml</td>
<td>Overall risk of bias Low</td>
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<tr>
<td></td>
<td>Median (IQR) - 7.1 (5.1-13.6)</td>
<td></td>
<td>Directness Directly applicable</td>
</tr>
<tr>
<td></td>
<td>Number of previous biopsies 1 - 23 participants 2/more - 27 participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Index test(s) mp-MRI</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Reference standard(s) Transperineal Template Mapping Biopsy</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Definition for clinically significant cancer Any biopsy core with Gleason score &gt;6 Also UCL1 and UCL2 definition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wu (2012)</td>
<td>Utility of PCA3 in patients undergoing repeat biopsy for prostate cancer</td>
<td>Study type Retrospective cohort study</td>
<td>Patient selection Low risk of bias Consecutive patients were enrolled in the study. The study was not of a case-control design</td>
</tr>
<tr>
<td></td>
<td>Study details</td>
<td>Study setting hospital</td>
<td>Index test Unclear risk of bias It is unclear if the biomarker results were interpreted prior to the biopsy. The thresholds used were predetermined based on past literature.</td>
</tr>
<tr>
<td></td>
<td>Study location USA</td>
<td>Study dates not declared</td>
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<tr>
<td></td>
<td>Study setting hospital</td>
<td>Sources of funding</td>
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### Study Characteristics

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<tbody>
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<td>None declared</td>
<td>Inclusion criteria</td>
<td>Reference standard</td>
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<tr>
<td>At least one negative TRUS biopsy</td>
<td>Low risk of bias</td>
<td>The reference standard was chosen by the committee and was regarded as gold standard</td>
</tr>
<tr>
<td>Persistent clinical suspicion of prostate cancer presence of high grade prostate intraepithelial neoplasia presence of atypical small acinar proliferation A persistently elevated or rising serum total PSA level Suspicious DRE</td>
<td>Flow and timing</td>
<td>The authors did not state the time lapse between the 2 tests.</td>
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<td>Exclusion criteria</td>
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<td>Sample characteristics</td>
<td>Due to uncertainties surrounding time lapse between the index test and reference standard</td>
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<td>103 participants</td>
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<tr>
<td>Mean age (SD)</td>
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<tr>
<td>63.5 years (7.4)</td>
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<tr>
<td>PSA ng/ml</td>
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<td></td>
</tr>
<tr>
<td>11.0 ng/ml (8.5)</td>
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<tr>
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<td></td>
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<tr>
<td>Prostate Cancer Gene 3</td>
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<tr>
<td>PSA density</td>
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<td></td>
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<tr>
<td>Reference standard(s)</td>
<td></td>
<td></td>
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<tr>
<td>Systematic TRUS biopsy</td>
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<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
</tr>
<tr>
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<tr>
<td>Yilmaz (2015)</td>
<td>Percentage of free prostate-specific antigen (PSA) is a useful method in deciding to perform prostate biopsy with higher core numbers in patients with low PSA cut-off values</td>
<td>Study type Retrospective cohort study Study details Study location Turkey Study setting Hospital Study dates between 2005 and 2011 Sources of funding None declared</td>
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<tr>
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<td>Inclusion criteria At least one negative TRUS biopsy tPSA between 2.5ng/ml and 10.0ng/ml Negative digital rectal examination (defined as benign)</td>
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<tr>
<td></td>
<td></td>
<td>Exclusion criteria patients with missing data Prostatic radiation therapy A total number of biopsies less than or greater than 12 patients who had undergone previous antiandrogen or 5-alfa reductase inhibitory treatment</td>
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<td></td>
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<td>Sample characteristics Sample size 605 participants Mean age (SD)</td>
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<td></td>
<td>Overall risk of bias Low</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Study Characteristics</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
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<td></td>
<td></td>
<td>median age (IQR) - 65 years (59-71)</td>
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<td>PSA ng/ml</td>
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<td></td>
<td>6.3 (5.1-7.8)ng/ml</td>
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<td>Mean prostate volume</td>
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<td>49.9cm3 (36.2-69.1)</td>
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<td>Mean fPSA</td>
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<td>1.1 (IQR - 0.8-1.5)ng/ml</td>
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<td>%fPSA</td>
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<td></td>
<td>Different cut off points - 10%, 15%, 20%, 25%</td>
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<td>Yuasa (2008)</td>
<td>Characterization of prostate cancer detected at repeat biopsy</td>
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<td></td>
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<td>None reported</td>
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<td>Sample characteristics</td>
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<td></td>
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<td>Sample size</td>
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<tr>
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<td>127 patients</td>
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<td>Mean age (SD)</td>
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<tr>
<td></td>
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<td>(Only provided in</td>
</tr>
<tr>
<td></td>
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<td>those who had cancer)</td>
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<tr>
<td></td>
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<td>72.0 (5.7) years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSA ng/ml</td>
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<tr>
<td></td>
<td></td>
<td>Only reported in those</td>
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<td>with cancer 12.6 (8.6)</td>
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<tr>
<td></td>
<td></td>
<td>ng/ml</td>
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<tr>
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<td></td>
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<td></td>
<td>Index test(s)</td>
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<td>PSAV</td>
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<td>PSA density</td>
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<td>Prostate biopsy - not</td>
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<td>specified</td>
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<td>clinically significant</td>
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<td>cancer</td>
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<tr>
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<td>Any cancer</td>
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Appendix F – Forest plots

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

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.84 [0.71, 0.92]</td>
<td>0.25 [0.17, 0.36]</td>
</tr>
<tr>
<td>Auprich 2012</td>
<td>0.92 [0.80, 0.97]</td>
<td>0.25 [0.18, 0.34]</td>
</tr>
<tr>
<td>Barbera 2012</td>
<td>0.73 [0.64, 0.80]</td>
<td>0.51 [0.46, 0.56]</td>
</tr>
<tr>
<td>Haese 2008</td>
<td>0.87 [0.76, 0.93]</td>
<td>0.28 [0.21, 0.35]</td>
</tr>
<tr>
<td>Marks 2007</td>
<td>0.98 [0.95, 0.99]</td>
<td>0.33 [0.27, 0.40]</td>
</tr>
<tr>
<td>Merola 2015</td>
<td>0.91 [0.76, 0.97]</td>
<td>0.28 [0.20, 0.38]</td>
</tr>
<tr>
<td>Pepe 2012</td>
<td>0.93 [0.77, 0.98]</td>
<td>0.21 [0.12, 0.35]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>0.93 [0.77, 0.98]</td>
<td>0.17 [0.10, 0.27]</td>
</tr>
<tr>
<td>Pepe and Aragona 2013</td>
<td>0.73 [0.65, 0.80]</td>
<td>0.51 [0.45, 0.56]</td>
</tr>
<tr>
<td>Remzi 2010</td>
<td>0.90 [0.74, 0.97]</td>
<td>0.15 [0.09, 0.26]</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>0.89 [0.82, 0.93]</td>
<td>0.30 [0.22, 0.38]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity, sensitivity:
\[ \text{Tau}^2 = 0.59, \text{Ch}^2 = 45.73, df=9 \]
(p<0.001), \( I^2 = 80.3\% \)

Heterogeneity, specificity
\[ \text{Tau}^2 = 0.33, \text{Ch}^2 = 101.25, df=9 \]
(p<0.001), \( I^2 = 91.1\% \)
1 Prostate cancer antigen 3 cut off 20 (Reference standard Biopsy)

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich 2012</td>
<td>1.13 [0.94, 1.35]</td>
<td>0.63 [0.29, 1.36]</td>
</tr>
<tr>
<td>Barbera 2012</td>
<td>1.23 [1.07, 1.41]</td>
<td>0.33 [0.12, 0.88]</td>
</tr>
<tr>
<td>Haese 2008</td>
<td>1.46 [1.27, 1.73]</td>
<td>0.54 [0.40, 0.72]</td>
</tr>
<tr>
<td>Marks 2007</td>
<td>1.20 [1.05, 1.37]</td>
<td>0.48 [0.24, 0.96]</td>
</tr>
<tr>
<td>Merola 2015</td>
<td>1.47 [1.34, 1.62]</td>
<td>0.06 [0.02, 0.16]</td>
</tr>
<tr>
<td>Pepe 2012</td>
<td>1.26 [1.06, 1.49]</td>
<td>0.34 [0.11, 1.04]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>1.18 [0.98, 1.41]</td>
<td>0.35 [0.08, 1.47]</td>
</tr>
<tr>
<td>Pepe and Aragona 2013</td>
<td>1.11 [0.96, 1.29]</td>
<td>0.43 [0.10, 1.79]</td>
</tr>
<tr>
<td>Remzi 2010</td>
<td>1.49 [1.28, 1.73]</td>
<td>0.52 [0.39, 0.71]</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>1.06 [0.91, 1.25]</td>
<td>0.65 [0.19, 2.19]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>1.26 [1.16, 1.39]</td>
<td>0.38 [0.25, 0.55]</td>
</tr>
</tbody>
</table>

Heterogeneity, positive LR:
\[ \tau^2 = 0.13, \chi^2 = 31.09, \text{df=9} \]
\( p<0.001 \), \( \text{I}^2 = 71.1\% \)

Heterogeneity, negative LR
\[ \tau^2 = 0.13, \chi^2 = 20.12, \text{df=9} \]
\( p<0.017 \), \( \text{I}^2 = 55.3\% \)
1 Prostate cancer antigen 3 cut off 35 (Reference standard Biopsy) sensitivity and specificity

![Graph showing sensitivity and specificity values for different studies.]

Heterogeneity, sensitivity: $\tau^2 = 0.74, \chi^2 = 133.93, \text{df} = 12 (p < 0.001), I^2 = 91.0\%$

Heterogeneity, specificity: $\tau^2 = 0.42, \chi^2 = 219.64, \text{df} = 12 (p < 0.001), I^2 = 94.5\%$
1 Prostate cancer antigen 3 cut off 35 (Reference standard Biopsy) positive and negative likelihood ratio

**Positive likelihood ratio**

<table>
<thead>
<tr>
<th>Study</th>
<th>LR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Aubin 2010</td>
<td>2.26</td>
<td>[1.88, 2.74]</td>
</tr>
<tr>
<td>Bussetto 2013</td>
<td>1.47</td>
<td>[1.23, 1.76]</td>
</tr>
<tr>
<td>Gittelman 2013</td>
<td>1.81</td>
<td>[1.54, 2.12]</td>
</tr>
<tr>
<td>Goode 2013</td>
<td>1.45</td>
<td>[0.77, 2.73]</td>
</tr>
<tr>
<td>Haese 2008</td>
<td>1.67</td>
<td>[1.30, 2.15]</td>
</tr>
<tr>
<td>Kaufmann 2016</td>
<td>1.09</td>
<td>[0.75, 1.58]</td>
</tr>
<tr>
<td>Marks 2007</td>
<td>2.11</td>
<td>[1.52, 2.92]</td>
</tr>
<tr>
<td>Morola 2015</td>
<td>2.37</td>
<td>[2.00, 2.80]</td>
</tr>
<tr>
<td>Pepe 2012</td>
<td>1.24</td>
<td>[0.93, 1.64]</td>
</tr>
<tr>
<td>Pepe and Aragona 2013</td>
<td>1.03</td>
<td>[0.82, 1.30]</td>
</tr>
<tr>
<td>Remzi 2010</td>
<td>1.67</td>
<td>[1.30, 2.15]</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>1.21</td>
<td>[0.94, 1.55]</td>
</tr>
<tr>
<td>Wu 2012</td>
<td>1.83</td>
<td>[1.22, 2.73]</td>
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<td>Summary estimate</td>
<td>1.64</td>
<td>[1.36, 1.99]</td>
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**Negative likelihood ratio**

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<tr>
<th>Study</th>
<th>LR</th>
<th>95% CI</th>
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<td>Aubin 2010</td>
<td>0.68</td>
<td>[0.57, 0.76]</td>
</tr>
<tr>
<td>Bussetto 2013</td>
<td>0.26</td>
<td>[0.13, 0.56]</td>
</tr>
<tr>
<td>Gittelman 2013</td>
<td>0.39</td>
<td>[0.27, 0.57]</td>
</tr>
<tr>
<td>Goode 2013</td>
<td>0.81</td>
<td>[0.51, 1.27]</td>
</tr>
<tr>
<td>Haese 2008</td>
<td>0.74</td>
<td>[0.62, 0.88]</td>
</tr>
<tr>
<td>Kaufmann 2016</td>
<td>0.82</td>
<td>[0.34, 1.95]</td>
</tr>
<tr>
<td>Marks 2007</td>
<td>0.58</td>
<td>[0.42, 0.79]</td>
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<tr>
<td>Morola 2015</td>
<td>0.09</td>
<td>[0.05, 0.16]</td>
</tr>
<tr>
<td>Pepe 2012</td>
<td>0.67</td>
<td>[0.37, 1.23]</td>
</tr>
<tr>
<td>Pepe and Aragona 2013</td>
<td>0.91</td>
<td>[0.40, 2.06]</td>
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<tr>
<td>Remzi 2010</td>
<td>0.74</td>
<td>[0.62, 0.88]</td>
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<tr>
<td>Scattoni 2013</td>
<td>0.59</td>
<td>[0.27, 1.30]</td>
</tr>
<tr>
<td>Wu 2012</td>
<td>0.51</td>
<td>[0.31, 0.85]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>0.52</td>
<td>[0.37, 0.68]</td>
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</tbody>
</table>

**Heterogeneity, Positive LR:**

\[ \text{Tau}^2 = 0.06, \text{Chi}^2 = 63.83, \text{df} = 12, (p<0.001), I^2 = 81.2\% \]

**Heterogeneity, Negative LR:**

\[ \text{Tau}^2 = 0.06, \text{Chi}^2 = 61.66, \text{df} = 12, (p<0.001), I^2 = 80.5\% \]
1 Prostate cancer antigen 3 cut off 50 (Reference standard Biopsy) sensitivity and specificity

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
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<tr>
<td>AuPric 2012</td>
<td>0.75 [0.61, 0.85]</td>
<td>0.58 [0.47, 0.68]</td>
</tr>
<tr>
<td>Barbera 2012</td>
<td>0.73 [0.59, 0.83]</td>
<td>0.42 [0.33, 0.51]</td>
</tr>
<tr>
<td>Bussetto 2013</td>
<td>0.68 [0.58, 0.78]</td>
<td>0.66 [0.56, 0.75]</td>
</tr>
<tr>
<td>Haese 2008</td>
<td>0.35 [0.27, 0.44]</td>
<td>0.82 [0.78, 0.86]</td>
</tr>
<tr>
<td>Kaufmann 2016</td>
<td>0.73 [0.52, 0.87]</td>
<td>0.63 [0.44, 0.78]</td>
</tr>
<tr>
<td>Marks 2007</td>
<td>0.47 [0.35, 0.59]</td>
<td>0.81 [0.74, 0.86]</td>
</tr>
<tr>
<td>Merola 2015</td>
<td>0.82 [0.76, 0.87]</td>
<td>0.79 [0.73, 0.84]</td>
</tr>
<tr>
<td>Panebianco 2011</td>
<td>0.79 [0.60, 0.90]</td>
<td>0.69 [0.42, 0.87]</td>
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<tr>
<td>Pepe and Aragona 2011</td>
<td>0.70 [0.52, 0.84]</td>
<td>0.43 [0.30, 0.57]</td>
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<tr>
<td>Wu 2012</td>
<td>0.38 [0.24, 0.54]</td>
<td>0.77 [0.65, 0.86]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>0.65 [0.53, 0.75]</td>
<td>0.67 [0.57, 0.76]</td>
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</tbody>
</table>

Heterogeneity, sensitivity: \( \tau^2 = 0.75, \chi^2 = 91.44, df = 9 \) \( p < 0.001 \), \( I^2 = 90.2\% \)

Heterogeneity, specificity: \( \tau^2 = 0.52, \chi^2 = 103.27, df = 9 \) \( p < 0.001 \), \( I^2 = 91.3\% \)
1 Prostate cancer antigen 3 threshold cut off 50 (Reference standard Biopsy) - Positive and Negative likelihood ratios

Positive likelihood ratio

- Auprich 2012: 1.78 [1.31, 2.41]
- Barbera 2012: 1.26 [1.00, 1.59]
- Bussetto 2013: 2.01 [1.45, 2.78]
- Haese 2008: 1.96 [1.41, 2.73]
- Kaufmann 2016: 1.98 [1.13, 3.42]
- Marks 2007: 2.42 [1.60, 3.60]
- Merola 2015: 3.95 [2.01, 5.18]
- Panebianco 2011: 2.55 [1.10, 5.90]
- Pepe and Aragona 2011: 1.22 [0.87, 1.73]
- Wu 2012: 1.66 [0.88, 3.12]
- Summary estimate: 2.01 [1.54, 2.62]

Negative likelihood ratio

- Auprich 2012: 0.43 [0.25, 0.74]
- Barbera 2012: 0.64 [0.39, 1.07]
- Bussetto 2013: 0.49 [0.34, 0.71]
- Haese 2008: 0.79 [0.69, 0.91]
- Kaufmann 2016: 0.43 [0.21, 0.91]
- Marks 2007: 0.66 [0.52, 0.85]
- Merola 2015: 0.23 [0.17, 0.31]
- Panebianco 2011: 0.31 [0.14, 0.69]
- Pepe and Aragona 2011: 0.70 [0.36, 1.36]
- Wu 2012: 0.81 [0.60, 1.07]
- Summary estimate: 0.52 [0.38, 0.68]

Heterogeneity, Positive LR:
- Tau² = 0.14, Ch² = 48.98, df = 9 (p < 0.001), I² = 81.6%

Heterogeneity, Negative LR
- Tau² = 0.17, Ch² = 63.17, df = 9 (p < 0.001), I² = 85.8%
Multiparametric MRI

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

<table>
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<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
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<tr>
<td>Boessen 2018</td>
<td>32</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>0.94 (0.79, 0.98)</td>
<td>0.44 (0.22, 0.68)</td>
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<td>Lista 2015</td>
<td>119</td>
<td>9</td>
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<td>53</td>
<td>0.93 (0.87, 0.96)</td>
<td>0.33 (0.25, 0.41)</td>
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<tr>
<td>Simmons 2017</td>
<td>26</td>
<td>2</td>
<td>76</td>
<td>46</td>
<td>0.93 (0.76, 0.98)</td>
<td>0.38 (0.30, 0.47)</td>
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<tr>
<td>Tatar 2016</td>
<td>160</td>
<td>3</td>
<td>114</td>
<td>32</td>
<td>0.97 (0.91, 0.99)</td>
<td>0.22 (0.16, 0.29)</td>
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<td>RE subtotal</td>
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<td>Within-stratum heterogeneity, sens: Tau²=0.00, Chi²=1.95, df=3 (p=0.582); R²=0.0%</td>
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<td>RE subtotal</td>
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<tr>
<td>Within-stratum heterogeneity, sens: Tau²=0.00, Chi²=1.95, df=3 (p=0.582); R²=0.0%</td>
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<td>Within-stratum heterogeneity, spec: Tau²=0.10, Chi²=9.49, df=3 (p=0.023); R²=68.4%</td>
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<td>RE meta-analysis</td>
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<td>Overall heterogeneity, sens: Tau²=0.00, Chi²=1.95, df=3 (p=0.582); R²=0.0%</td>
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<tr>
<td>Overall heterogeneity, spec: Tau²=0.10, Chi²=9.49, df=3 (p=0.023); R²=68.4%</td>
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1 Multiparametric MRI (score ≥3) positive and negative likelihood ratios Any cancer

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<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Boesen 2018</td>
<td>32</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>0.13 (0.03, 0.58)</td>
<td>1.67 (1.98, 2.60)</td>
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<tr>
<td>Lista 2015</td>
<td>119</td>
<td>9</td>
<td>108</td>
<td>53</td>
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<td>1.39 (1.23, 1.55)</td>
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<td>Simmons 2017</td>
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<td>46</td>
<td>0.19 (0.05, 0.73)</td>
<td>1.49 (1.25, 1.77)</td>
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<tr>
<td>Tahhan 2015</td>
<td>100</td>
<td>3</td>
<td>114</td>
<td>32</td>
<td>0.13 (0.04, 0.42)</td>
<td>1.24 (1.13, 1.36)</td>
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<td>0.16 (0.11, 0.30)</td>
<td>1.56 (1.23, 1.50)</td>
</tr>
<tr>
<td>Within-stratum heterogeneity, LR-: Tau^2=0.00, Chi^2=5.24, df=3 (p=0.079); I^2=0.0%</td>
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<tr>
<td>Within-stratum heterogeneity, LR+: Tau^2=0.00, Chi^2=5.24, df=3 (p=0.155); I^2=42.6%</td>
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<th>LR+ (95%CI)</th>
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<td>no data</td>
<td>0.16 (0.11, 0.30)</td>
<td>1.56 (1.23, 1.50)</td>
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<td>RE subtotal</td>
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<td>0.16 (0.11, 0.30)</td>
<td>1.56 (1.23, 1.50)</td>
</tr>
<tr>
<td>Within-stratum heterogeneity, LR-: Tau^2=0.00, Chi^2=5.24, df=3 (p=0.079); I^2=0.0%</td>
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<tr>
<td>Within-stratum heterogeneity, LR+: Tau^2=0.00, Chi^2=5.24, df=3 (p=0.155); I^2=42.6%</td>
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Overall heterogeneity, LR-: Tau^2=0.00, Chi^2=5.24, df=3 (p=0.155); I^2=42.6%
2 Multiparametric MRI (score ≥3) sensitivity and specificity - clinically significant prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
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<td>Reesen 2018</td>
<td>85</td>
<td>2</td>
<td>141</td>
<td>50</td>
<td>0.56 (0.91, 0.99)</td>
<td>0.30 (0.24, 0.37)</td>
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<tr>
<td>Simmons 2017</td>
<td>100</td>
<td>3</td>
<td>114</td>
<td>32</td>
<td>0.97 (0.91, 0.99)</td>
<td>0.22 (0.16, 0.28)</td>
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<td>Tsiklan 2016</td>
<td>25</td>
<td>0</td>
<td>15</td>
<td>9</td>
<td>0.98 (0.76, 1.00)</td>
<td>0.38 (0.21, 0.58)</td>
</tr>
<tr>
<td>RE subtotal</td>
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<td></td>
<td></td>
<td></td>
<td>0.97 (0.94, 0.99)</td>
<td>0.28 (0.21, 0.36)</td>
</tr>
<tr>
<td>Within-stratum heterogeneity, sens: Tau²=0.00, I²=0.0%</td>
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<tr>
<td>Within-stratum heterogeneity, spec: Tau²=0.05, I²=52.1%</td>
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</tbody>
</table>

| Per sector        |     |     |     |     |               |               |
| RE subtotal       |     |     |     |     | 0.97 (0.94, 0.99) | 0.28 (0.21, 0.36) |
| Within-stratum heterogeneity, sens: Tau²=0.00, I²=0.0% |     |     |     |     |               |               |
| Within-stratum heterogeneity, spec: Tau²=0.05, I²=52.1% |     |     |     |     |               |               |

Definition of clin. sig. cancer: any Gleason 7+
- Per patient: no data
- Per sector: no data

Definition of clin. sig. cancer: any cancer
- Per patient: no data
- Per sector: no data

RE meta-analysis: 0.97 (0.94, 0.99) | 0.28 (0.21, 0.36)
Overall heterogeneity, sens: Tau²=0.00, I²=0.0% | 0.99 (0.93)
Overall heterogeneity, spec: Tau²=0.05, I²=52.1% | 0.124
1. Multiparametric MRI (score ≥3) positive and negative likelihood ratio clinically significant cancer
1 Multiparametric MRI (score ≥4) sensitivity and specificity - clinically significant cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
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<tr>
<td>Boesen 2018</td>
<td>81</td>
<td>7</td>
<td>49</td>
<td>152</td>
<td>0.92 (0.84, 0.96)</td>
<td>0.76 (0.69, 0.81)</td>
</tr>
<tr>
<td>Simmons 2017</td>
<td>83</td>
<td>20</td>
<td>46</td>
<td>100</td>
<td>0.81 (0.72, 0.87)</td>
<td>0.68 (0.51, 0.75)</td>
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<td>RE subtotal</td>
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<td>0.87 (0.71, 0.95)</td>
<td>0.72 (0.65, 0.79)</td>
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Within-substratum heterogeneity, sens: Tau²=0.42, Chi²=4.84, df=1 (p=0.028); I²=79.3%
Within-substratum heterogeneity, spec: Tau²=0.03, Chi²=2.15, df=1 (p=0.142); I²=53.5%

RE meta analysis: 0.87 (0.71, 0.95) 0.72 (0.65, 0.79)
Overall heterogeneity, sens: Tau²=0.42, Chi²=4.84, df=1 (p=0.028); I²=79.3%
Overall heterogeneity, spec: Tau²=0.03, Chi²=2.15, df=1 (p=0.142); I²=53.5%
1. Multiparametric MRI (score ≥4) positive and negative likelihood ratio – clinically significant cancer

<table>
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<tr>
<th>Study</th>
<th>TP</th>
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<th>LR (95%CI)</th>
<th>LR+ (95%CI)</th>
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<tr>
<td>Boessen 2018</td>
<td>81</td>
<td>7</td>
<td>49</td>
<td>152</td>
<td>0.11 (0.05, 0.22)</td>
<td>3.78 (2.94, 4.95)</td>
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<td>2.56 (1.98, 3.31)</td>
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<td>0.18 (0.07, 0.48)</td>
<td>3.11 (2.12, 4.56)</td>
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Within-stratum heterogeneity, LR: Tau²=0.40, Chi²=5.57, df=1 (p=0.018); I²=82.0%
Within-stratum heterogeneity, LR+: Tau²=0.08, Chi²=4.51, df=1 (p=0.034); I²=77.8%

Overall heterogeneity, LR: Tau²=0.40, Chi²=5.57, df=1 (p=0.018); I²=82.0%
Overall heterogeneity, LR+: Tau²=0.08, Chi²=4.51, df=1 (p=0.034); I²=77.8%

Decreasing probability of disease given (positive or negative) result
Increasing probability of disease given (positive or negative) result
Total prostate specific antigen

2 Threshold 3.5-4.4ng/ml  Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
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<th>Sens. (95%CI)</th>
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<td>Goode 2013</td>
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<td>Remzi 2003</td>
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<td>0.95 (0.88, 0.99)</td>
<td>0.08 (0.07, 0.10)</td>
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<td>Scattoni 2003</td>
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<td>63</td>
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<td>0.30 (0.13, 0.57)</td>
<td>0.03 (0.01, 0.11)</td>
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<td>RE subtotal</td>
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<td>0.90 (0.78, 0.99)</td>
<td>0.10 (0.03, 0.27)</td>
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<td>Within-stratum heterogeneity, sens: Tau²=0.40; Chi²=4.42, df=2 (p=0.110); I²=54.7%</td>
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<tr>
<td>Within-stratum heterogeneity, spec: Tau²=0.91; Chi²=31.60, df=2 (p&lt;0.001); I²=93.7%</td>
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<td>no data</td>
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<td>0.00 (0.78, 0.96)</td>
<td>0.10 (0.03, 0.27)</td>
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<tr>
<td>Within-stratum heterogeneity, sens: Tau²=0.40; Chi²=4.42, df=2 (p=0.110); I²=54.7%</td>
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<tr>
<td>Within-stratum heterogeneity, spec: Tau²=0.91; Chi²=31.60, df=2 (p&lt;0.001); I²=93.7%</td>
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</tbody>
</table>

Definition of clin. sig. cancer: any Gleason 7+

Per patient  
no data
Per sector  
no data

Definition of clin. sig. cancer: any cancer

Per patient  
no data
Per sector  
no data

RE meta analysis  
0.90 (0.78, 0.96)  0.10 (0.03, 0.27)

Overall heterogeneity, sens: Tau²=0.40; Chi²=4.42, df=2 (p=0.110); I²=54.7%
Overall heterogeneity, spec: Tau²=0.91; Chi²=31.60, df=2 (p<0.001); I²=93.7%
1 Threshold 3.5-4.4 ng/ml Positive and Negative Likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geoda 2013</td>
<td>12.5</td>
<td>3.4</td>
<td>72</td>
<td>26</td>
<td>0.90 (0.29, 2.18)</td>
<td>1.07 (0.81, 1.42)</td>
</tr>
<tr>
<td>Ramzi 2003</td>
<td>79</td>
<td>4</td>
<td>752</td>
<td>68</td>
<td>0.58 (0.22, 1.55)</td>
<td>1.04 (0.58, 1.09)</td>
</tr>
<tr>
<td>Scantoni 2003</td>
<td>27</td>
<td>3</td>
<td>63</td>
<td>2</td>
<td>3.25 (0.57, 18.44)</td>
<td>0.53 (0.62, 1.05)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.90 (0.40, 2.02)</td>
<td>1.01 (0.34, 1.09)</td>
</tr>
</tbody>
</table>

Within-stratum heterogeneity, LR+: $\tau^2=0.00$, $sd_{	au}=2.63$, $df=2$ ($p=0.268$); $I^2=24.0\%$

Per sector
no data

Within-stratum heterogeneity, LR: $\tau^2=0.16$, $sd_{	au}=2.60$, $df=2$ ($p=0.237$); $I^2=30.6\%$

Definition of clin. sig. cancer: any Gleason 7+

| Per patient | no data |

Definition of clin. sig. cancer: any cancer

| Per patient | no data |

| Per sector | no data |

**RE meta-analysis**

<table>
<thead>
<tr>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.90 (0.40, 2.02)</td>
<td>1.01 (0.34, 1.09)</td>
</tr>
</tbody>
</table>

Overall heterogeneity, LR+: $\tau^2=0.00$, $sd_{	au}=2.63$, $df=2$ ($p=0.268$); $I^2=24.0\%$

Overall heterogeneity, LR: $\tau^2=0.16$, $sd_{	au}=2.60$, $df=2$ ($p=0.237$); $I^2=30.6\%$
1 Threshold 4.5-5.4ng/ml Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Auprich 2012</td>
<td>42</td>
<td>2</td>
<td>71</td>
<td>12</td>
<td>0.95 (0.84, 0.99)</td>
<td>0.14 (0.08, 0.24)</td>
</tr>
<tr>
<td>Okagawa 2003</td>
<td>22</td>
<td>1</td>
<td>68</td>
<td>6</td>
<td>0.96 (0.75, 0.99)</td>
<td>0.08 (0.04, 0.17)</td>
</tr>
<tr>
<td>Rema 2003</td>
<td>75</td>
<td>8</td>
<td>722</td>
<td>98</td>
<td>0.99 (0.92, 0.96)</td>
<td>0.12 (0.10, 0.14)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92 (0.86, 0.96)</td>
<td>0.12 (0.10, 0.14)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, sens: Tau^2=0.00; Chi^2=1.39, df=2 (p=0.500); I^2=0.0%
Within-substratum heterogeneity, spec: Tau^2=0.00; Chi^2=1.52, df=2 (p=0.469); I^2=0.0%
1 Threshold 4.5-5.4ng/ml Positive and Negative Likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR+ (95%CI)</th>
<th>LR- (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ausprich 2012</td>
<td>42</td>
<td>2</td>
<td>71</td>
<td>12</td>
<td>0.31 (0.07, 1.34)</td>
<td>1.12 (1.00, 1.24)</td>
</tr>
<tr>
<td>Okuyama 2003</td>
<td>22</td>
<td>1</td>
<td>66</td>
<td>6</td>
<td>0.54 (0.67, 4.23)</td>
<td>1.04 (0.53, 1.16)</td>
</tr>
<tr>
<td>Remy 2003</td>
<td>75</td>
<td>5</td>
<td>722</td>
<td>58</td>
<td>0.91 (0.41, 1.60)</td>
<td>1.03 (0.95, 1.11)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td>0.67 (0.37, 1.21)</td>
<td>1.05 (1.60, 1.11)</td>
<td>0.67 (0.37, 1.21)</td>
<td>1.05 (1.60, 1.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Within-study heterogeneity, LR: Tau²=0.00, Ch²=1.37, df=2 (p=0.504); I²=0.0%
Within-study heterogeneity, LR+: Tau²=0.00, Ch²=1.57, df=2 (p=0.458); I²=0.0%

overall heterogeneity, LR: Tau²=0.00, Ch²=1.37, df=2 (p=0.504); I²=0.0%
overall heterogeneity, LR+: Tau²=0.00, Ch²=1.57, df=2 (p=0.458); I²=0.0%

Decreasing probability of disease, given (positive or negative) result
Increasing probability of disease, given (positive or negative) result
1 Threshold 5.5 – 6.4ng/ml Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aasvech 2012</td>
<td>37</td>
<td>7</td>
<td>68</td>
<td>15</td>
<td>0.94 (0.70, 0.92)</td>
<td>0.18 (0.11, 0.28)</td>
</tr>
<tr>
<td>Chi 2011</td>
<td>21</td>
<td>5</td>
<td>73</td>
<td>113</td>
<td>0.91 (0.61, 0.92)</td>
<td>0.81 (0.54, 0.68)</td>
</tr>
<tr>
<td>Ohtani 2000</td>
<td>18</td>
<td>1</td>
<td>43</td>
<td>13</td>
<td>0.95 (0.71, 0.99)</td>
<td>0.23 (0.14, 0.36)</td>
</tr>
<tr>
<td>Scattini 2013</td>
<td>24</td>
<td>6</td>
<td>49</td>
<td>16</td>
<td>0.92 (0.62, 0.97)</td>
<td>0.25 (0.16, 0.36)</td>
</tr>
<tr>
<td>RE meta-analysis</td>
<td>0.83 (0.75, 0.89)</td>
<td>0.30 (0.13, 0.56)</td>
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</tr>
</tbody>
</table>

Within-substratum heterogeneity, sens: Tau²=0.00, Chi²=1.93, df=3 (p=0.687), I²=0.0%
Within-substratum heterogeneity, spec: Tau²=1.14, Chi²=58.22, df=3 (p=0.001), I²=94.8%
1 Threshold 5.5 – 6.4ng/ml Likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR (95%CI)</th>
<th>LR+ (95%CI)</th>
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<tbody>
<tr>
<td>Per patient</td>
<td>37</td>
<td>7</td>
<td>66</td>
<td>15</td>
<td>6.88 (6.39, 2.00)</td>
<td>1.63 (0.87, 2.12)</td>
</tr>
<tr>
<td>Chen 2011</td>
<td>21</td>
<td>5</td>
<td>73</td>
<td>113</td>
<td>6.32 (6.14, 0.70)</td>
<td>2.66 (1.55, 2.67)</td>
</tr>
<tr>
<td>Ghigashi 2005</td>
<td>18</td>
<td>4</td>
<td>43</td>
<td>9</td>
<td>6.23 (6.02, 1.02)</td>
<td>1.23 (1.03, 1.45)</td>
</tr>
<tr>
<td>Scartozzi 2013</td>
<td>24</td>
<td>6</td>
<td>49</td>
<td>16</td>
<td>6.91 (6.35, 1.67)</td>
<td>1.66 (0.85, 1.23)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
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<td></td>
<td></td>
<td>6.56 (6.31, 1.02)</td>
<td>1.27 (0.97, 1.67)</td>
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</tbody>
</table>

Within-substratum heterogeneity, LR- Tau²=0.13; Chi²=4.72, df=3 (p=0.39); I²=36.4%
Within-substratum heterogeneity, LR+ Tau²=0.05; Chi²=27.36, df=3 (p<0.001); I²=86.9%

RE meta-analysis 6.56 (6.31, 1.02) 1.27 (0.97, 1.67)
Overall heterogeneity, LR- Tau²=0.13; Chi²=4.72, df=3 (p=0.39); I²=36.4%
Overall heterogeneity, LR+ Tau²=0.05; Chi²=27.36, df=3 (p<0.001); I²=86.9%
## 1 Threshold 6.5 - 7.4ng/ml Sensitivity and Specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Por patient</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Aspinich 2012</td>
<td>33</td>
<td>11</td>
<td>58</td>
<td>25</td>
<td>0.75 (0.60, 0.86)</td>
<td>0.30 (0.21, 0.41)</td>
</tr>
<tr>
<td>Ohgashi 2005</td>
<td>16</td>
<td>3</td>
<td>34</td>
<td>22</td>
<td>0.84 (0.51, 0.95)</td>
<td>0.39 (0.27, 0.53)</td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>16</td>
<td>7</td>
<td>50</td>
<td>24</td>
<td>0.70 (0.48, 0.85)</td>
<td>0.32 (0.23, 0.44)</td>
</tr>
<tr>
<td>RE subtotal</td>
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<td></td>
<td></td>
<td></td>
<td><strong>0.75 (0.65, 0.83)</strong></td>
<td><strong>0.33 (0.27, 0.40)</strong></td>
</tr>
</tbody>
</table>

*Within-substratum heterogeneity, sens: Tau²=0.00, Ch²=1.20, df=2 (p=0.550); I²=0.0%*
*Within-substratum heterogeneity, spec: Tau²=0.00, Ch²=1.30, df=2 (p=0.523); I²=0.0%*
1 Threshold 6.5 -7.4ng/ml Likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auropsch 2012</td>
<td>33</td>
<td>11</td>
<td>58</td>
<td>25</td>
<td>0.83 (0.45, 1.52)</td>
<td>1.07 (0.86, 1.34)</td>
</tr>
<tr>
<td>Onogesi 2006</td>
<td>16</td>
<td>3</td>
<td>34</td>
<td>22</td>
<td>0.40 (0.14, 1.19)</td>
<td>1.91 (1.04, 1.65)</td>
</tr>
<tr>
<td>Olegawa 2003</td>
<td>15</td>
<td>7</td>
<td>50</td>
<td>24</td>
<td>0.54 (0.27, 1.09)</td>
<td>1.03 (0.75, 1.41)</td>
</tr>
</tbody>
</table>

RE subtotal:
- **LR-** (95%CI): 0.78 (0.51, 1.19)
- **LR+** (95%CI): 1.15 (0.96, 1.36)

Within-stratum heterogeneity, **LR-**: $\tau^2=0.00$, $\chi^2=1.73$, df=2 ($p=0.420$), $\%I^2=0.0\%$

Within-stratum heterogeneity, **LR+**: $\tau^2=0.00$, $\chi^2=2.49$, df=2 ($p=0.269$), $\%I^2=19.5\%$

RE meta-analysis:
- **LR-** (95%CI): 0.78 (0.51, 1.19)
- **LR+** (95%CI): 1.15 (0.96, 1.36)

Overall heterogeneity, **LR-**: $\tau^2=0.00$, $\chi^2=1.73$, df=2 ($p=0.420$), $\%I^2=0.0\%$

Overall heterogeneity, **LR+**: $\tau^2=0.00$, $\chi^2=2.49$, df=2 ($p=0.269$), $\%I^2=19.5\%$
Prostate specific antigen Density

2 Threshold 0.10ng/ml/ml sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>22</td>
<td>1</td>
<td>84</td>
<td>10</td>
<td>0.96 (0.75, 0.99)</td>
<td>0.14 (0.07, 0.23)</td>
</tr>
<tr>
<td>Remzi 2003</td>
<td>73</td>
<td>4</td>
<td>699</td>
<td>121</td>
<td>0.95 (0.88, 0.98)</td>
<td>0.15 (0.12, 0.17)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95 (0.89, 0.98)</td>
<td>0.15 (0.12, 0.17)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, sens: Tau^2=0.00, Chi^2=0.01, df=1 (p=0.925), I^2=0.0%
Within-substratum heterogeneity, spec: Tau^2=0.00, Chi^2=0.00, df=1 (p=0.772), I^2=0.0%
# Threshold 10ng/ml/ml positive and negative likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okazawa 2003</td>
<td>22</td>
<td>1</td>
<td>64</td>
<td>10</td>
<td>0.32 (0.84, 2.38)</td>
<td>1.11 (0.98, 1.25)</td>
</tr>
<tr>
<td>Remzi 2003</td>
<td>75</td>
<td>4</td>
<td>699</td>
<td>121</td>
<td>0.33 (0.12, 0.86)</td>
<td>1.12 (1.06, 1.18)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33 (0.14, 0.78)</td>
<td>1.11 (1.06, 1.17)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, LR-: $\tau^2=0.00$, $\chi^2=0.00$, df=1 ($p=0.999$), $I^2=0.0\%$

Within-substratum heterogeneity, LR+: $\tau^2=0.00$, $\chi^2=0.02$, df=1 ($p=0.892$), $I^2=0.0\%$

---

**RE meta-analysis**

<table>
<thead>
<tr>
<th></th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.33 (0.14, 0.78)</td>
<td>1.11 (1.06, 1.17)</td>
</tr>
</tbody>
</table>

Overall heterogeneity, LR-: $\tau^2=0.00$, $\chi^2=0.00$, df=1 ($p=0.999$), $I^2=0.0\%$

Overall heterogeneity, LR+: $\tau^2=0.00$, $\chi^2=0.02$, df=1 ($p=0.892$), $I^2=0.0\%$
1 Threshold $\geq 0.10$ng/ml sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Michielsen 1998</td>
<td>55</td>
<td>4</td>
<td>23</td>
<td>6</td>
<td>0.33 (0.83, 0.97)</td>
<td>0.21 (0.10, 0.39)</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>18</td>
<td>1</td>
<td>43</td>
<td>13</td>
<td>0.95 (0.71, 0.95)</td>
<td>0.23 (0.14, 0.36)</td>
</tr>
<tr>
<td>Remzi 2003</td>
<td>75</td>
<td>8</td>
<td>640</td>
<td>180</td>
<td>0.90 (0.82, 0.95)</td>
<td>0.22 (0.19, 0.25)</td>
</tr>
<tr>
<td><strong>RE subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.92 (0.86, 0.95)</td>
<td>0.22 (0.19, 0.25)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, sens: Tau$^2=0.00$, Chi$^2=0.00$, df=2 (p=0.741); I$^2=0.0$

Within-substratum heterogeneity, spec: Tau$^2=0.00$, Chi$^2=0.00$, df=2 (p=0.562); I$^2=0.0$

RE meta-analysis, sens: 0.92 (0.86, 0.95) 0.22 (0.19, 0.25)

Overall heterogeneity, sens: Tau$^2=0.00$, Chi$^2=0.00$, df=2 (p=0.741); I$^2=0.0$

Overall heterogeneity, spec: Tau$^2=0.00$, Chi$^2=0.08$, df=2 (p=0.962); I$^2=0.0$
## 1 Threshold ≥0.10ng/ml positive and negative likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR− (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michaelsen 1998</td>
<td>55</td>
<td>4</td>
<td>23</td>
<td>6</td>
<td>0.33 (0.10, 1.07)</td>
<td>1.18 (0.96, 1.43)</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>18</td>
<td>1</td>
<td>43</td>
<td>13</td>
<td>0.23 (0.03, 1.62)</td>
<td>1.23 (1.03, 1.48)</td>
</tr>
<tr>
<td>Remzi 2003</td>
<td>75</td>
<td>8</td>
<td>640</td>
<td>180</td>
<td>0.44 (0.22, 0.86)</td>
<td>1.16 (1.07, 1.25)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.39 (0.22, 0.86)</td>
<td>1.17 (1.05, 1.25)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, LR−: Tau²=0.00; Chisq=0.50, df=2 (p=0.781); I²=0.0%
Within-substratum heterogeneity, LR+: Tau²=0.00; Chisq=0.41, df=2 (p=0.515); I²=0.0%

---

**RE meta-analysis**

0.39 (0.22, 0.86) 1.17 (1.05, 1.25)

Overall heterogeneity, LR−: Tau²=0.00; Chisq=0.50, df=2 (p=0.781); I²=0.0%
Overall heterogeneity, LR+: Tau²=0.00; Chisq=0.41, df=2 (p=0.515); I²=0.0%

![Likelihood ratio graph](image)

- Decreasing probability of disease, given (positive or negative) result
- Increasing probability of disease, given (positive or negative) result
1. **Threshold ≥15ng/ml/ml sensitivity and specificity**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boesen 2018</td>
<td>0.83 [0.74, 0.89]</td>
<td>0.45 [0.38, 0.52]</td>
</tr>
<tr>
<td>Keetch 1996</td>
<td>0.68 [0.57, 0.77]</td>
<td>0.57 [0.51, 0.63]</td>
</tr>
<tr>
<td>Lista 2015</td>
<td>0.54 [0.36, 0.70]</td>
<td>0.61 [0.52, 0.69]</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>0.84 [0.62, 0.94]</td>
<td>0.29 [0.18, 0.41]</td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>0.74 [0.54, 0.87]</td>
<td>0.39 [0.29, 0.51]</td>
</tr>
<tr>
<td>Wu 2012</td>
<td>0.65 [0.49, 0.78]</td>
<td>0.60 [0.47, 0.71]</td>
</tr>
<tr>
<td>Chen 2011</td>
<td>0.77 [0.58, 0.89]</td>
<td>0.69 [0.62, 0.75]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>0.73 [0.64, 0.80]</td>
<td>0.52 [0.42, 0.62]</td>
</tr>
</tbody>
</table>

Overall heterogeneity, sens: $\tau^2=0.15$, $\text{Chi}^2=12.83$, $df=6$ ($p=0.046$), $I^2=53.2\%$

Overall heterogeneity, spec: $\tau^2=0.22$, $\text{Chi}^2=46.01$, $df=6$ ($p<0.001$), $I^2=87.0\%$
1. **Threshold ≥15ng/ml/cm³** Negative and likelihood ratio

- **Positive likelihood ratio**
  - Boesen 2018: 1.50 [1.28, 1.76]
  - Keech 1996: 1.58 [1.28, 1.94]
  - Lista 2015: 1.36 [0.90, 2.05]
  - Ohigashi 2005: 1.18 [0.91, 1.52]
  - Okegawa 2003: 1.22 [0.90, 1.65]
  - Wu 2012: 1.61 [1.08, 2.39]
  - Chen 2011: 2.47 [1.83, 3.33]
  - Summary estimate: 1.53 [1.31, 1.81]

- **Negative likelihood ratio**
  - Boesen 2018: 0.38 [0.23, 0.62]
  - Keech 1996: 0.56 [0.40, 0.79]
  - Lista 2015: 0.77 [0.50, 1.17]
  - Ohigashi 2005: 0.55 [0.18, 1.69]
  - Okegawa 2003: 0.67 [0.32, 1.40]
  - Wu 2012: 0.59 [0.36, 0.96]
  - Chen 2011: 0.34 [0.17, 0.68]
  - Summary estimate: 0.52 [0.42, 0.65]

---

*Overall heterogeneity, LR+:* $\tau^2=0.03; \chi^2=15.36, \text{df}=6 (p=0.012); I^2=63.3\%$

---

*Overall heterogeneity, LR+:* $\tau^2=0.01; \chi^2=6.77, \text{df}=6 (p=0.342); I^2=11.4\%$
### 1 Threshold ≥30ng/ml/cm³ sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Per patient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okada 2010</td>
<td>34</td>
<td>16</td>
<td>15</td>
<td>75</td>
<td>0.68 (0.54, 0.79)</td>
<td>0.83 (0.74, 0.90)</td>
</tr>
<tr>
<td>Yuasa 2008</td>
<td>14</td>
<td>5</td>
<td>34</td>
<td>70</td>
<td>0.61 (0.40, 0.73)</td>
<td>0.67 (0.59, 0.75)</td>
</tr>
<tr>
<td><strong>RE subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.66 (0.54, 0.76)</td>
<td>0.76 (0.57, 0.88)</td>
</tr>
</tbody>
</table>

**Within-substratum heterogeneity, sens:** $\tau^2=0.00$, $\chi^2=0.35$, $df=1$ ($p=0.552$), $I^2=0.0%$

**Within-substratum heterogeneity, spec:** $\tau^2=0.33$, $\chi^2=6.36$, $df=1$ ($p=0.049$), $I^2=84.3%$

**RE meta-analysis**

<table>
<thead>
<tr>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.66 (0.54, 0.76)</td>
<td>0.76 (0.57, 0.88)</td>
</tr>
</tbody>
</table>

**Overall heterogeneity, sens:** $\tau^2=0.00$, $\chi^2=0.35$, $df=1$ ($p=0.552$), $I^2=0.0%$

**Overall heterogeneity, spec:** $\tau^2=0.33$, $\chi^2=6.36$, $df=1$ ($p=0.012$), $I^2=84.3%$

---

Prostate cancer: diagnosis and management] evidence reviews for managing people at risk DRAFT [[Sept 2018]]
1 Threshold ≥30ng/ml/ml negative and positive likelihood ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR– (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada 2010</td>
<td>34</td>
<td>16</td>
<td>15</td>
<td>75</td>
<td>0.38 (0.25, 0.58)</td>
<td>4.08 (2.48, 6.72)</td>
</tr>
<tr>
<td>Yuasa 2008</td>
<td>14</td>
<td>9</td>
<td>34</td>
<td>70</td>
<td>0.58 (0.34, 0.99)</td>
<td>1.96 (1.21, 2.86)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.46 (0.31, 0.68)</td>
<td>2.73 (1.26, 5.88)</td>
</tr>
</tbody>
</table>

Within-stratum heterogeneity, LR–: Tau²=0.033, Ch²=1.47, df=1 (p=0.226), I²=32.0%
Within-stratum heterogeneity, LR+: Tau²=0.253, Ch²=5.46, df=1 (p=0.019), I²=81.1%

**RE meta-analysis**

0.46 (0.31, 0.68) 2.73 (1.26, 5.88)

Overall heterogeneity, LR–: Tau²=0.033, Ch²=1.47, df=1 (p=0.226), I²=32.0%
Overall heterogeneity, LR+: Tau²=0.253, Ch²=5.46, df=1 (p=0.019), I²=81.1%
Prostate specific antigen density of the transition zone

2 Threshold <0.20ng/ml/ml sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>22</td>
<td>1</td>
<td>57</td>
<td>17</td>
<td>0.96 (0.75, 0.99)</td>
<td>0.23 (0.16, 0.34)</td>
</tr>
<tr>
<td>Remzi 2003</td>
<td>79</td>
<td>4</td>
<td>645</td>
<td>175</td>
<td>0.95 (0.88, 0.98)</td>
<td>0.21 (0.19, 0.24)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95 (0.89, 0.98)</td>
<td>0.21 (0.19, 0.24)</td>
</tr>
</tbody>
</table>
| Within-substratum heterogeneity, sens: TAU²=0.00, CHI²=0.01, df=1 (p=0.925); I²=0.0%
| Within-substratum heterogeneity, spec: TAU²=0.00, CHI²=0.11, df=1 (p=0.744); I²=0.0% |
| RE meta-analysis    |     |     |     |     | 0.95 (0.88, 0.98) | 0.21 (0.19, 0.24) |
| Overall heterogeneity, sens: TAU²=0.00, CHI²=0.01, df=1 (p=0.925); I²=0.0%
| Overall heterogeneity, spec: TAU²=0.00, CHI²=0.11, df=1 (p=0.744); I²=0.0% |
1 Threshold <0.20ng/ml positive and negative likelihood ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>22</td>
<td>1</td>
<td>57</td>
<td>17</td>
<td>0.19 (0.03, 1.35)</td>
<td>1.24 (1.07, 1.45)</td>
</tr>
<tr>
<td>Remo 2003</td>
<td>76</td>
<td>4</td>
<td>646</td>
<td>175</td>
<td>0.23 (0.09, 0.58)</td>
<td>1.21 (1.14, 1.29)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.22 (0.09, 0.52)</td>
<td>1.21 (1.15, 1.28)</td>
</tr>
</tbody>
</table>

Within-substratum heterogeneity, LR-: $\tau^2=0.00$, $\chi^2=0.03$, df=1 ($p=0.874$), $I^2=0.00$
Within-substratum heterogeneity, LR+: $\tau^2=0.00$, $\chi^2=0.10$, df=1 ($p=0.756$), $I^2=0.00$

RE meta analysis

<table>
<thead>
<tr>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>decreasing</td>
</tr>
<tr>
<td>probability</td>
</tr>
<tr>
<td>of disease, given</td>
</tr>
<tr>
<td>(positive or negative) result</td>
</tr>
<tr>
<td>increasing</td>
</tr>
<tr>
<td>probability</td>
</tr>
<tr>
<td>of disease, given</td>
</tr>
<tr>
<td>(positive or negative) result</td>
</tr>
</tbody>
</table>

0.22 (0.09, 0.52)
1.21 (1.15, 1.28)

Overall heterogeneity, LR-: $\tau^2=0.00$, $\chi^2=0.03$, df=1 ($p=0.874$), $I^2=0.00$
Overall heterogeneity, LR+: $\tau^2=0.00$, $\chi^2=0.10$, df=1 ($p=0.756$), $I^2=0.00$
Prostate specific antigen velocity

2 Threshold 0.75 ng/ml/year - sensitivity and specificity

Overall heterogeneity, sens: $\tau^2=0.28; \chi^2=18.38, df=8 (p=0.005); I^2=67.4\%$

Overall heterogeneity, spec: $\tau^2=0.23; \chi^2=52.41, df=8 (p<0.001); I^2=88.8\%$
1 Threshold 0.75 ng/ml/year - Positive and Negative likelihood ratios

### Positive likelihood ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich 2012</td>
<td>1.16 [0.97, 1.40]</td>
</tr>
<tr>
<td>Ciatto 2008</td>
<td>1.34 [0.98, 1.83]</td>
</tr>
<tr>
<td>Koetch 1996</td>
<td>1.43 [1.15, 1.78]</td>
</tr>
<tr>
<td>Lista 2015</td>
<td>1.30 [1.04, 1.62]</td>
</tr>
<tr>
<td>Shaida 2009</td>
<td>2.74 [1.54, 4.88]</td>
</tr>
<tr>
<td>Yuasa 2008</td>
<td>2.14 [1.54, 2.99]</td>
</tr>
<tr>
<td>Chen 2011</td>
<td>2.17 [1.52, 3.10]</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td><strong>1.57 [1.27, 1.97]</strong></td>
</tr>
</tbody>
</table>

### Negative likelihood ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich 2012</td>
<td>0.57 [0.27, 1.23]</td>
</tr>
<tr>
<td>Ciatto 2008</td>
<td>0.81 [0.62, 1.05]</td>
</tr>
<tr>
<td>Koetch 1996</td>
<td>0.66 [0.49, 0.90]</td>
</tr>
<tr>
<td>Lista 2015</td>
<td>0.48 [0.21, 1.11]</td>
</tr>
<tr>
<td>Shaida 2009</td>
<td>0.42 [0.21, 0.83]</td>
</tr>
<tr>
<td>Yuasa 2008</td>
<td>0.34 [0.16, 0.75]</td>
</tr>
<tr>
<td>Chen 2011</td>
<td>0.50 [0.29, 0.85]</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td><strong>0.57 [0.43, 0.72]</strong></td>
</tr>
</tbody>
</table>

*Overall heterogeneity, LR+:* \( \tau^2 = 0.03, \ Chi^2 = 15.07, \ df = 6 (p = 0.020); \ I^2 = 60.2\% 

*Overall heterogeneity, LR−:* \( \tau^2 = 0.04, \ Chi^2 = 9.93, \ df = 6 (p = 0.128); \ I^2 = 39.6\% 

Prostate cancer: diagnosis and management: evidence reviews for managing people at risk DRAFT [(Sept 2018)]
%Free Prostate specific antigen

2 Threshold 10% sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazzem 2012</td>
<td>17</td>
<td>54</td>
<td>13</td>
<td>138</td>
<td>0.24 (0.15, 0.35)</td>
<td>0.91 (0.86, 0.95)</td>
</tr>
<tr>
<td>Murray 2016</td>
<td>14</td>
<td>27</td>
<td>21</td>
<td>102</td>
<td>0.34 (0.21, 0.50)</td>
<td>0.83 (0.75, 0.95)</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>27</td>
<td>3</td>
<td>96</td>
<td>9</td>
<td>0.90 (0.73, 0.97)</td>
<td>0.14 (0.07, 0.25)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.51 (0.18, 0.82)</td>
<td>0.67 (0.18, 0.95)</td>
</tr>
</tbody>
</table>

*Within-substratum heterogeneity, sens: Tau²=1.61; Chi²=25.15, df=2 (p<0.001); I²=92.0%*

*Within-substratum heterogeneity, spec: Tau²=3.73; Chi²=89.42, df=2 (p<0.001); I²=97.8%*

---

**RE meta-analysis**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.51 (0.18, 0.82)</td>
<td>0.67 (0.18, 0.95)</td>
</tr>
</tbody>
</table>

*Overall heterogeneity, sens: Tau²=1.61; Chi²=25.15, df=2 (p<0.001); I²=92.2%*

*Overall heterogeneity, spec: Tau²=3.73; Chi²=89.42, df=2 (p<0.001); I²=97.9%*
2 Threshold <10% positive and negative likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR- (95%CI)</th>
<th>LR+ (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient</td>
<td>17</td>
<td>54</td>
<td>13</td>
<td>138</td>
<td>0.83 (0.72, 0.96)</td>
<td>2.78 (1.43, 5.41)</td>
</tr>
<tr>
<td>Lazzaroni 2012</td>
<td>14</td>
<td>27</td>
<td>21</td>
<td>192</td>
<td>0.79 (0.63, 1.00)</td>
<td>2.09 (1.12, 3.56)</td>
</tr>
<tr>
<td>Murray 2016</td>
<td>27</td>
<td>3</td>
<td>56</td>
<td>9</td>
<td>0.72 (0.21, 2.48)</td>
<td>1.04 (0.50, 2.22)</td>
</tr>
<tr>
<td>Scattori 2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.82 (0.73, 0.93)</td>
<td>1.69 (0.89, 3.23)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall heterogeneity, LR- Tau²=0.00, Ch²=0.16, df=2 (p=0.929), I²=0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall heterogeneity, LR+ Tau²=0.00, Ch²=11.80, df=2 (p=0.003), I²=83.1%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE meta-analysis</td>
<td>0.82 (0.73, 0.93)</td>
<td>1.69 (0.89, 3.23)</td>
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<td></td>
<td></td>
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</tbody>
</table>
1 **Threshold 15% Sensitivity and specificity**

## Sensitivity

<table>
<thead>
<tr>
<th>Study</th>
<th>Sensitivity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lista 2015</td>
<td>0.50</td>
<td>[0.33, 0.67]</td>
</tr>
<tr>
<td>Murray 2016</td>
<td>0.83</td>
<td>[0.69, 0.91]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>0.67</td>
<td>[0.48, 0.81]</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>0.80</td>
<td>[0.63, 0.90]</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>0.22</td>
<td>[0.15, 0.30]</td>
</tr>
<tr>
<td>Ciatto 2008</td>
<td>0.54</td>
<td>[0.39, 0.68]</td>
</tr>
<tr>
<td>Morgan 1996</td>
<td>0.91</td>
<td>[0.62, 0.98]</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td>0.59</td>
<td>[0.40, 0.75]</td>
</tr>
</tbody>
</table>

## Specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>Specificity</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lista 2015</td>
<td>0.68</td>
<td>[0.59, 0.76]</td>
</tr>
<tr>
<td>Murray 2016</td>
<td>0.49</td>
<td>[0.40, 0.58]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>0.51</td>
<td>[0.37, 0.65]</td>
</tr>
<tr>
<td>Scattoni 2013</td>
<td>0.28</td>
<td>[0.18, 0.40]</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>0.92</td>
<td>[0.88, 0.94]</td>
</tr>
<tr>
<td>Ciatto 2008</td>
<td>0.73</td>
<td>[0.67, 0.79]</td>
</tr>
<tr>
<td>Morgan 1996</td>
<td>0.86</td>
<td>[0.74, 0.93]</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td>0.67</td>
<td>[0.47, 0.82]</td>
</tr>
</tbody>
</table>

**Overall heterogeneity, sens:** $\tau^2=1.35$; $\chi^2=63.71$, $df=6$ ($p<0.001$); $I^2=90.6$

**Overall heterogeneity, spec:** $\tau^2=1.06$; $\chi^2=141.90$, $df=6$ ($p<0.001$); $I^2=95.8$
1. Threshold <15% positive and negative likelihood ratio

<table>
<thead>
<tr>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liste 2015</strong></td>
<td><strong>Liste 2015</strong></td>
</tr>
<tr>
<td>1.56 [1.00, 2.46]</td>
<td>0.73 [0.50, 1.09]</td>
</tr>
<tr>
<td><strong>Murray 2016</strong></td>
<td><strong>Murray 2016</strong></td>
</tr>
<tr>
<td>1.62 [1.30, 2.02]</td>
<td>0.35 [0.17, 0.70]</td>
</tr>
<tr>
<td><strong>Pepe and Aragona 2011</strong></td>
<td><strong>Pepe and Aragona 2011</strong></td>
</tr>
<tr>
<td>1.36 [0.92, 2.02]</td>
<td>0.65 [0.36, 1.19]</td>
</tr>
<tr>
<td><strong>Scattoni 2013</strong></td>
<td><strong>Scattoni 2013</strong></td>
</tr>
<tr>
<td>1.11 [0.88, 1.40]</td>
<td>0.72 [0.32, 1.63]</td>
</tr>
<tr>
<td><strong>Yilmaz 2015</strong></td>
<td><strong>Yilmaz 2015</strong></td>
</tr>
<tr>
<td>2.84 [1.80, 4.36]</td>
<td>0.85 [0.77, 0.94]</td>
</tr>
<tr>
<td><strong>Ciatto 2008</strong></td>
<td><strong>Ciatto 2008</strong></td>
</tr>
<tr>
<td>1.99 [1.39, 2.85]</td>
<td>0.63 [0.45, 0.89]</td>
</tr>
<tr>
<td><strong>Morgan 1998</strong></td>
<td><strong>Morgan 1998</strong></td>
</tr>
<tr>
<td>6.38 [3.28, 12.41]</td>
<td>0.11 [0.02, 0.69]</td>
</tr>
<tr>
<td><strong>Summary estimate</strong></td>
<td><strong>Summary estimate</strong></td>
</tr>
<tr>
<td>1.79 [1.37, 2.38]</td>
<td>0.62 [0.48, 0.76]</td>
</tr>
</tbody>
</table>

Overall heterogeneity, LR+: $\tau^2=0.13$; $\chi^2=31.86$, df=6 ($p<0.001$); $I^2=81.2\%$

Overall heterogeneity, LR−: $\tau^2=0.05$; $\chi^2=13.84$, df=6 ($p=0.031$); $I^2=56.7\%$
2 Threshold 20% sensitivity and specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>Sens. (95%CI)</th>
<th>Spec. (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per patient:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ausprich 2012</td>
<td>37</td>
<td>7</td>
<td>49</td>
<td>34</td>
<td>9.34 (0.76, 0.92)</td>
<td>4.01 (0.31, 0.52)</td>
</tr>
<tr>
<td>Lazzenni 2012</td>
<td>39</td>
<td>32</td>
<td>66</td>
<td>85</td>
<td>9.55 (0.43, 0.66)</td>
<td>0.96 (0.48, 0.64)</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>23</td>
<td>4</td>
<td>34</td>
<td>13</td>
<td>0.86 (0.67, 0.94)</td>
<td>0.28 (0.17, 0.42)</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>47</td>
<td>68</td>
<td>76</td>
<td>252</td>
<td>0.41 (0.32, 0.50)</td>
<td>0.77 (0.72, 0.81)</td>
</tr>
<tr>
<td>RE subtotal</td>
<td>0.67 (0.45, 0.84)</td>
<td>0.52 (0.31, 0.72)</td>
<td>0.67 (0.45, 0.84)</td>
<td>0.52 (0.31, 0.72)</td>
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<td></td>
</tr>
</tbody>
</table>

Within-stratum heterogeneity, sens: Tau²=0.76; Chi²=26.75; df=3 (p<0.001); I²=69.9%
Within-stratum heterogeneity, spec: Tau²=0.76; Chi²=65.89; df=3 (p<0.001); I²=65.4%

Per sector: no data

RE subtotal | 0.67 (0.45, 0.84) | 0.52 (0.31, 0.72) | 0.67 (0.45, 0.84) | 0.52 (0.31, 0.72) |

Within-stratum heterogeneity, sens: Tau²=0.76; Chi²=26.75; df=3 (p<0.001); I²=69.9%
Within-stratum heterogeneity, spec: Tau²=0.76; Chi²=65.89; df=3 (p<0.001); I²=65.4%

---

**Definition of clin. sig. cancer: any Gleason 7+**

Per patient: no data

Per sector: no data

**Definition of clin. sig. cancer: any cancer**

Per patient: no data

Per sector: no data

**RE meta-analysis: 0.67 (0.45, 0.84) 0.52 (0.31, 0.72) 0.67 (0.45, 0.84) 0.52 (0.31, 0.72)**

Overall heterogeneity, sens: Tau²=0.76; Chi²=26.75; df=3 (p<0.001); I²=69.9%
Overall heterogeneity, spec: Tau²=0.76; Chi²=65.89; df=3 (p<0.001); I²=65.4%
1 Threshold 20% positive and negative likelihood ratios

<table>
<thead>
<tr>
<th>Study</th>
<th>TP</th>
<th>FN</th>
<th>FP</th>
<th>TN</th>
<th>LR+ (95%CI)</th>
<th>LR- (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition of clin. sig. cancer: UCL1</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Per patient</td>
<td>37</td>
<td>7</td>
<td>49</td>
<td>34</td>
<td>0.39 (0.13, 0.90)</td>
<td>1.42 (1.14, 1.78)</td>
</tr>
<tr>
<td>Lazzaroni 2012</td>
<td>39</td>
<td>32</td>
<td>66</td>
<td>85</td>
<td>0.80 (0.60, 1.07)</td>
<td>1.26 (0.95, 1.66)</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>23</td>
<td>4</td>
<td>34</td>
<td>13</td>
<td>0.54 (0.19, 1.48)</td>
<td>1.18 (0.93, 1.49)</td>
</tr>
<tr>
<td>Yilmaz 2016</td>
<td>47</td>
<td>68</td>
<td>76</td>
<td>252</td>
<td>0.77 (0.65, 0.91)</td>
<td>1.76 (1.31, 2.37)</td>
</tr>
<tr>
<td><strong>RE subtotal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.73 (0.60, 0.89)</td>
<td>1.37 (1.17, 1.62)</td>
</tr>
<tr>
<td>Within-stratum heterogeneity, LR-</td>
<td>Tau²=0.01, Ch²=3.66, df=3 (p=0.277), I²=22.2%</td>
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</tr>
<tr>
<td>Within-stratum heterogeneity, LR+</td>
<td>Tau²=0.01, Ch²=4.88, df=3 (p=0.181), I²=38.5%</td>
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<tr>
<td><strong>Per sector</strong></td>
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</tr>
<tr>
<td><strong>Definition of clin. sig. cancer: any Gleason 7+</strong></td>
<td></td>
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<td>Per patient</td>
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<tr>
<td>Per sector</td>
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<tr>
<td><strong>Definition of clin. sig. cancer: any cancer</strong></td>
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<tr>
<td>Per patient</td>
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<td>Per sector</td>
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</tr>
<tr>
<td><strong>RE meta-analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.73 (0.60, 0.89)</td>
<td>1.37 (1.17, 1.62)</td>
</tr>
<tr>
<td>Overall heterogeneity, LR-</td>
<td>Tau²=0.01, Ch²=3.66, df=3 (p=0.277), I²=22.2%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overall heterogeneity, LR+</td>
<td>Tau²=0.01, Ch²=4.88, df=3 (p=0.181), I²=38.5%</td>
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</table>
1 Threshold 25% sensitivity and specificity

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich 2012</td>
<td>0.95 [0.85, 0.99]</td>
</tr>
<tr>
<td>Lazzeri 2012</td>
<td>0.92 [0.83, 0.96]</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>0.84 [0.62, 0.94]</td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>0.83 [0.63, 0.93]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>0.96 [0.82, 0.99]</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>0.70 [0.62, 0.78]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>0.87 [0.76, 0.93]</td>
</tr>
<tr>
<td></td>
<td>0.23 [0.15, 0.33]</td>
</tr>
<tr>
<td>Lazzeri 2012</td>
<td>0.14 [0.09, 0.20]</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>0.32 [0.21, 0.45]</td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>0.51 [0.40, 0.62]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>0.15 [0.07, 0.28]</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>0.46 [0.41, 0.52]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>0.28 [0.17, 0.42]</td>
</tr>
</tbody>
</table>

Overall heterogeneity, sens: \( \tau^2 = 0.73; \ Chi^2 = 20.80, df = 5 \) (\( p < 0.001 \)); \( I^2 = 76.0\% \)

Overall heterogeneity, spec: \( \tau^2 = 0.60; \ Chi^2 = 64.72, df = 5 \) (\( p < 0.001 \)); \( I^2 = 92.3\% \)
1 Threshold 25% positive and negative likelihood ratio

<table>
<thead>
<tr>
<th></th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auprich 2012</td>
<td>1.24 [1.08, 1.42]</td>
<td>0.20 [0.05, 0.81]</td>
</tr>
<tr>
<td>Lazzeri 2012</td>
<td>1.06 [0.97, 1.17]</td>
<td>0.61 [0.26, 1.44]</td>
</tr>
<tr>
<td>Ohigashi 2005</td>
<td>1.24 [0.95, 1.62]</td>
<td>0.49 [0.16, 1.48]</td>
</tr>
<tr>
<td>Okegawa 2003</td>
<td>1.70 [1.26, 2.29]</td>
<td>0.34 [0.14, 0.85]</td>
</tr>
<tr>
<td>Pepe and Aragona 2011</td>
<td>1.13 [0.98, 1.30]</td>
<td>0.25 [0.03, 1.91]</td>
</tr>
<tr>
<td>Yilmaz 2015</td>
<td>1.31 [1.12, 1.53]</td>
<td>0.64 [0.47, 0.87]</td>
</tr>
<tr>
<td>Summary estimate</td>
<td>1.21 [1.10, 1.36]</td>
<td>0.49 [0.35, 0.66]</td>
</tr>
</tbody>
</table>

Overall heterogeneity, LR: $\tau^2=0.00$, $\chi^2=4.62$, df=5 ($p=0.463$); $I^2=0.0\%$
Overall heterogeneity, LR+: $\tau^2=0.01$, $\chi^2=12.97$, df=5 ($p=0.024$); $I^2=61.4\%$
1 Threshold 30% sensitivity and specificity

Overall heterogeneity, sens: $\tau^2=0.18; \chi^2=8.95, df=4 (p=0.062); I^2=55.3\%$

Overall heterogeneity, spec: $\tau^2=0.22; \chi^2=31.33, df=4 (p<0.001); I^2=87.2\%$
2 Threshold 30% positive and negative likelihood ratio

Overall heterogeneity, LR⁻: $\tau^2=0.05; \text{Chi}^2=5.94, df=4 (p=0.204); I^2=32.6\%$

Overall heterogeneity, LR⁺: $\tau^2=0.04; \text{Chi}^2=12.72, df=4 (p=0.013); I^2=68.5\%$
Abnormal digital rectal examination

2 Positive DRE - Sensitivity and specificity

Overall heterogeneity, sens: $\tau^2=0.46$; $\chi^2=16.14$, df=4 ($p=0.003$); $I^2=75.2\%$

Overall heterogeneity, spec: $\tau^2=0.88$; $\chi^2=30.78$, df=4 ($p<0.001$); $I^2=87.0\%$
2 Positive DRE - Positive and negative likelihood ratios

Overall heterogeneity, LR: $\tau^2=0.01$, $\chi^2=6.93$, df=4 ($p=0.139$); $I^2=42.3\%$

Overall heterogeneity, LR+: $\tau^2=0.13$, $\chi^2=6.85$, df=4 ($p=0.144$); $I^2=41.6\%$
Appendix G – GRADE tables

Prostate cancer antigen 3 urinary assay

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

### Multiparametric MRI score ≥3 - (reference standard: biopsy) analysis by person - any cancer

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 studies</td>
<td>Cross sectional</td>
<td></td>
<td>0.94 (0.91, 0.96)</td>
<td>0.32 (0.24, 0.41)</td>
<td>LR+ 1.36 (1.23, 1.50)</td>
<td>Not Serious</td>
<td>Very serious²</td>
<td>Not Serious</td>
<td>Not serious</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR- 0.18 (0.11, 0.30)</td>
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</tbody>
</table>

### Multiparametric MRI score ≥3 - (reference standard: biopsy) analysis by person - clinically significant cancer

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Studies</td>
<td>Cross sectional</td>
<td></td>
<td>0.97 (0.94, 0.99)</td>
<td>0.28 (0.21, 0.36)</td>
<td>LR+ 1.34 (1.20, 1.49)</td>
<td>Not Serious</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Low</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
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</tr>
<tr>
<td>Boesen (2018)</td>
<td>Cross Sectional</td>
<td>538</td>
<td>0.87 (0.71, 0.95)</td>
<td>0.72 (0.65, 0.79)</td>
<td>LR+ 3.11 (2.12, 4.56)</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>High</td>
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<tr>
<td>Simmons (2017)</td>
<td>Cross Sectional</td>
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<td>Not Serious</td>
<td>Not Serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Low</td>
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</tbody>
</table>

**Multiparametric MRI score ≥4 - (reference standard: biopsy) analysis by person – clinically significant cancer**

<table>
<thead>
<tr>
<th>Multiparametric MRI score 5 - (reference standard: biopsy) analysis by person – clinically significant cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>1 study Boesen (2018)</td>
</tr>
<tr>
<td>Abd Alazez (2014)</td>
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</table>

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I² was greater than 66.7%, downgraded twice
### Total prostate specific antigen

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total prostate specific antigen (reference standard: biopsy) threshold 4ng/ml</strong></td>
<td>3 studies Goode (2013) Remzi (2003), Scattoni (2003),</td>
<td>Cross-sectional 1,112</td>
<td>0.90 (0.78, 0.96)</td>
<td>0.10 (0.03, 0.27)</td>
<td>LR+ 1.01 (0.94, 1.09)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.90 (0.40, 2.02)</td>
<td>Serious¹</td>
<td>Very Serious²</td>
<td>Not serious</td>
<td>Very Serious³</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Total prostate specific antigen (reference standard: biopsy) threshold 5ng/ml</strong></td>
<td>3 studies Auprich (2012) Remzi (2003), Okegawa (2003),</td>
<td>Cross-sectional 1,000</td>
<td>0.92 (0.86, 0.96)</td>
<td>0.12 (0.10, 0.14)</td>
<td>LR+ 1.05 (1.00, 1.43)</td>
<td>Serious¹</td>
<td>Very Serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.67 (0.37, 1.21)</td>
<td>Serious¹</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Very Low</td>
</tr>
<tr>
<td><strong>Total prostate specific antigen (reference standard: biopsy) threshold 6ng/ml</strong></td>
<td>4 studies Auprich (2012) Ohigashi (2005) Scattoni (2013) Chen (2011)</td>
<td>Cross-sectional 509</td>
<td>0.83 (0.75, 0.89)</td>
<td>0.30 (0.13, 0.56)</td>
<td>LR+ 1.27 (0.97, 1.67)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.56 (0.31, 1.02)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Total prostate specific antigen (reference standard: biopsy) threshold 7ng/ml</strong></td>
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</table>

Prostate cancer: diagnosis and management: evidence reviews for managing people at risk DRAFT ([Sept 2018])
### Total prostate specific antigen (reference standard: biopsy) threshold 8.5ng/ml

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study</td>
<td>Cross-sectional</td>
<td>355</td>
<td>0.30 (0.19, 0.43)</td>
<td>0.72 (0.67, 0.77)</td>
<td>LR+1.07 (0.69, 1.66)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-0.54 (0.18, 1.62)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I² was greater than 66.7%, downgraded twice
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
5. The I² was greater than 33.3%, downgraded once

### Prostate specific antigen Density

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td>2 studies</td>
<td>Cross-sectional</td>
<td>1,000</td>
<td>0.95 (0.89, 0.98)</td>
<td>0.15 (0.12, 0.17)</td>
<td>LR+ 1.11 (1.06, 1.17)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
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<tr>
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<td></td>
<td></td>
<td>LR- 0.33 (0.14, 0.78)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
</tr>
<tr>
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<td>-------------</td>
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</tr>
<tr>
<td>Remzi (2003)</td>
<td>Cross-sectional</td>
<td>1,066</td>
<td>0.92 (0.86, 0.95)</td>
<td>0.22 (0.19, 0.25)</td>
<td>LR+ 1.17 (1.09, 1.25)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.39 (0.22, 0.68)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Low</td>
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</table>

**Prostate specific antigen density (reference standard: biopsy) threshold ≥0.10ng/ml/ml (0.10-0.14ng/ml/ml)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 studies</td>
<td>Cross-sectional</td>
<td>1,319</td>
<td>0.73 (0.64, 0.80)</td>
<td>0.52 (0.42, 0.62)</td>
<td>LR+ 1.53 (1.31, 1.81)</td>
<td>Serious¹</td>
<td>Very Serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very Low</td>
</tr>
<tr>
<td>Michielsen (1998), Ohigashi (2005), Remzi (2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.52 (0.42, 0.65)</td>
<td>Serious¹</td>
<td>Serious⁴</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

**Prostate specific antigen density (reference standard: biopsy) threshold ≥0.15ng/ml/ml (0.15-0.20ng/ml/ml)**

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies</td>
<td>Cross-sectional</td>
<td>267</td>
<td>0.66 (0.54, 0.76)</td>
<td>0.76 (0.57, 0.88)</td>
<td>LR+ 2.73 (1.26, 5.88)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Very Low</td>
</tr>
<tr>
<td>Okada (2010), Yuasa</td>
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<td></td>
<td>LR- 0.46 (0.31, 0.68)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Prostate specific antigen density (reference standard: biopsy) threshold ≥0.30ng/ml/ml (0.30-0.34ng/ml/ml)**
### Prostate specific antigen density (reference standard: biopsy) threshold 0.35ng/ml/ml

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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<tr>
<td>(2008),</td>
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</tr>
<tr>
<td>1 study</td>
<td>Cross-sectional</td>
<td>67</td>
<td>0.89 (0.66, 0.97)</td>
<td>0.52 (0.38, 0.66)</td>
<td>LR+ 1.87 (1.34, 2.61)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
<tr>
<td>Shaida (2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.20 (0.05, 0.77)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I² was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

### Prostate specific antigen velocity

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate specific antigen velocity (reference standard: biopsy) threshold ≥0.75ng/ml/year (0.75-0.80ng/ml/year)</td>
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</tr>
<tr>
<td>7 studies</td>
<td>Cross-sectional</td>
<td>1,364</td>
<td>0.69 (0.57, 0.79)</td>
<td>0.56 (0.43, 0.68)</td>
<td>LR+ 1.57 (1.27, 1.97)</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Low</td>
</tr>
<tr>
<td>Auprich (2012)</td>
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<tr>
<td>Ciatto (2008)</td>
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<td>Chen (2011)</td>
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<td>Keetch (1996)</td>
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<td>Lista (2015)</td>
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<tr>
<td>Shaida (2009)</td>
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<td></td>
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</tr>
<tr>
<td>LR- 0.57 (0.43, 0.72))</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Low</td>
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</table>
### Prostate specific antigen velocity (reference standard: biopsy) threshold 0.28ng/ml/year

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study</td>
<td>Cross-sectional</td>
<td>127</td>
<td>0.95 (0.84, 0.99)</td>
<td>0.05 (0.02, 0.12)</td>
<td>LR+ 1.00 (0.93, 1.09)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.94 (0.18, 4.95)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not Serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once

2. The I² was greater than 33.3%, downgraded once

3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

### Prostate specific antigen velocity (reference standard: biopsy) threshold 1.19ng/ml/year

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 study</td>
<td>Cross-sectional</td>
<td>127</td>
<td>0.75 (0.60, 0.86)</td>
<td>0.42 (0.32, 0.53)</td>
<td>LR+ 1.30 (1.01, 1.67)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not Serious</td>
<td>Not Serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.59 (0.34, 1.05)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not Serious</td>
<td>Serious³</td>
<td>Low</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once

2. The I² was greater than 33.3%, downgraded once

3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

### Prostate specific antigen density of the transition zone

#### Prostate specific antigen density of the transition zone (reference standard: biopsy) threshold 0.20ng/ml/ml

<table>
<thead>
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<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies</td>
<td>Cross-sectional</td>
<td>1,000</td>
<td>0.95 (0.89, 0.98)</td>
<td>0.21 (0.19, 0.24)</td>
<td>LR+ 1.21 (1.15, 1.28)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td>Remzi (2003)</td>
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<td></td>
<td></td>
<td></td>
<td>LR- 0.22 (0.09, 0.52)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Low</td>
</tr>
<tr>
<td>Okegawa (2003)</td>
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</table>
### Prostate cancer: diagnosis and management

#### Prostate specific antigen density of the transition zone (reference standard: biopsy) threshold 25 ng/ml/ml

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 studies</td>
<td>Cross-sectional</td>
<td>978</td>
<td>0.91 (0.84, 0.95)</td>
<td>0.23 (0.14, 0.35)</td>
<td>LR+ 1.21 (1.13, 1.30)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very low</td>
</tr>
<tr>
<td>Ohigashi (2005) Remzi (2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.36 (0.19, 0.67)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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

#### Prostate health index

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Study</td>
<td>Cross-sectional</td>
<td>95</td>
<td>0.90 (0.73, 0.97)</td>
<td>0.08 (0.03, 0.17)</td>
<td>LR+0.98 (0.85, 1.12)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td>Scattoni (2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 1.30 (0.33, 5.09)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious</td>
<td>Low</td>
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#### Prostate health index (reference standard: biopsy) threshold 25

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Study</td>
<td>Cross-sectional</td>
<td>222</td>
<td>0.90 (0.81, 0.95)</td>
<td>0.25 (0.19, 0.33)</td>
<td>LR+1.20 (1.07, 1.36)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td>Lazzeri (2012)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.39 (0.18, 0.83)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious</td>
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#### Prostate health index (reference standard: biopsy) threshold 30

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<thead>
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<th>Specificity (95%CI)</th>
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<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Study</td>
<td>Cross-sectional</td>
<td>222</td>
<td>0.90 (0.81, 0.95)</td>
<td>0.25 (0.19, 0.33)</td>
<td>LR+1.20 (1.07, 1.36)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
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<tr>
<td>Lazzeri (2012)</td>
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<td></td>
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<td>LR- 0.39 (0.18, 0.83)</td>
<td>Serious¹</td>
<td>N/A</td>
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<td>Serious</td>
<td>Low</td>
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#### Prostate health index (reference standard: biopsy) threshold 35

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<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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<tbody>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
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<tr>
<td>1 Study Scattoni (2003)</td>
<td>Cross-sectional</td>
<td>95</td>
<td>0.80 (0.62, 0.91)</td>
<td>0.48 (0.36, 0.60)</td>
<td>LR+ 1.53 (1.14, 2.05)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.42 (0.20, 0.90)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
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<tr>
<td>Prostate health index (reference standard: biopsy) threshold 40</td>
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<tr>
<td>1 Study Lazzeri (2012)</td>
<td>Cross-sectional</td>
<td>222</td>
<td>0.62 (0.50, 0.72)</td>
<td>0.60 (0.52, 0.67)</td>
<td>LR+ 1.53 (1.18, 2.00)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious⁴</td>
<td>Very Low</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>LR- 0.64 (0.46, 0.88)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
</tr>
<tr>
<td>Prostate health index (reference standard: biopsy) threshold 48.9</td>
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<tr>
<td>1 study Porpiglia (2014)</td>
<td>Cross-sectional</td>
<td>170</td>
<td>0.40 (0.28, 0.54)</td>
<td>0.78 (0.70, 0.85)</td>
<td>LR+ 1.83 (1.14, 2.94)</td>
<td>Serious¹</td>
<td>N/A</td>
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<td>Serious</td>
<td>Moderate</td>
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<td></td>
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<td></td>
<td></td>
<td>LR- 0.76 (0.60, 0.98)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
</tr>
<tr>
<td>Prostate health index (reference standard: biopsy) threshold 62</td>
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<tr>
<td>1 study Lazzeri (2012)</td>
<td>Cross-sectional</td>
<td>222</td>
<td>0.30 (0.20, 0.41)</td>
<td>0.91 (0.85, 0.94)</td>
<td>LR+ 3.19 (1.73, 5.90)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.78 (0.66, 0.91)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate health index (reference standard: biopsy) threshold 25</strong></td>
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</tr>
<tr>
<td>1 Study Gnanapragas (2016)</td>
<td>Cross-sectional</td>
<td>94</td>
<td>0.97 (0.79, 1.00)</td>
<td>0.11 (0.05, 0.21)</td>
<td>LR+ 1.08 (0.97, 1.21)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
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<tr>
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<td></td>
<td>LR-0.32 (0.04, 2.48)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
</tr>
<tr>
<td><strong>Prostate health index (reference standard: biopsy) threshold 30</strong></td>
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<tr>
<td>1 Study Gnanapragas (2016)</td>
<td>Cross-sectional</td>
<td>94</td>
<td>0.95 (0.82, 0.99)</td>
<td>0.26 (0.16, 0.40)</td>
<td>LR+ 1.29 (1.08, 1.54)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
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<td></td>
<td>LR-0.18 (0.04, 0.77)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
</tr>
<tr>
<td><strong>Prostate health index (reference standard: biopsy) threshold 35</strong></td>
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</tr>
<tr>
<td>1 Study Gnanapragas (2016)</td>
<td>Cross-sectional</td>
<td>94</td>
<td>0.94 (0.84, 0.98)</td>
<td>0.43 (0.29, 0.58)</td>
<td>LR+ 1.65 (1.26, 2.16)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
<td>Moderate</td>
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<td></td>
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<td></td>
<td></td>
<td>LR-0.13 (0.04, 0.43)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td><strong>Prostate health index (reference standard: biopsy) threshold 40</strong></td>
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</tr>
<tr>
<td>1 Study Gnanapragas (2016)</td>
<td>Cross-sectional</td>
<td>94</td>
<td>0.76 (0.65, 0.85)</td>
<td>0.65 (0.46, 0.81)</td>
<td>LR+ 2.21 (1.28, 3.81)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Very Serious³</td>
<td>Very Low</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>LR-0.36 (0.22, 0.60)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Serious²</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% free Prostate specific antigen (reference standard: Biopsy) threshold 10% (5-9%)</strong></td>
<td></td>
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</tr>
<tr>
<td>3 Studies Lazzeri (2012) Murray (2016), Scattoni (2003), Cross-sectional</td>
<td>481</td>
<td>0.51 (0.18, 0.82)</td>
<td>0.67 (0.18, 0.95)</td>
<td>LR+ 1.69 (0.89, 3.23)</td>
<td>Serious¹</td>
<td>Very Serious²</td>
<td>Not serious</td>
<td>Very serious</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>LR- 0.82 (0.73, 0.93)</td>
<td>Serious¹</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td><strong>% free Prostate specific antigen (reference standard: Biopsy) threshold 15% (10-14%)</strong></td>
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<tr>
<td>7 studies Ciatto (2008) Lista (2015) Morgan (1996) Murray (2016) Pepe and Aragona (2011) Scattoni (2013) Yilmaz (2015), Cross-sectional</td>
<td>1,253</td>
<td>0.59 (0.40, 0.75)</td>
<td>0.67 (0.47, 0.82)</td>
<td>LR+1.79 (1.37, 2.38)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Serious⁴</td>
<td>Very Low</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-0.62 (0.48, 0.76)</td>
<td>Serious¹</td>
<td>Serious⁵</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Low</td>
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<td><strong>% free Prostate specific antigen (reference standard: Biopsy) threshold 20% (15-19%)</strong></td>
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<tr>
<td>4 studies Cross-sectional</td>
<td>720</td>
<td>0.67 (0.45, 0.84)</td>
<td>0.52 (0.31, 0.72)</td>
<td>LR+1.37 (1.17, 1.62)</td>
<td>Serious¹</td>
<td>Very serious²</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very Low</td>
<td></td>
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<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
</tr>
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<tr>
<td>Auprich (2012), Yilmaz (2015), Lazzeri (2012), Pepe and Aragona (2011)</td>
<td>Cross Sectional</td>
<td>1,038</td>
<td>0.86 (0.76, 0.93)</td>
<td>0.28 (0.17, 0.42)</td>
<td>LR-0.73 (0.60, 0.89)</td>
<td>Serious(^1)</td>
<td>Very serious(^2)</td>
<td>Not Serious</td>
<td>Serious(^4)</td>
<td>Very Low</td>
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<tr>
<td>% free Prostate specific antigen (reference standard: Biopsy) threshold 25% (20-24%)</td>
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<tr>
<td>6 studies Auprich (2012), Lazzeri (2012), Ohigashi (2005), Pepe and Aragona (2011), Yilmaz (2015)</td>
<td>Cross Sectional</td>
<td>1,290</td>
<td>0.83 (0.72, 0.90)</td>
<td>0.28 (0.17, 0.44)</td>
<td>LR+1.21 (1.10, 1.36)</td>
<td>Serious(^1)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
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<td></td>
<td>LR-0.49 (0.35, 0.66)</td>
<td>Serious(^1)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td>% free Prostate specific antigen (reference standard: Biopsy) threshold 30% (25-29%)</td>
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</tr>
<tr>
<td>5 Studies Yilmaz (2015) Chen (2011) Haese (2008)</td>
<td>Cross Sectional</td>
<td>1,290</td>
<td>0.83 (0.72, 0.90)</td>
<td>0.28 (0.17, 0.44)</td>
<td>LR+1.16 (1.05, 1.33)</td>
<td>Serious(^1)</td>
<td>Very Serious(^3)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Very Low</td>
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<td></td>
<td></td>
<td>LR-0.63 (0.47, 0.82)</td>
<td>Serious(^1)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Serious(^4)</td>
<td>Low</td>
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</table>
## % free Prostate specific antigen (reference standard: Biopsy) threshold 35% (30-34%)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okegawa (2003) Ohigashi (2005)</td>
<td>Cross sectional</td>
<td>820</td>
<td>0.95(0.88, 0.98)</td>
<td>0.34 (0.30, 0.37)</td>
<td>LR+1.43 (1.34, 1.53)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR-0.14 (0.05, 0.38)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of studies (the study) were (was) assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I² was greater than 66.7%, downgraded twice
3. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
4. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
5. The I² was greater than 33.3%, downgraded once

## PSA doubling time

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Prostate specific antigen doubling time (reference standard: biopsy) 24 months</td>
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</tr>
<tr>
<td>No. of studies</td>
<td>Study design</td>
<td>Sample size</td>
<td>Sensitivity (95%CI)</td>
<td>Specificity (95%CI)</td>
<td>Effect size (95%CI)</td>
<td>Risk of bias</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Quality</td>
</tr>
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</tr>
<tr>
<td>1 study</td>
<td>Cross sectional</td>
<td>355</td>
<td>0.47 (0.35, 0.60)</td>
<td>0.36 (0.31, 0.42)</td>
<td>LR+ 0.74 (0.56, 0.98)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 1.47 (1.01, 1.96)</td>
<td>Serious¹</td>
<td>N/A</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Prostate specific antigen doubling time (reference standard: biopsy) 30 months**

| 1 study        | Cross sectional | 77          | 0.37(0.21, 0.56)    | 0.40(0.14, 0.41)    | LR+ 0.62 (0.36, 1.06) | Serious¹   | N/A          | Not serious | Not serious | Moderate |
|                |                |             |                     |                     | LR- 1.54 (1.01, 2.46) | Serious¹    | N/A          | Not serious | Serious²    | Low     |

**Prostate specific antigen doubling time (reference standard: biopsy) 50 months**

| 1 study        | Cross sectional | 77          | 0.30 (0.16, 0.49)   | 0.42 (0.29, 0.56)   | LR+ 0.51 (0.27, 0.96) | Serious¹   | N/A          | Not serious | Not serious | Moderate |
|                |                |             |                     |                     | LR- 1.68 (1.12, 2.52) | Serious¹    | N/A          | Not serious | Serious²    | Low     |

**Prostate specific antigen doubling time (reference standard: biopsy) 70 months**

| 1 study        | Cross sectional | 77          | 0.11 (0.04, 0.29)   | 0.42 (0.29, 0.56)   | LR+ 0.19 (0.06, 0.57) | Serious¹   | N/A          | Not serious | Not serious | Moderate |
|                |                |             |                     |                     | LR- 2.12 (1.49, 3.01) | Serious¹    | N/A          | Not serious | Serious²    | Low     |

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

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Sample size</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>Effect size (95%CI)</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 studies</td>
<td>Cross-sectional</td>
<td>0.23 (0.14, 0.35)</td>
<td>0.89 (0.80, 0.94)</td>
<td>LR+2.07 (1.38, 3.03)</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Very Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR- 0.87 (0.78, 0.93)</td>
<td>Serious¹</td>
<td>Serious²</td>
<td>Not serious</td>
<td>Serious³</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

1. Moderate risk of bias majority of study were assessed as moderate due to due to uncertainties surrounding patient section and time lapse between the index test and reference standard, downgraded once
2. The I² was greater than 33.3%, downgraded once
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
## Appendix H – Excluded studies

### Clinical studies

<table>
<thead>
<tr>
<th>Short Title</th>
<th>Title</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdalla (1998)</td>
<td>Comparison of serum prostate-specific antigen levels and PSA density in African-American, white, and Hispanic men without prostate cancer</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Abdel-Khalek (2004)</td>
<td>Is extended 11-core biopsy valuable in benign prostatic hyperplasia patients with intermediate serum prostate-specific antigen (4.1-10 ng/ml) and prior negative sextant biopsy?</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Abdi (2015)</td>
<td>Multiparametric magnetic resonance imaging-targeted biopsy for the detection of prostate cancer in patients with prior negative biopsy results</td>
<td>Study does not contain any relevant index tests Study looked mp-MRI - targeted TRUS-B</td>
</tr>
<tr>
<td>Adam (2011)</td>
<td>The role of the PCA3 assay in predicting prostate biopsy outcome in a South African setting</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Ahyai (2010)</td>
<td>The presence of prostate cancer on saturation biopsy can be accurately predicted</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Al (2008)</td>
<td>Role of repeated biopsy of the prostate in predicting disease progression in patients with prostate cancer on active surveillance</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Al-Ghazo (2005)</td>
<td>Ultrasound-guided transrectal extended prostate biopsy: a prospective study</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Allhoff (1993)</td>
<td>Efficient pathway for early detection of prostate cancer concluded from a 5-year prospective study</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Amirrasouli (2010)</td>
<td>Accurate cut-off point for free to total prostate-specific antigen ratio used to improve differentiation of prostate cancer from benign prostate hyperplasia in Iranian population</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Amsellem-Ouazana (2005)</td>
<td>Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B-value of at least 800s/mm²</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Anastasiadis</td>
<td>MRI-Guided Biopsy of the Prostate Increases Diagnostic Performance in Men with Elevated or Increasing PSA Levels after Previous Negative TRUS Biopsies</td>
<td>MRI protocol not satisfying the following criteria - dynamic constrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Andriole</td>
<td>The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Ankerst</td>
<td>Serial Percent Free Prostate Specific Antigen in Combination with Prostate Specific Antigen for Population Based Early Detection of Prostate Cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Arai</td>
<td>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</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Arsov</td>
<td>Repeat transrectal ultrasound biopsies with additional targeted cores according to results of functional prostate MRI detects high-risk prostate cancer in patients with previous negative biopsy and increased PSA - a pilot study</td>
<td>only patients with suspicious lesions went through with the biopsy</td>
</tr>
<tr>
<td>Arumainayagam</td>
<td>Multiparametric MR imaging for detection of clinically significant prostate cancer: A validation cohort study with transperineal template prostate mapping as the reference standard</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Aubin</td>
<td>Prostate cancer gene 3 score predicts prostate biopsy outcome in men receiving dutasteride for prevention of prostate cancer: Results from the REDUCE trial</td>
<td>Study not investigating prostate cancer</td>
</tr>
<tr>
<td>Ayyildiz</td>
<td>Serum proPSA as a marker for reducing repeated prostate biopsy numbers</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Aziz</td>
<td>Prostate-specific antigen and prostate volume: a meta-analysis of prostate cancer screening criteria</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Bakardzhiev</td>
<td>Repeat transrectal prostate biopsies in diagnosing prostate cancer</td>
<td>Not possible to calculate a 2x2 table from data</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Reason for exclusion</td>
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<tr>
<td>------------</td>
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</tr>
<tr>
<td>Baltaci(2003)</td>
<td>Use of percent free prostate-specific antigen density to improve the specificity for detecting prostate cancer in patients with normal rectal examinations and intermediate prostate-specific antigen levels</td>
<td>Participants were biopsy/MRI naive candidates</td>
</tr>
<tr>
<td>Basillote (2003)</td>
<td>Influence of prostate volume in the detection of prostate cancer</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Benecchi (2008)</td>
<td>A Novel Nomogram to Predict the Probability of Prostate Cancer on Repeat Biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Benecchi (2008)</td>
<td>Optimal measure of PSA kinetics to identify prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Benecchi (2011)</td>
<td>Evaluation of prostate specific antigen acceleration for prostate cancer diagnosis</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Beyersdorf (2002)</td>
<td>Patients with a history of elevated prostate-specific antigen levels and negative transrectal US-guided quadrant or sextant biopsy results: value of MR imaging</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Bhindi (2017)</td>
<td>Creation and internal validation of a biopsy avoidance prediction tool to aid in the choice of diagnostic approach in patients with prostate cancer suspicion</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Boegeman (2016)</td>
<td>The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged &lt;=65 years</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Boesen (2017)</td>
<td>A Prospective Comparison of Selective Multiparametric Magnetic Resonance Imaging Fusion-Targeted and Systematic Transrectal Ultrasound-Guided Biopsies for Detecting Prostate Cancer in Men Undergoing Repeated Biopsies</td>
<td>MRI as the index test only suspicious lesions went through to biopsy</td>
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<tr>
<td>Bokhorst (2012)</td>
<td>Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial*</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
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</tr>
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<tr>
<td>Borboroglu</td>
<td>Extensive repeat transrectal ultrasound guided prostate biopsy in patients with previous benign sextant biopsies</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Borkowetz</td>
<td>Assessment of tumour aggressiveness in tranperineal mri/ultrasound-fusion biopsy in comparison to transrectal systematic prostate biopsy</td>
<td>Conference abstract</td>
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<tr>
<td>Boulos</td>
<td>Should prostate-specific antigen or prostate-specific antigen density be used as the determining factor when deciding which prostates should undergo biopsy during prostate ultrasound</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Brown</td>
<td>Reflex PCA3 messenger ribonucleic acid testing: validation of postbiopsy urine samples and correlation with prostate biopsy findings in ~2000 patients</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Busby</td>
<td>Determining variables for repeat prostate biopsy</td>
<td>Review article but not a systematic review</td>
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<tr>
<td>Campos-</td>
<td>Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<td>Fernandes</td>
<td>Race is not a predictor of prostate cancer detection on repeat prostate biopsy</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Catalona</td>
<td>Serum free prostate specific antigen and prostate specific antigen density measurements for predicting cancer in men with prior negative prostatic biopsies</td>
<td>Not possible to calculate a 2x2 table from data presented in the study only sensitivity figures and cutoffs provided</td>
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<tr>
<td>Celhay</td>
<td>Fluctuating prostate-specific antigen levels in patients with initial negative biopsy: should we be reassured?</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Chang</td>
<td>The Influence of Serum Prostate-Specific Antigen on the Accuracy of Magnetic Resonance Imaging Targeted Biopsy versus Saturation Biopsy in Patients with Previous Negative Biopsy</td>
<td>Not a relevant study design (diagnostic test accuracy) Case control design</td>
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<tr>
<td>Cheikh</td>
<td>Evaluation of T2-weighted and dynamic contrast-enhanced MRI in localizing prostate cancer before repeat biopsy</td>
<td>Biopsy naive participants</td>
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<td>Chen</td>
<td>Age-Specific Cutoff Value for the Application of Percent Free Prostate-Specific Antigen (PSA) in Chinese</td>
<td>Biopsy naive participants</td>
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<tr>
<td>Short Title</td>
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<tr>
<td></td>
<td>Men with Serum PSA Levels of 4.0-10.0 ng/ml</td>
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<tr>
<td>Ciatto</td>
<td>Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, PSA, PSA density and free-to-total PSA ratio in a population-based screening setting</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>(2001)</td>
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<tr>
<td>Ciatto</td>
<td>Predictors of random sextant biopsy outcome in screened men with PSA &gt; 4 ng/mL and a negative sextant biopsy at previous screening. Experience in a population-based screening program in Florence</td>
<td>Not possible to calculate a 2x2 table from data presented in the study Participants were biopsy /MRI naive candidates</td>
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<td>(2004)</td>
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<tr>
<td>Ciatto</td>
<td>Free to total PSA ratio is not a reliable predictor of prostate biopsy outcome</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>(2004)</td>
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<td>Cirillo</td>
<td>Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B-value of at least 800s/mm²</td>
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<td>(2008)</td>
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<tr>
<td>Collins</td>
<td>Free prostate-specific antigen ‘in the field’: a useful adjunct to standard clinical practice</td>
<td>Biopsy naive participants</td>
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<td>(1999)</td>
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<tr>
<td>Comet-Batlle</td>
<td>The value of endorectal MRI in the early diagnosis of prostate cancer</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
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<tr>
<td>(2003)</td>
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<tr>
<td>Cookson</td>
<td>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</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<td>(1995)</td>
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<tr>
<td>Costa</td>
<td>Diagnosis of relevant prostate cancer using supplementary cores from magnetic resonance imaging-prompted areas following multiple failed biopsies</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B-value of at least 800s/mm²</td>
</tr>
<tr>
<td>(2013)</td>
<td></td>
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<tr>
<td>Costa</td>
<td>An initial negative round of targeted biopsies in men with highly suspicious multiparametric magnetic resonance findings does not exclude clinically significant prostate cancer-Preliminary experience</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>(2017)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford</td>
<td>Diagnostic performance of PCA3 to detect prostate cancer in men with increased prostate specific antigen: A prospective study of 1,962 cases</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>(2012)</td>
<td></td>
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</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Reason for exclusion</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Dason (2016)</td>
<td>Transurethral Resection of the Prostate Biopsy of Suspected Anterior Prostate Cancers Identified by Multiparametric Magnetic Resonance Imaging: A Pilot Study of a Novel Technique</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B value of at least 800s/mm²</td>
</tr>
<tr>
<td>De La Taille (2011)</td>
<td>Clinical evaluation of the PCA3 assay in guiding initial biopsy decisions</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>De Luca (2012)</td>
<td>Histological chronic prostatitis and high-grade prostate intra-epithelial neoplasia do not influence urinary prostate cancer gene 3 score</td>
<td>Study not investigating prostate cancer Histological chronic prostatitis and high-grade prostate intra-epithelial neoplasia</td>
</tr>
<tr>
<td>De Luca (2014)</td>
<td>Comparison of prostate cancer gene 3 score, prostate health index and percentage free prostate-specific antigen for differentiating histological inflammation from prostate cancer and other non-neoplastic alterations of the prostate at initial biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>De Luca (2015)</td>
<td>Prostate health index and prostate cancer gene 3 score but not percent-free Prostate Specific Antigen have a predictive role in differentiating histological prostatitis from PCa and other nonneoplastic lesions (BPH and HG-PIN) at repeat biopsy</td>
<td>Not investigating prostate cancer</td>
</tr>
<tr>
<td>De Luca (2015)</td>
<td>Pathological patterns of prostate biopsy in men with fluctuations of prostate cancer gene 3 score: a preliminary report</td>
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</tr>
<tr>
<td>De Visschere (2016)</td>
<td>What kind of prostate cancers do we miss on multiparametric magnetic resonance imaging?</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Deliktas (2017)</td>
<td>What should be the prostate specific antigen threshold for prostate biopsy?</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Deliveliotis (2002)</td>
<td>Biopsies of the transitional zone of the prostate: Should it be done on a routine basis, when and why?</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Deras (2008)</td>
<td>PCA3: a molecular urine assay for predicting prostate biopsy outcome</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Dincel (1999)</td>
<td>Prospective evaluation of prostate specific antigen (PSA), PSA density, free-to-total PSA ratio and a new formula (prostate malignancy index)</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with...</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
<td>Reason for exclusion</td>
</tr>
<tr>
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<td>------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>for detecting prostate cancer and preventing negative biopsies in patients with normal rectal examinations and intermediate PSA levels</td>
<td>no stratification</td>
</tr>
<tr>
<td>Djavan (1998)</td>
<td>Prostate specific antigen density of the transition zone for early detection of prostate cancer</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Djavan (1999)</td>
<td>Combination and multivariate analysis of PSA-based parameters for prostate cancer prediction</td>
<td>Participants prostate cancer/prostate biopsy history unclear/unknown</td>
</tr>
<tr>
<td>Djavan (1999)</td>
<td>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</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Djavan (1999)</td>
<td>Total and transition zone prostate volume and age: how do they affect the utility of PSA-based diagnostic parameters for early prostate cancer detection?</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Djavan (2000)</td>
<td>Optimal predictors of prostate cancer on repeat prostate biopsy: a prospective study of 1,051 men</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Djavan (2001)</td>
<td>Pathological features of prostate cancer detected on initial and repeat prostate biopsy: results of the prospective European Prostate Cancer Detection study</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Djavan (2002)</td>
<td>Complexed prostate-specific antigen, complexed prostate-specific antigen density of total and transition zone, complexed/total prostate-specific antigen ratio, free-to-total prostate-specific antigen ratio, density of total and transition zone prostate-specific antigen: results of the prospective multicenter European trial</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Djavan (2005)</td>
<td>Are repeat biopsies required in men with PSA levels &lt; or =4 ng/ml? A Multiinstitutional Prospective European Study</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Druskin (2017)</td>
<td>Prostate mri prior to radical prostatectomy: Effects on nerve sparing and pathological margin status</td>
<td>Not a relevant study design (diagnostic test accuracy)</td>
</tr>
<tr>
<td>Durand (2011)</td>
<td>What information can a PCA3 urine test provide in the diagnosis and treatment of prostate cancer?</td>
<td>Review article but not a systematic review</td>
</tr>
<tr>
<td>Durkan (1999)</td>
<td>Elevated serum prostate specific antigen levels in conjunction with an</td>
<td>Not possible to calculate a 2x2 table from data</td>
</tr>
<tr>
<td>Short Title</td>
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<tr>
<td></td>
<td>initial prostatic biopsy negative for carcinoma: who should undergo a repeat biopsy?</td>
<td>presented in the study</td>
</tr>
<tr>
<td>Durmus (2013)</td>
<td>MRI-guided biopsy of the prostate: Correlation between the cancer detection rate and the number of previous negative TRUS biopsies</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Dwivedi (2012)</td>
<td>A positive magnetic resonance spectroscopic imaging with negative initial biopsy may predict future detection of prostate cancer</td>
<td>Not possible to calculate a 2x2 table from data presented in the study Not a relevant study design (diagnostic test accuracy)</td>
</tr>
<tr>
<td>Eggener (2005)</td>
<td>Predictors of subsequent prostate cancer in men with a prostate specific antigen of 2.6 to 4.0 ng/ml and an initially negative biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>el-Galley (1995)</td>
<td>Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Elshafei (2013)</td>
<td>The utility of PSA velocity in prediction of prostate cancer and high grade cancer after an initially negative prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Feneley (1995)</td>
<td>Post-operative serial prostate-specific antigen and transrectal ultrasound for staging incidental carcinoma of the prostate</td>
<td>Study population already have prostate cancer</td>
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<tr>
<td>Ferro (2012)</td>
<td>Predicting prostate biopsy outcome: Prostate health index (phi) and prostate cancer antigen 3 (PCA3) are useful biomarkers</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Fiamegos (2016)</td>
<td>Serum testosterone as a biomarker for second prostatic biopsy in men with negative first biopsy for prostatic cancer and PSA&gt;4ng/mL, or with PIN biopsy result</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Filella (2014)</td>
<td>The influence of prostate volume in prostate health index performance in patients with total PSA lower than 10 mug/L</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Filella (2014)</td>
<td>Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer</td>
<td>Study population already have prostate cancer mixed population some participants had a diagnosis of cancer</td>
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<tr>
<td>Fleshner (1997)</td>
<td>Prevalence and predictors of a positive repeat transrectal ultrasound guided needle biopsy of the prostate</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
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<tr>
<td>Foo (2013)</td>
<td>The detection rate of prostate cancer using Prostate Specific Antigen (PSA) and Digital Rectal Examination (DRE) in Sabah</td>
<td>Unable to source article</td>
</tr>
<tr>
<td>Freedland (2003)</td>
<td>Comparison of preoperative prostate specific antigen density and prostate specific antigen for predicting recurrence after radical prostatectomy: results from the search database</td>
<td>Study population already have prostate cancer</td>
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<tr>
<td>Friedl (2017)</td>
<td>Prostate-specific Antigen Parameters and Prostate Health Index Enhance Prostate Cancer Prediction With the In-bore 3-T Magnetic Resonance Imaging-guided Transrectal Targeted Prostate Biopsy After Negative 12-Core Biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Fujita (2011)</td>
<td>Prostatic inflammation detected in initial biopsy specimens and urinary Pyuria are predictors of negative repeat prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Galasso (2010)</td>
<td>PCA3: A new tool to diagnose prostate cancer (PCa) and a guidance in biopsy decisions. Preliminary report of the UrOP study</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Ganie (2013)</td>
<td>Endorectal coil MRI and MR-spectroscopic imaging in patients with elevated serum prostate specific antigen with negative trus transrectal ultrasound guided biopsy</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td>Gann (2010)</td>
<td>Risk factors for prostate cancer detection after a negative biopsy: A novel multivariable longitudinal approach</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Garcia-Cruz (2012)</td>
<td>Low testosterone level predicts prostate cancer in re-biopsy in patients with high grade prostatic intraepithelial neoplasia</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Gerstenbluth (2002)</td>
<td>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?</td>
<td>only a subset of study population ended up having a repeat biopsy, and of these 2x2 tables could not be calculated</td>
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<tr>
<td>Giulianielli (2011)</td>
<td>Saturation biopsy technique increase the capacity to diagnose adenocarcinoma of prostate in</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
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<tr>
<td>patients with PSA &lt; 10 ng/ml, after a first negative biopsy</td>
<td>tests</td>
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<tr>
<td>The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant prostate cancers in a repeat biopsy population</td>
<td>Study population already have prostate cancer Some participants had a previous diagnosis of prostate cancer</td>
<td></td>
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<tr>
<td>Use of PCA3 in detecting prostate cancer in initial and repeat prostate biopsy patients</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Budget Impact Model for the Use of PCA3 Urine Testing in Prostate Cancer Screening</td>
<td>Health economics paper</td>
<td></td>
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<tr>
<td>Comparison between PSA density, free PSA percentage and PSA density in the transition zone in the detection of prostate cancer in patients with serum PSA between 4 and 10 ng/mL</td>
<td>Reference standard in study does not match that specified in protocol</td>
<td></td>
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<tr>
<td>Diagnostic accuracy of magnetic resonance imaging (MRI) prostate imaging reporting and data system (PI-RADS) scoring in a transperineal prostate biopsy setting</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification and also people on active surveillance</td>
<td></td>
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<tr>
<td>Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Value of prostate multiparametric magnetic resonance imaging for predicting biopsy results in first or repeat biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Role of magnetic resonance imaging before initial biopsy: Comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection</td>
<td>Biopsy naive participants</td>
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<tr>
<td>Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy</td>
<td>Duplicate reference</td>
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<td>Hansen (2017)</td>
<td>Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Hara (2006)</td>
<td>Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Haroun (2011)</td>
<td>Utility of free prostate specific antigen serum level and its related parameters in the diagnosis of prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Hayek (1999)</td>
<td>The necessity of a second prostate biopsy cannot be predicted by PSA or PSA derivatives (density or free:total ratio) in men with prior negative prostatic biopsies</td>
<td>only a subset of study population ended up having a repeat biopsy, and of these 2x2 tables could not be calculated</td>
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<tr>
<td>Heldwein (2011)</td>
<td>Antibiotics and observation have a similar impact on asymptomatic patients with a raised PSA</td>
<td>Reference standard in study does not match that specified in protocol</td>
</tr>
<tr>
<td>Henderson (2010)</td>
<td>The role of PCA3 testing in patients with a raised prostate-specific antigen level after Greenlight photoselective vaporization of the prostate</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Hessels (2009)</td>
<td>The use of PCA3 in the diagnosis of prostate cancer</td>
<td>Review article but not a systematic review</td>
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<tr>
<td>Heyns (2001)</td>
<td>Serum prostate-specific antigen as surrogate for the histological diagnosis of prostate cancer</td>
<td>Unable to source article</td>
</tr>
<tr>
<td>Hoeks (2012)</td>
<td>Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B-value of at least 800s/mm²</td>
</tr>
<tr>
<td>Hoffmann (2017)</td>
<td>Diagnostic Performance of Multiparametric Magnetic Resonance Imaging and Fusion Targeted Biopsy to Detect Significant Prostate Cancer</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Hong (2004)</td>
<td>Impact of prior biopsy scheme on pathologic features of cancers detected on repeat biopsies</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Horninger (1998)</td>
<td>Improvement of specificity in PSA-based screening by using PSA-transition zone density and percent</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
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<tr>
<td>Igerc (2008)</td>
<td>The value of 18F-choline PET/CT in patients with elevated PSA-level and negative prostate needle biopsy for localisation of prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Irani (2005)</td>
<td>Urinary/serum prostate-specific antigen ratio: comparison with free/total serum prostate-specific antigen ratio in improving prostate cancer detection</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Issa (2006)</td>
<td>The value of digital rectal examination as a predictor of prostate cancer diagnosis among United States Veterans referred for prostate biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Itatani (2014)</td>
<td>Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Ito (2002)</td>
<td>The diagnostic accuracy of the age-adjusted and prostate volume-adjusted biopsy method in males with prostate specific antigen levels of 4.1-10.0 ng/mL</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Jang (2015)</td>
<td>Repeat targeted prostate biopsy under guidance of multiparametric MRI-correlated real-time contrast-enhanced ultrasound for patients with previous negative biopsy and elevated prostate-specific antigen: A prospective study</td>
<td>Reference standard in study does not match that specified in protocol</td>
</tr>
<tr>
<td>Janjua (2002)</td>
<td>The predictive value of percent free PSA using a Chiron assay in patients with a PSA of 4-10 ng/ml and a previous negative prostatic biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Javali (2014)</td>
<td>Magnetic resonance spectroscopy imaging-directed transrectal ultrasound biopsy increases prostate cancer detection in men with prostate-specific antigen between 4-10 ng/mL and normal digital rectal examination</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Jeong (2008)</td>
<td>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</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
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<tr>
<td>Jimenez (2017)</td>
<td>Role of 18F-Choline PET/CT in guiding biopsy in patients with risen PSA levels and previous negative biopsy for prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Jimenez (2017)</td>
<td>Role of 18F-Choline PET/CT in guiding biopsy in patients with risen PSA levels and previous negative biopsy for prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Johnston (2016)</td>
<td>INNOVATE: A prospective cohort study combining serum and urinary biomarkers with novel diffusion-weighted magnetic resonance imaging for the prediction and characterization of prostate cancer</td>
<td>Study does not contain any relevant index tests&lt;br&gt;Reference standard in study does not match that specified in protocol&lt;br&gt;Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Jue (2017)</td>
<td>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</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Karademir (2013)</td>
<td>Prostate volumes derived from MRI and volume-adjusted serum prostate-specific antigen: Correlation with Gleason score of prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Kato (2016)</td>
<td>Analysis of repeated 24-core saturation prostate biopsy: Inverse association between asymptomatic histological inflammation and prostate cancer detection</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Kaufmann (2015)</td>
<td>Direct comparison of targeted MRI-guided biopsy with systematic transrectal ultrasound-guided biopsy in patients with previous negative prostate biopsies</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, B-value of at least 800s/mm2</td>
</tr>
<tr>
<td>Keetch (1994)</td>
<td>Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Keetch (1995)</td>
<td>Prostatic transition zone biopsies in men with previous negative biopsies and persistently elevated serum prostate specific antigen values</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Kefi (2005)</td>
<td>Predictive value of the international prostate symptom score for positive prostate needle biopsy in the low-intermediate prostate-specific antigen range</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<td>Short Title</td>
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<td>Kesch (2017)</td>
<td>Multicentre comparison of target and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy</td>
<td>Conference abstract</td>
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<td>Khan (2003)</td>
<td>Can prostate specific antigen derivatives and pathological parameters predict significant change in expectant management criteria for prostate cancer?</td>
<td>Study population already have prostate cancer</td>
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<tr>
<td>Khang (2012)</td>
<td>Differences in postoperative pathological outcomes between prostate cancers diagnosed at initial and repeat biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Kim (2012)</td>
<td>The Prostate Cancer Detection Rate on the Second Prostate Biopsy according to Prostate-Specific Antigen Trend</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Kim (2014)</td>
<td>Association between obesity, prostate-specific antigen level and prostate-specific antigen density in men with a negative prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Kitagawa (2015)</td>
<td>Simple Risk Stratification to Detect Prostate Cancer with High Gleason Score in Repeat Biopsies in a Population Screening Follow-up Study</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Koca (2011)</td>
<td>Significance of atypical small acinar proliferation and high-grade prostatic intraepithelial neoplasia in prostate biopsy</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Kosarek (2018)</td>
<td>Initial series of magnetic resonance imaging (MRI)-fusion targeted prostate biopsy using the first transperineal targeted platform available in the USA</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Kravchick (2009)</td>
<td>7 to 10 years' follow-up of 573 patients with elevated prostate-specific antigen (&gt;4 ng/mL) or/and suspected rectal examination: biopsies protocol and follow-up guides</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Kroenig (2016)</td>
<td>Diagnostic Accuracy of Robot-Guided, Software Based Transperineal MRI/TRUS Fusion Biopsy of the Prostate in a High Risk Population of Previously Biopsy Negative Men</td>
<td>Study does not contain any relevant index tests</td>
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<td>Kubota (2008)</td>
<td>The potential role of prebiopsy magnetic resonance imaging combined with prostate-specific</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Kumar (2009)</td>
<td>Correction of prostate-specific antigen velocity for variation may improve prediction of cancer following prostate repeat biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Lai (2016)</td>
<td>Cognitive MRI-TRUS fusion-targeted prostate biopsy according to PI-RADS classification in patients with prior negative systematic biopsy results</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Langer (1996)</td>
<td>Strategy for repeat biopsy of patients with prostatic intraepithelial neoplasia detected by prostate needle biopsy</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Lawrentschuk (2009)</td>
<td>The role of magnetic resonance imaging in targeting prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels</td>
<td>Not a peer-reviewed publication</td>
</tr>
<tr>
<td>Lazzeri (2013)</td>
<td>Serum isoform [2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: A multicentric European study</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Lazzeri (2016)</td>
<td>Clinical performance of prostate health index in men with tPSA&gt;10ng/ml: Results from a multicentric European study</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Lee (1992)</td>
<td>Predicted prostate specific antigen results using transrectal ultrasound gland volume. Differentiation of benign prostatic hyperplasia and prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Lee (2011)</td>
<td>Using a saturation biopsy scheme increases cancer detection during repeat biopsy in men with high-grade prostatic intra-epithelial neoplasia</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Lee (2011)</td>
<td>Percentage of free prostate-specific antigen: implications in modern extended scheme prostate biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Lee (2011)</td>
<td>Utility of percent free prostate-specific antigen in repeat prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<td>Lee (2012)</td>
<td>Magnetic resonance imaging targeted biopsy in men with previously negative prostate biopsy results</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Lee (2016)</td>
<td>Visually estimated MRI targeted prostate biopsy could improve the detection of significant prostate cancer in patients with a PSA level &lt;10 ng/mL</td>
<td>Biopsy naive participants</td>
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<tr>
<td>Lee (2017)</td>
<td>Indications for a second prostate biopsy in patients suspected with prostate cancer after an initial negative prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Letran (1998)</td>
<td>The effect of prostate volume on the yield of needle biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Letran (1998)</td>
<td>Repeat ultrasound guided prostate needle biopsy: use of free-to-total prostate specific antigen ratio in predicting prostatic carcinoma</td>
<td>Study comparing 2 methods of measuring PSA Dianon and Hybritech</td>
</tr>
<tr>
<td>Li (2014)</td>
<td>Potential benefit of transrectal saturation prostate biopsy as an initial biopsy strategy: Decreased likelihood of finding significant cancer on future biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Lian (2017)</td>
<td>Assessment of free-hand transperineal targeted prostate biopsy using multiparametric magnetic resonance imaging-transrectal ultrasound fusion in Chinese men with prior negative biopsy and elevated prostate-specific antigen</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Liu (2014)</td>
<td>Role of PSA-related variables in improving positive ratio of biopsy of prostate cancer within serum PSA gray zone</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Lopez-Corona (2003)</td>
<td>A nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Lu (2017)</td>
<td>Negative Multimodal Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically Significant Prostate Cancer on 12-Core Template Prostate Biopsy</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Lughezzani (2014)</td>
<td>Multicenter European external validation of a prostate health index-based nomogram for predicting prostate cancer at extended biopsy</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Luo (2014)</td>
<td>The PCA3 test for guiding repeat biopsy of prostate cancer and its cut-off score: A systematic review and meta-analysis</td>
<td>Systematic review</td>
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<tr>
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<tr>
<td>Lynn (2000)</td>
<td>Comparative analysis of the role of prostate specific antigen parameters in clinical practice</td>
<td>Participants prostate cancer/prostate biopsy history unclear/unknown</td>
</tr>
<tr>
<td>Matsui (2004)</td>
<td>The use of artificial neural network analysis to improve the predictive accuracy of prostate biopsy in the Japanese population</td>
<td>Study does not contain any relevant index tests. Reference standard in study does not match that specified in protocol</td>
</tr>
<tr>
<td>McMahon (2009)</td>
<td>Dynamic contrast-enhanced MR imaging in the evaluation of patients with prostate cancer</td>
<td>Review article but not a systematic review</td>
</tr>
<tr>
<td>Mearini (2014)</td>
<td>Evaluation of prostate-specific antigen isoform p2PSA and its derivatives, %p2PSA, prostate health index and prostate dimension-adjusted related index in the detection of prostate cancer at first biopsy: An exploratory, prospective study</td>
<td>Participants were biopsy/MRI naive candidates</td>
</tr>
<tr>
<td>Men (2001)</td>
<td>Detection of prostatic carcinoma: the role of TRUS, TRUS guided biopsy, digital rectal examination, PSA and PSA density</td>
<td>Participants were biopsy/MRI naive candidates</td>
</tr>
<tr>
<td>Mendhiratta (2015)</td>
<td>Prebiopsy MRI and MRI-ultrasound Fusion-targeted Prostate Biopsy in Men with Previous Negative Biopsies: Impact on Repeat Biopsy Strategies</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Merdan (2015)</td>
<td>Assessment of long-term outcomes associated with urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion at repeat biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Mian (2002)</td>
<td>Predictors of cancer in repeat extended multisite prostate biopsy in men with previous negative extended multisite biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Moore (2013)</td>
<td>Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review</td>
<td>Participants were biopsy/MRI naive candidates</td>
</tr>
<tr>
<td>Moreira (2012)</td>
<td>Association of prostate-specific antigen doubling time and cancer in men undergoing repeat prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Moreira (2014)</td>
<td>Baseline prostate inflammation is associated with a reduced risk of prostate cancer in men undergoing repeat prostate biopsy: Results from the REDUCE study</td>
<td>Not a relevant study design (diagnostic test accuracy). Randomised control trial with half the participants receiving medication that</td>
</tr>
<tr>
<td>Short Title</td>
<td>Title</td>
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<tr>
<td>Morgan</td>
<td>Prospective use of free PSA to avoid repeat prostate biopsies in men with elevated total PSA</td>
<td>reduces prostate specific antigen</td>
</tr>
<tr>
<td>Morgan</td>
<td>Prospective use of free prostate-specific antigen to avoid repeat prostate biopsies in men with elevated total prostate-specific antigen</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Morote</td>
<td>Comparison of percent free prostate specific antigen and prostate specific antigen density as methods to enhance prostate specific antigen specificity in early prostate cancer detection in men with normal rectal examination and prostate specific antigen between 4.1 and 10 ng./ml</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Moul</td>
<td>Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Moussa</td>
<td>Development and validation of a nomogram for predicting a positive repeat prostate biopsy in patients with a previous negative biopsy session in the era of extended prostate sampling</td>
<td>Validation study</td>
</tr>
<tr>
<td>Murphy</td>
<td>MRI-directed cognitive fusion-guided biopsy of the anterior prostate tumors</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Na</td>
<td>Prostate health index significantly reduced unnecessary prostate biopsies in patients with PSA 2-10 ng/mL and PSA &gt;10 ng/mL: Results from a Multicenter Study in China</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Nafie</td>
<td>Transperineal template prostate biopsies in men with raised PSA despite two previous sets of negative TRUS-guided prostate biopsies</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Naya</td>
<td>Can volume measurement of the prostate enhance the performance of complexed prostate-specific antigen?</td>
<td>Study population already have prostate cancer</td>
</tr>
<tr>
<td>Ng</td>
<td>Prostate cancer detection with digital rectal examination, prostate-specific antigen, transrectal ultrasonography and biopsy in clinical urological practice</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Short Title</td>
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<tr>
<td>Nicholson</td>
<td>The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation</td>
<td>Systematic review</td>
</tr>
<tr>
<td>Noguchi</td>
<td>Necessity of repeat biopsies in men for suspected prostate cancer</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Nordstrom</td>
<td>A population-based study on the association between educational length, prostate-specific antigen testing and use of prostate biopsies</td>
<td>Reference standard in study does not match that specified in protocol Not possible to calculate a 2x2</td>
</tr>
<tr>
<td>Novara</td>
<td>Detection rate and factors predictive the presence of prostate cancer in patients undergoing ultrasonography-guided transperineal saturation biopsies of the prostate</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Nyberg</td>
<td>PCA3 as a diagnostic marker for prostate cancer: a validation study on a Swedish patient population</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Ochiai</td>
<td>Prostate cancer gene 3 urine assay for prostate cancer in Japanese men undergoing prostate biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Ochiai</td>
<td>Clinical utility of the prostate cancer gene 3 (PCA3) urine assay in Japanese men undergoing prostate biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Ohi</td>
<td>Diagnostic significance of PSA density adjusted by transition zone volume in males with PSA levels between 2 and 4ng/ml</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Okada</td>
<td>Correlation of histological inflammation in needle biopsy specimens with serum prostate-specific antigen levels in men with negative biopsy for prostate cancer</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Okegawa</td>
<td>Comparison of two investigative assays for the complexed prostate-specific antigen in total prostate-specific antigen between 4.1 and 10.0 ng/mL</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Okegawa</td>
<td>Comparisons of the various combinations of free, complexed,</td>
<td>Study does not contain any relevant index</td>
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<tr>
<td>Short Title</td>
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<td>Reason for exclusion</td>
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<tr>
<td>Ong (2015)</td>
<td>Transperineal biopsy prostate cancer detection in first biopsy and repeat biopsy after negative transrectal ultrasound-guided biopsy: The Victorian Transperineal Biopsy Collaboration experience</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Osredkar (2016)</td>
<td>The performance of proPSA and prostate health index tumor markers in prostate cancer diagnosis</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Panebianco (2010)</td>
<td>Role of magnetic resonance spectroscopic imaging ([1H]MRSI) and dynamic contrast-enhanced MRI (DCE-MRI) in identifying prostate cancer foci in patients with negative biopsy and high levels of prostate-specific antigen (PSA)</td>
<td>Not a relevant study design (diagnostic test accuracy) Randomised controlled trial</td>
</tr>
<tr>
<td>Park (2003)</td>
<td>Predictors of prostate cancer on repeat transrectal ultrasound-guided systematic prostate biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Park (2014)</td>
<td>Clinicopathologic differences between prostate cancers detected during initial and repeat transrectal ultrasound-guided biopsy in Korea</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Park (2015)</td>
<td>Comparison of re-biopsy with preceded MRI and re-biopsy without preceded MRI in patients with previous negative biopsy and persistently high PSA</td>
<td>Not a relevant study design (diagnostic test accuracy) Case control design</td>
</tr>
<tr>
<td>Parsons (2004)</td>
<td>Complexed prostate specific antigen (PSA) reduces unnecessary prostate biopsies in the 2.6-4.0 ng/mL range of total PSA</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Patel (2004)</td>
<td>Parasagittal biopsies add minimal information in repeat saturation prostate biopsy</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Pepe (2007)</td>
<td>Saturation prostate needle biopsy and prostate cancer detection at initial and repeat evaluation</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Pepe (2008)</td>
<td>Is quantitative histologic examination useful to predict nonorgan-confined prostate cancer when saturation biopsy is performed?</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
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<tr>
<td>Pepe (2010)</td>
<td>Can Sonovue targeted biopsy replace extended or saturation biopsy in prostate cancer diagnosis? Our experience at primary and repeat biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Pepe (2010)</td>
<td>Prostate cancer detection after one or more negative extended needle biopsy: Results of a multicenter case-findings protocol</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Pepe (2011)</td>
<td>Does an inflammatory pattern at primary biopsy suggest a lower risk for prostate cancer at repeated saturation prostate biopsy?</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Pepe (2014)</td>
<td>Detection rate of anterior prostate cancer in 226 patients submitted to initial and repeat transperineal biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Pepe (2015)</td>
<td>Can 3-Tesla pelvic phased-array multiparametric MRI avoid unnecessary repeat prostate biopsy in patients with PSA &lt; 10 ng/mL?</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5 Tesla magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Pepe (2015)</td>
<td>Anterior prostate biopsy at initial and repeat evaluation: is it useful to detect significant prostate cancer?</td>
<td>Participants were biopsy /MRI naive candidates some participants were biopsy naive</td>
</tr>
<tr>
<td>Pepe (2017)</td>
<td>Multiparametric MRI Apparent Diffusion Coefficient (ADC) accuracy in diagnosing clinically significant prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Philip (2006)</td>
<td>Importance of peripheral biopsies in maximising the detection of early prostate cancer in repeat 12-core biopsy protocols</td>
<td>Not a relevant study design (diagnostic test accuracy)</td>
</tr>
<tr>
<td>Philip (2009)</td>
<td>Prostate cancer diagnosis: should patients with prostate specific antigen &gt;10ng/mL have stratified prostate biopsy protocols?</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Pinsky (2007)</td>
<td>Repeat prostate biopsy in the prostate, lung, colorectal and ovarian cancer screening trial</td>
<td>Duplicate reference</td>
</tr>
<tr>
<td>Pinsky (2007)</td>
<td>Repeat prostate biopsy in the prostate, lung, colorectal and ovarian cancer screening trial</td>
<td>Mixed studies with other cancers</td>
</tr>
<tr>
<td>Ploussard (2010)</td>
<td>The prostate cancer gene 3 (PCA3) urine test in men with previous negative biopsies: Does free-to-total prostate-specific antigen ratio influence the performance of the PCA3 score in predicting positive biopsies?</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Short Title</td>
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<tr>
<td>Ploussard</td>
<td>Risk of repeat biopsy and prostate cancer detection after an initial</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>(2013)</td>
<td>extended negative biopsy: Longitudinal follow-up from a prospective trial</td>
<td></td>
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<tr>
<td>Ploussard</td>
<td>Does PCA3 really help urologists?</td>
<td>Review article but not a systematic review</td>
</tr>
<tr>
<td>(2014)</td>
<td></td>
<td></td>
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<tr>
<td>Pokorny</td>
<td>Prospective study of diagnostic accuracy comparing prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>(2014)</td>
<td>detection by transrectal ultrasound-guided biopsy versus magnetic</td>
<td></td>
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<td></td>
<td>resonance (MR) imaging with subsequent MR-guided biopsy in men</td>
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<td></td>
<td>without previous prostate biopsies</td>
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<tr>
<td>Ponholzer</td>
<td>Magnetic resonance imaging guided prostate biopsy in men with repeat</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced,</td>
</tr>
<tr>
<td>(2011)</td>
<td>negative biopsies and increased prostate specific antigen</td>
<td>diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Portalez</td>
<td>Prospective comparison of T2w-MRI and dynamic-contrast-enhanced</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced,</td>
</tr>
<tr>
<td>(2010)</td>
<td>MRI, 3D-MR spectroscopic imaging or diffusion-weighted MRI in repeat</td>
<td>diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td></td>
<td>TRUS-guided biopsies</td>
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<tr>
<td>Pourmand</td>
<td>Preventing Unnecessary Invasive Cancer-Diagnostic Tests: Changing the</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>(2012)</td>
<td>Cut-off Points</td>
<td></td>
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<tr>
<td>Prando</td>
<td>Prostatic biopsy directed with endorectal MR spectroscopic imaging</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced,</td>
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<tr>
<td>(2005)</td>
<td>findings in patients with elevated prostate specific antigen levels</td>
<td>diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td></td>
<td>and prior negative biopsy findings: early experience</td>
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<tr>
<td>Prestigiacomo</td>
<td>Can free and total prostate specific antigen and prostatic volume</td>
<td>Study population already have prostate cancer</td>
</tr>
<tr>
<td>(1997)</td>
<td>distinguish between men with negative and positive systematic</td>
<td></td>
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<tr>
<td></td>
<td>ultrasound guided prostate biopsies?</td>
<td></td>
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<tr>
<td>Quentin</td>
<td>Evaluation of a structured report of functional prostate magnetic</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer</td>
</tr>
<tr>
<td>(2012)</td>
<td>resonance imaging in patients with suspicion for prostate cancer or</td>
<td>with no stratification</td>
</tr>
<tr>
<td></td>
<td>under active surveillance</td>
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<td>Rabets</td>
<td>Prostate cancer detection with office based saturation biopsy in a</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>(2004)</td>
<td>repeat biopsy population</td>
<td></td>
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<tr>
<td>Short Title</td>
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<td>Reason for exclusion</td>
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<tr>
<td>Radtke</td>
<td>Combined Clinical Parameters and Multiparametric Magnetic Resonance Imaging for Advanced Risk Modeling of Prostate Cancer-Patient-tailored Risk Stratification Can Reduce Unnecessary Biopsies</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Ramos</td>
<td>PCA3 sensitivity and specificity for prostate cancer detection in patients with abnormal PSA and/or suspicious digital rectal examination. First Latin American experience</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Ravery</td>
<td>Diagnostic value of ten systematic TRUS-guided prostate biopsies</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Reissigl</td>
<td>Usefulness of the ratio free/total prostate-specific antigen in addition to total PSA levels in prostate cancer screening</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Reljic</td>
<td>Diagnostic value of age specific prostate specific antigen in prostate cancer patients</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Remzi</td>
<td>Can total and transition zone volume of the prostate determine whether to perform a repeat biopsy?</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Remzi</td>
<td>Can power doppler enhanced transrectal ultrasound guided biopsy improve prostate cancer detection on first and repeat prostate biopsy?</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Roberts</td>
<td>Digital rectal examination and prostate-specific antigen abnormalities at the time of prostate biopsy and biopsy outcomes, 1980 to 1997</td>
<td>Biopsy naive participants</td>
</tr>
<tr>
<td>Rochester</td>
<td>Development and validation of risk score for predicting positive repeat prostate biopsy in patients with a previous negative biopsy in a UK population</td>
<td>Study does not contain any relevant index tests, study is a validation study of a risk score including a number of variables including age, psa and DRE</td>
</tr>
<tr>
<td>Roehrborn</td>
<td>Diagnostic yield of repeated transrectal ultrasound-guided biopsies stratified by specific histopathologic diagnoses and prostate specific antigen levels</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Roethke</td>
<td>MRI-guided prostate biopsy detects clinically significant cancer: analysis of a cohort of 100 patients after previous negative TRUS biopsy</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla</td>
</tr>
<tr>
<td>Short Title</td>
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<td>Reason for exclusion</td>
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<tr>
<td>Roobol (2004)</td>
<td>No reason for immediate repeat sextant biopsy after negative initial sextant biopsy in men with PSA level of 4.0 ng/mL or greater (ERSPC, Rotterdam)</td>
<td>magnetic, Bvalue of at least 800s/mm2</td>
</tr>
<tr>
<td>Roobol (2007)</td>
<td>The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC)</td>
<td>Not a relevant study design (diagnostic test accuracy) Randomised control trial</td>
</tr>
<tr>
<td>Roobol (2007)</td>
<td>The value of different screening tests in predicting prostate biopsy outcome in screening for prostate cancer data from a multicenter study (ERSPC)</td>
<td>Reference standard in study does not match that specified in protocol</td>
</tr>
<tr>
<td>Roobol (2010)</td>
<td>Performance of prostate cancer antigen 3 (PCA3) and prostate-specific antigen in prescreened men: Reproducibility and detection characteristics for prostate cancer patients with high PCA3 scores (&gt;=100)</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Roobol (2010)</td>
<td>Performance of the prostate cancer antigen 3 (PCA3) gene and prostate-specific antigen in prescreened men: exploring the value of PCA3 for a first-line diagnostic test</td>
<td>Duplicate reference Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
</tr>
<tr>
<td>Roobol (2010)</td>
<td>Performance of prostate cancer antigen 3 (PCA3) and prostate-specific antigen in Prescreened men: reproducibility and detection characteristics for prostate cancer patients with high PCA3 scores (? 100)</td>
<td>Duplicate reference</td>
</tr>
<tr>
<td>Rosenkran tz (2016)</td>
<td>Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR</td>
<td>Review article but not a systematic review</td>
</tr>
<tr>
<td>Rovner (1997)</td>
<td>Transurethral biopsy of the prostate for persistently elevated or increasing prostate specific antigen following multiple negative transrectal biopsies</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Short Title</td>
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<td>Reason for exclusion</td>
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<tr>
<td>Rubens (1996)</td>
<td>Clinical evaluation of prostate biopsy parameters: gland volume and elevated prostate-specific antigen level</td>
<td>Participants were biopsy /MRI naive candidates Only 5 patients had repeat biopsy</td>
</tr>
<tr>
<td>Ruffion (2013)</td>
<td>PCA3 and PCA3-based nomograms improve diagnostic accuracy in patients undergoing first prostate biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Ryden (2007)</td>
<td>Prevalence of prostate cancer at different levels of serum prostate-specific antigen (PSA) and different free: Total PSA ratios in a consecutive series of men referred for prostate biopsies</td>
<td>Participants prostate cancer/prostate biopsy history unclear/unknown</td>
</tr>
<tr>
<td>Ryu (2010)</td>
<td>Predictive factors of prostate cancer at repeat biopsy in patients with an initial diagnosis of atypical small acinar proliferation of the prostate</td>
<td>Population diagnosed with ASAP</td>
</tr>
<tr>
<td>Saema (2012)</td>
<td>PSA density and prostate cancer detection</td>
<td>Unable to source article</td>
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<tr>
<td>Salami (2015)</td>
<td>In patients with a previous negative prostate biopsy and a suspicious lesion on magnetic resonance imaging, is a 12-core biopsy still necessary in addition to a targeted biopsy?</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Saleem (1998)</td>
<td>Factors predicting cancer detection in biopsy of the prostatic fossa after radical prostatectomy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
</tr>
<tr>
<td>Satkunasivam (2014)</td>
<td>Human kallikrein-2 gene and protein expression predicts prostate cancer at repeat biopsy</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Satoh (2006)</td>
<td>Is interval from an initial biopsy a significant predictor of prostate cancer at repeat biopsies?</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Scattoni (2011)</td>
<td>The optimal rebiopsy prostatic scheme depends on patient clinical characteristics: Results of a recursive partitioning analysis based on a 24-core systematic scheme</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Schimmoller (2016)</td>
<td>MRI-guided in-bore biopsy: Differences between prostate cancer detection and localization in primary and secondary biopsy settings</td>
<td>Study does not contain any relevant index tests in-bore biopsy</td>
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<tr>
<td>Short Title</td>
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<tr>
<td>Schouten (2015)</td>
<td>Location of Prostate Cancers Determined by Multiparametric and MRI-Guided Biopsy in Patients With Elevated Prostate-Specific Antigen Level and at Least One Negative Transrectal Ultrasound-Guided Biopsy</td>
<td>Reference standard in study does not match that specified in protocol</td>
</tr>
<tr>
<td>Sciarra (2010)</td>
<td>Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study Randomised control trial MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td>Segaran (2017)</td>
<td>The ability of free to total prostate-specific antigen and prostate-specific antigen density to detect clinically significant prostate cancer in men undergoing transperineal template biopsy</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Serdar (2002)</td>
<td>Diagnostic approach to prostate cancer using total prostate specific antigen-based parameters together</td>
<td>Study population already have prostate cancer</td>
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<tr>
<td>Servian (2016)</td>
<td>Clinical Significance of Proliferative Inflammatory Atrophy in Negative Prostatic Biopsies</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Shappell (2009)</td>
<td>PCA3 urine mRNA testing for prostate carcinoma: patterns of use by community urologists and assay performance in reference laboratory setting</td>
<td>Not possible to calculate a 2x2 table from data presented in the study Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
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<tr>
<td>Shinohara (2014)</td>
<td>Management of an increasing prostate-specific antigen level after negative prostate biopsy</td>
<td>Review article but not a systematic review</td>
</tr>
<tr>
<td>Shoji (2015)</td>
<td>Manually controlled targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: An early experience</td>
<td>Participants were biopsy /MRI naive candidates</td>
</tr>
<tr>
<td>Siegrist (2012)</td>
<td>PCA3 permutation increases the prostate biopsy yield</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with no stratification</td>
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<tr>
<td>Short Title</td>
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<tr>
<td>Singh (2003)</td>
<td>Repeating the measurement of prostate-specific antigen in symptomatic men can avoid unnecessary prostatic biopsy</td>
<td>Participants were biopsy/MRI naive candidates</td>
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<tr>
<td>Singh (2008)</td>
<td>Patient selection determines the prostate cancer yield of dynamic contrast-enhanced magnetic resonance imaging-guided transrectal biopsies in a closed 3-Tesla scanner</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast-enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td>Sonn (2014)</td>
<td>Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<td>Spajic (2004)</td>
<td>Prostate cancer detection in repeat extended prostate biopsy in men with previous negative biopsy findings</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Spyropoulou (2017)</td>
<td>Prostate Cancer Predictive Simulation Modelling, Assessing the Risk Technique (PCP-SMART): Introduction and Initial Clinical Efficacy Evaluation Data Presentation of a Simple Novel Mathematical Simulation Modelling Method, Devised to Predict the Outcome of Prostate Biopsy on an Individual Basis</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Stamatiou (2007)</td>
<td>Impact of additional sampling in the TRUS-guided biopsy for the diagnosis of prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Stephan (2005)</td>
<td>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 &lt; 4 ng/mL</td>
<td>Participants prostate cancer/prostate biopsy history unclear/unknown</td>
</tr>
<tr>
<td>Steuber (2005)</td>
<td>Association of free-prostate specific antigen subfractions and human glandular kallikrein 2 with volume of benign and malignant prostatic tissue</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Stroumbakis (1997)</td>
<td>Clinical significance of repeat sextant biopsies in prostate cancer patients</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Su (2013)</td>
<td>Dichotomous estimation of prostate volume: a diagnostic study of the accuracy of the digital rectal examination</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Tamsel (2008)</td>
<td>Transrectal ultrasound in detecting prostate cancer compared with</td>
<td>Not possible to calculate a 2x2 table from data</td>
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<td></td>
<td>serum total prostate-specific antigen levels</td>
<td>presented in the study for total prostate specific antigen levels</td>
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<tr>
<td>Tan (2008)</td>
<td>Prostate cancers diagnosed at repeat biopsy are smaller and less likely to be high grade</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Tan (2017)</td>
<td>In-bore 3-T MR-guided transrectal targeted prostate biopsy: Prostate Imaging Reporting and Data System version 2-based diagnostic performance for detection of prostate cancer</td>
<td>Study does not contain any relevant index tests</td>
</tr>
<tr>
<td>Tang (2013)</td>
<td>Transition zone PSA density improves the prostate cancer detection rate both in PSA 4.0-10.0 and 10.1-20.0 ng/ml in Chinese men</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Tarcan (1997)</td>
<td>Evaluation of prostate specific antigen density and transrectal ultrasonography-guided biopsies in 100 consecutive patients with a negative digital rectal examination and intermediate serum prostate specific antigen levels</td>
<td>Biopsy naive participants</td>
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<tr>
<td>Teoh (2017)</td>
<td>The performance characteristics of prostate-specific antigen and prostate-specific antigen density in Chinese men</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Testa (2010)</td>
<td>Accuracy of MRI/MRSI-based transrectal ultrasound biopsy in peripheral and transition zones of the prostate gland in patients with prior negative biopsy</td>
<td>MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2</td>
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<tr>
<td>Thompson (2006)</td>
<td>Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Thompson (2007)</td>
<td>Prediction of prostate cancer for patients receiving finasteride: Results from the prostate cancer prevention trial</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Thompson (2008)</td>
<td>The performance of prostate specific antigen for predicting prostate cancer is maintained after a prior negative prostate biopsy</td>
<td>Duplicate reference</td>
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<tr>
<td>Thompson (2017)</td>
<td>Diagnostic accuracy of multi-parametric MRI and transrectal ultrasound-guided biopsy in prostate cancer</td>
<td>Review article but not a systematic review</td>
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<tr>
<td>Tijani (2017)</td>
<td>The role of the percentage free PSA in the diagnosis of prostate cancer in Blacks: Findings in indigenous West</td>
<td>Biopsy naive participants</td>
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<td>Tombal (2013)</td>
<td>Clinical judgment versus biomarker prostate cancer gene 3: which is best when determining the need for repeat prostate biopsy?</td>
<td>Not a relevant study design (diagnostic test accuracy)</td>
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<tr>
<td>Tosoian (2017)</td>
<td>Prostate Health Index density improves detection of clinically significant prostate cancer</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Tosoian (2017)</td>
<td>Use of the Prostate Health Index for detection of prostate cancer: results from a large academic practice</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<tr>
<td>Truong (2018)</td>
<td>Multi-institutional nomogram predicting benign prostate pathology on magnetic resonance/ultrasound fusion biopsy in men with a prior negative 12-core systematic biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Tsao (2013)</td>
<td>Combining prostate-specific antigen and Gleason score increases the diagnostic power of endorectal coil magnetic resonance imaging in prostate cancer pathological stage</td>
<td>Study population already have prostate cancer</td>
</tr>
<tr>
<td>Uemura (2004)</td>
<td>Effectiveness of percent free prostate specific antigen as a predictor of prostate cancer detection on repeat biopsy</td>
<td>Not a relevant study design (diagnostic test accuracy)</td>
</tr>
<tr>
<td>Ukimura (1997)</td>
<td>Role of PSA and its indices in determining the need for repeat prostate biopsies</td>
<td>The thresholds used for the index tests are not clear</td>
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<tr>
<td>Van Poppel (2012)</td>
<td>The relationship between Prostate CANcer gene 3 (PCA3) and prostate cancer significance</td>
<td>Participants were biopsy /MRI naive candidates</td>
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<td>Vickers (2010)</td>
<td>Prostate specific antigen velocity does not aid prostate cancer detection in men with prior negative biopsy</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Vourganti (2012)</td>
<td>Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies</td>
<td>Not possible to calculate a 2x2 table from data presented in the study</td>
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<tr>
<td>Walz (2006)</td>
<td>High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series</td>
<td>Study does not contain any relevant index tests</td>
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<tr>
<td>Wang (2017)</td>
<td>Determination of the Role of Negative Magnetic Resonance</td>
<td>Mixed population - biopsy naive and repeat biopsy or diagnosed with prostate cancer with</td>
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</table>
|             | Imaging of the Prostate in Clinical Practice: Is Biopsy Still Necessary? | no stratification  
As well as patient on active surveillance                                                  |
| Washino (2017) | Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naive patients | Participants were biopsy /MRI naive candidates                                          |
| Wei (2014)   | Can urinary PCA3 supplement PSA in the early detection of prostate cancer? | Not a relevant study design (diagnostic test accuracy)  
Randomised control trial                                                                 |
<p>| Wetter (2005) | Three-dimensional 1H-magnetic resonance spectroscopy of the prostate in clinical practice: technique and results in patients with elevated prostate-specific antigen and negative or no previous prostate biopsies | MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2 |
| Yamamoto (2014) | Management of men with a suspicion of prostate cancer after negative initial prostate biopsy results | Not possible to calculate a 2x2 table from data presented in the study                 |
| Yeniyol (2001) | The relation of prostate biopsy results and ratio of free to total PSA in patients with a total PSA between 4-20 ng/mL | Participants were biopsy /MRI naive candidates                                          |
| Yu (1998)    | The usefulness of prostate-specific antigen (PSA) density in patients with intermediate serum PSA level in a country with low incidence of prostate cancer | Participants were biopsy /MRI naive candidates                                          |
| Yu (2016)    | Performance of the Prostate Health Index in predicting prostate biopsy outcomes among men with a negative digital rectal examination and transrectal ultrasonography | Participants were biopsy /MRI naive candidates                                          |
| Yuen (2004)  | Clinical, biochemical and pathological features of initial and repeat transrectal ultrasonography prostate biopsy positive patients | Participants were biopsy /MRI naive candidates                                          |
| Yuen (2004)  | Endorectal magnetic resonance imaging and spectroscopy for the detection of tumor foci in men with prior negative transrectal ultrasound prostate biopsy | MRI protocol not satisfying the following criteria - dynamic contrast- enhanced, diffusion weighted, at least 1.5Tesla magnetic, Bvalue of at least 800s/mm2 |
| Yun (2015)   | Is histological prostate inflammation in an initial prostate biopsy a predictor of prostate cancer on repeat biopsy? | Not possible to calculate a 2x2 table from data presented in the study                  |</p>
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<tr>
<td>Zhang (2014)</td>
<td>The value of magnetic resonance imaging in the detection of prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels: a meta-analysis</td>
<td>Systematic Review - relevant articles already included in this review</td>
</tr>
<tr>
<td>Zhao (2014)</td>
<td>Developing a follow-up strategy for patients with PSA ranging from 4 to 10 ng/ml via a new model to reduce unnecessary prostate biopsies</td>
<td>Not a relevant study design (diagnostic test accuracy)</td>
</tr>
<tr>
<td>Zheng (2008)</td>
<td>The use of prostate specific antigen (PSA) density in detecting prostate cancer in Chinese men with PSA levels of 4-10 ng/mL</td>
<td>Participants were biopsy /MRI naive candidates</td>
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### Economic studies

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<td>Blute (2015)</td>
<td>Addressing the need for repeat prostate biopsy: new technology and approaches</td>
<td>Not economic evaluation</td>
</tr>
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</table>

### Appendix I – References

5 **Clinical studies - included**


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suspicious for prostate cancer undergoing repeated biopsy. Scandinavian journal of urology 49(1), 25-34


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Clinical studies – Excluded


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Efficient pathway for early detection of prostate cancer concluded from a 5-year prospective study. World journal of urology 11(4), 201-5 \(^6\)

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The effect of dutasteride on the usefulness of prostate specific antigen for the diagnosis of high grade and clinically relevant prostate cancer in men with a previous negative biopsy: results from the REDUCE study. Journal of urology 185(1), 126-131 \(^11\)

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17 Economic studies - Excluded

## Appendix J – Research recommendations

### Question 1

What is the most suitable surveillance protocol for people who are on active surveillance, as assessed by multiparametric MRI and biopsy, when there are no clinical concerns during follow-up?

<table>
<thead>
<tr>
<th>Population</th>
<th>People on active surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Active surveillance protocol</td>
</tr>
<tr>
<td>Comparator</td>
<td>Other surveillance protocols</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Prostate cancer specific mortality, Prostate cancer related morbidity, Clinical progression/‘late’ diagnosis of progression, Quality of life, Patient reported outcomes</td>
</tr>
<tr>
<td>Study design</td>
<td>RCT/Prospective cohort study</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential criterion</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance to patients, service users or the population</td>
<td>There is a variation in how follow up protocols across the country and these have not been evaluated to understand their effectiveness. The role of both primary and secondary care is not clear.</td>
</tr>
<tr>
<td>Relevance to NICE guidance</td>
<td>Current guidance is based on consensus</td>
</tr>
<tr>
<td>Current evidence base</td>
<td>Limited evidence base</td>
</tr>
<tr>
<td>Equality</td>
<td>No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>There is a large enough population on active surveillance to make studies in this area feasible</td>
</tr>
</tbody>
</table>

### Question 2

In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?

<table>
<thead>
<tr>
<th>Population</th>
<th>People with negative MRI (Likert score 1 or 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index tests</td>
<td>Any test given within 6 months of MRI to further exclude clinically significant prostate cancer.</td>
</tr>
<tr>
<td>Reference standard</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Sensitivity, Specificity, Positive and negative likelihood ratios, QoL outcomes, Adverse events</td>
</tr>
<tr>
<td>Study design</td>
<td>Diagnostic cross sectional studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potential criterion</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Importance to patients, service users or the population</td>
<td>No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.</td>
</tr>
<tr>
<td>Relevance to NICE guidance</td>
<td>There is a large enough population on active surveillance to make studies in this area feasible</td>
</tr>
<tr>
<td>Current evidence base</td>
<td>Limited evidence base</td>
</tr>
<tr>
<td>Equality</td>
<td>No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>There is a large enough population on active surveillance to make studies in this area feasible</td>
</tr>
</tbody>
</table>
### Question

**In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?**

### Importance to patients, service users or the population

The evidence shows that about 20% of men with a Likert score 1 or 2 on MRI may have clinically significant cancer. Since the new pathway discourages biopsy in men with negative MRI, the research will help formulate a pathway that these people may follow to identify any missed clinically significant cancer.

### Relevance to NICE guidance

Current guidance on the follow-up protocol for men with negative is not evidence based as this is a new population as a result as the new pathway.

### Current evidence base

Limited evidence as this population is relatively new.

### Equality

No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.

### Feasibility

A large enough number of people receive a MRI of the prostate to make this study feasible.

---

### Question

**What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?**

### Population

People suspected of cancer (biopsy naïve or repeat biopsy)

### Index test

Transperineal non mapping biopsy

### References

Transperineal mapping biopsy

### Outcomes

Sensitivity

Specificity

Positive and Negative Likelihood ratios

### Study design

Diagnostic cross sectional studies

### Potential criterion | Explanation

**Importance to patients, service users or the population**

The committee explained that a number of providers across the country use the transperineal route for biopsy rather than the transrectal route, however transperineal biopsy can be a mapping biopsy where a large number of samples are taken from around the prostate (currently considered the ‘gold standard’ diagnostic test) or a non-mapping biopsy where a smaller number of samples are taken in a more focussed way (for example guided by MRI). The diagnostic accuracy of the non-mapping method is not known. Transperineal mapping biopsy is more resource intensive than non-mand the NHS is not equipped to perform a large number of these.

**Relevance to NICE guidance**

This research will enable NICE guideline to be more specific about which biopsy is most appropriate in which situation.

**Current evidence base**

The current evidence base suggests that transperineal template biopsy is the most accurate diagnostic tool for prostate cancer. It is unknown how non-mapping transperineal biopsy compares to this.
<table>
<thead>
<tr>
<th>Question</th>
<th>What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equality</td>
<td>No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.</td>
</tr>
<tr>
<td>Feasibility</td>
<td>There is a large enough population of people with locally advanced prostate cancer, carrying out a trial in this area should be feasible</td>
</tr>
</tbody>
</table>