National Institute for Health and Care Excellence

FINAL

# Prostate cancer: diagnosis and management

## [F] Evidence review for identifying prostate cancer clinical progression in people with low- to intermediate-risk cancer

*NICE guideline NG131*

*Evidence reviews*

*May 2019*

*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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# Contents

# RQ3 identifying prostate cancer clinical progression in people with low - intermediate risk cancer

## Review question

- Which of the following, alone or in combination, constitutes the most clinically and cost- effective pathway for excluding the clinically significant progression of prostate cancer in people with low to intermediate risk (as defined in NICE CG175): Multiparametric/ functional MRI, TRUS biopsy, Transperineal template biopsy?

### Introduction

Following histological diagnosis of prostate cancer, the biochemical, clinical, histological features are combined, often with imaging features, to assess the risk that the cancer poses to the person's health. Many cancers are deemed low or intermediate risk, and the treatment of the cancer with radiotherapy or surgery may be, in the short term at least, more potentially harmful than a surveillance strategy.

This review question set out to determine which tests are the most effective in monitoring those on active surveillance, balancing the need for early detection of disease progression and intervention against the morbidity and anxiety of repeated biopsy.

The diagnostic accuracy of multiparametric MRI (mpMRI) alone, TRUS biopsy alone and mpMRI influenced biopsy were compared, using transperineal template biopsy and radical prostatectomy samples as reference standards.

This review identified studies that fulfilled the conditions specified in Table 1. For full details of the review protocol, see appendix A.

**Table 1: PICO for identifying prostate cancer clinical progression in people with low-intermediate risk cancer**

| | |
|---|---|
| **Population** | • People with low to intermediate risk prostate cancer |
| **Index tests** | • Multiparametric MRI<br>• MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy)TRUS biopsy alone (systematic or standard)<br>*TRUS biopsy also referred to as saturation or extended biopsy* |
| **Reference standard** | • Transperineal template biopsy<br>• TRUS biopsy<br>• Radical prostatectomy |
| **Outcomes** | • Diagnostic accuracy<br>  ○ Sensitivity and specificity<br>  ○ Likelihood ratios<br>*If available from studies reporting diagnostic accuracy we will also extract information on:*<br>• Number of Adverse events |

| | |
|---|---|
| | ○ Haemorrhage<br>○ Sepsis<br>○ Failure to diagnose<br>○ Pain<br>○ Sexual dysfunction<br>○ Urine retention<br>○ Hospitalisation<br>○ Prostatitis<br>• Missed higher grade cancers<br>• Health-related quality of life<br>○ psychological aspects of quality of life to be reported separately if possible |

## Methods and process

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

The search strategies used in this review are detailed in appendix C.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

## Clinical evidence

### Included studies

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

A systematic literature search for diagnostic cross-sectional studies and systematic reviews of diagnostic cross-sectional studies with a date limit of no earlier than 2007 yielded 5,716 references. These were screened on title and abstract, with 150 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 diagnosed with low- to intermediate prostate cancer and if they did not include the index tests and the reference standards as specified in the protocol. Studies were further excluded at data extraction if it was not possible to calculate sensitivity and specificity or if the study did not meet any of the other criteria in the protocol.

Five papers were included after full text screening.

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 917 references for this review question. These were screened on title and abstract and no additional relevant references was found.

A sixth paper was included following stakeholder comments.

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

### Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion. Full references are listed in Appendix I

## Summary of clinical studies included in the evidence review

**Table 2: Summary of studies identifying prostate cancer clinical progression in people who have low-intermediate risk**

| Study (year) | Study Period | N | Time on Active surveillance | Index test | Reference Standard | MRI Scoring | MRI Protocol | +ve MRI | Patients were reclassified if the following |
|---|---|---|---|---|---|---|---|---|---|
| Barzell (2012) USA | Between 2002 and 2009 | 77 | 3 months | Repeat TRUS Biopsy | Systematic template prostate mapping biopsy using brachytherapy grid under general anaesthesia. | n/a | n/a | n/a | 1. UCL definition 1: Gleason ≥4+3 and/or maximum cancer core length (CCLmax) ≥6mm<br>2. UCL definition 2: Gleason ≥3+4 and/or CCLmax ≥4mm<br>3. Epstein 1<br>4. Epstein 2 |
| Chen (2017) Singapore | Not reported | 19 | Not reported | MRI targeted biopsy | Robotic transperineal template biopsy | "PIRADS v1<br><br>2014 onwards used the PIRADS v2 " | Included<br>- '3Tesla scanner<br>- multi channel phased channel array coil<br>- T2 weighted images in the axial, coronal and sagittal planes<br>- Diffusion weighted imaging in the axial plane (b values 0-50, 500 and 1000s/mm2) and DCE images | ≥3 | Gleason component Grade 4 or higher grade |

| Study (year) | Study Period | N | Time on Active surveillance | Index test | Reference Standard | MRI Scoring | MRI Protocol | +ve MRI | Patients were reclassified if the following |
|---|---|---|---|---|---|---|---|---|---|
| Da Rosa (2015) Canada | March 2011 to December 2012 | 81 | Median (IQR) 38 months (0.9-162) | MRI ultrasound fusion | TRUS Biopsy | Likert Scale | 3Tesla MRI imaging system without an endorectal coil. A six channel cardiac surface coil was positioned over the pelvis. Multiparametric MRI combining axial, sagittal and coronal t2-weighted, diffusion weighted , b values 100, 400, 1000 slice thickness 3 mm | ≥4 | Any cancer of Gleason score ≥7<br>- Gleason score = 6 with >50% involvement in any one core |
| Feng (2015) USA | January 2010 to July 2013 | 342 | Not reported | mpMRI | Radical Prostatectomy | PIRADS | Imaging using 3.0T MRI system equipped with a 12-channel pelvic phased array coil. Anatomic images included T1- and T2 weighted turbo spin echo, acquired in the axial, sagittal and coronal planes. Diffusion weighted imaging was acquired using a standard single-shot echo planar imaging sequence. The orthogonal diffusion directions including a single b0 | 3 – 9uspicious Extracapsular Extension (ECE)<br><br>4 and 5-definite ECE | Presence of extracapsular extension disease – Defined as presence of tumour beyond the confines of the prostate |

| Study (year) | Study Period | N | Time on Active surveillance | Index test | Reference Standard | MRI Scoring | MRI Protocol | +ve MRI | Patients were reclassified if the following |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | measurement were acquired at 2 nonzero b values 400 and 800s/mm2 | | |
| Pessoa (2017) Brazil | March 2014 to January 2016 | 105 | Max 6 months | MRI targeted biopsy | 12 core systematic biopsy | PIRADS v1 | mpMRI images were evaluated using axial-oblique, fast spin-echo T2 –weighted, diffusion weighted imaging and dynamic contrast enhanced – MRI or a 16 channel cardiac surface external 3.0T MRI system. | ≥2 | If the confirmatory biopsy established significant cancer and was determined as any fragment with Gleason ≥7, more than three fragments positive for prostate cancer, or a highest tumour volume in any core >50% |

| Study (year) | Study Period | N | Time on Active surveillance | Index test | Reference Standard | MRI Scoring | MRI Protocol | +ve MRI | Patients were reclassified if the following |
|---|---|---|---|---|---|---|---|---|---|
| Thurtle (2018) United Kingdom | From 2011 onwards | 145 | Median 39 months (Range 15-63 months) | Multiparametric MRI, prostate specific Antigen | Systematic biopsies (transperineal or transrectal biopsy) | Likert scale | on a 3-T Discovery MR750-HDx or 1.5-T MR450 system (GE Healthcare, Waukesha, WI, USA) with a surface phased-array coil, including standard anatomical and functional diffusion-weighted imaging using multiple b-values, | ≥3 | Progression on AS was defined as pathological progression on a re-biopsy or progression on mpMRI from T2 to T3. Pathological progression was defined as a Grade Group increase between diagnostic and repeat biopsy. |

See appendix E for full evidence tables.

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

See appendix G for full GRADE tables.

## Economic evidence

Standard health economics filters were applied to the clinical search strategy for this review question. In total, 802 references were returned, of which 790 could be confidently excluded on screening of titles and abstracts. The remaining 12 studies were reviewed in full text, and all of them were found not to be relevant.

An additional study was identified by the committee and found to be relevant.

### Included studies

The role of multiparametric magnetic resonance imaging in active surveillance for men with low-risk prostate cancer: A cost-effectiveness modelling study, by Patel et al. (2018)

### Excluded studies

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

## Summary of studies included in the economic evidence review

Patel et al. (2018) developed a probabilistic lifetime Markov model with yearly cycles to accumulate the cost, adopting the healthcare perspective and using the € of year 2016, and health outcomes, measured by quality adjusted life years (QALYs), of 3 strategies to follow-up people with low-risk prostate cancer. The strategies were:

- Trans-rectal ultrasound (TRUS) guided biopsy every 3 years;
- Multi-parametric magnetic resonance imaging (Mp-MRI), and if positive, TRUS guided biopsy every 3 years;
- Mp-MRI only every 3 years.

The model consisted of 5 health states:

- Low-risk disease;
- Low-risk post-treatment;
- High-risk disease;
- High-risk post-treatment;
- Death due to prostate cancer or any other cause death.

Low-risk prostate cancer was defined as prostate serum antigen (PSA) ≤10; Gleason score ≤6. High-risk disease was defined as having Gleason score ≥7. The accuracy data of the tests and the health-related utility data were obtained from existing literature. The authors applied decrement in utility caused by TRUS and by adverse events associated with prostate cancer treatments. They found that the strategy, where people with low-risk disease received Mp-MRI, and if positive, followed by TRUS, was associated with greater QALYs and less costs than the other two strategies.

## Economic model

This question was not prioritised for economic modelling.

## Evidence statements

The evidence statements in these sections are written with reference to the size of the likelihood ratios in the GRADE tables in appendix G, using the interpretation detailed in the methods section on diagnostic test accuracy (Table 3).

### Clinical evidence statements

Evidence on **TRUS biopsy**

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A positive TRUS biopsy leads to a **slight increase** in the probability that a person diagnosed with low- or intermediate-risk prostate cancer has clinically significant disease (Very low-quality evidence from 1 prospective study comprising 124 participants; 95% confidence intervals range from moderate decrease 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 negative TRUS biopsy **does not alter the probability** that a person diagnosed with low- or intermediate-risk prostate cancer has clinically significant disease (Moderate-quality evidence from 1 prospective study comprising 124 participants; 95% confidence intervals range from slight decrease to slight increase).

Evidence on **MRI-influenced biopsy**

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
    - A positive MRI-influenced biopsy has **no diagnostic value** in determining clinically significant cancer in a person diagnosed with low risk prostate cancer within 8 weeks of initial prostate biopsy (High quality evidence from 1 cross-sectional study comprising 19 participants)
    - A positive MRI-influenced biopsy leads to a **moderate increase** in the probability of clinically significant cancer in a person diagnosed with low risk prostate cancer within 6 months of initial prostate biopsy (High quality evidence from 1 cross-sectional study comprising 87 participants, 95% confidence intervals ranged 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 MRI-influenced biopsy has **no diagnostic value** in determining clinically significant cancer in a person diagnosed with low risk prostate cancer within 8 weeks of initial prostate biopsy (High quality evidence from 1 cross-sectional study comprising 19 participants)
    - A negative MRI-influenced biopsy leads to a **moderate decrease** in the probability of clinically significant cancer in a person diagnosed with low risk prostate cancer within 6 months of initial prostate biopsy (High quality evidence from 1 cross-sectional study comprising 87 participants, 95% confidence intervals ranged from slight decrease to moderate decrease moderate decrease to large decrease)

Evidence on **MRI/TRUS fusion biopsy**

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
  - A positive MRI/TRUS fusion biopsy leads to a **large increase** in the probability of clinically significant cancer (defined as any cancer of Gleason score 7 or greater) in a person on active surveillance for 38 months (range 0.9-134.7months) (High quality evidence from 1 cross-sectional study comprising 72 participants, 95% confidence intervals ranged from moderate increase to large increase)
  - A positive MRI/TRUS fusion biopsy leads to a **moderate increase** in the probability of clinically significant cancer (defined as cancer of Gleason score 6 with greater than 50% involvement in any core) in a person on active surveillance for 38 months (range 0.9-134.7months) (Moderate quality evidence from 1 cross-sectional study comprising 72 participants, 95% confidence intervals ranged from moderate 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 negative MRI/TRUS fusion biopsy **does not alter the probability** of clinically significant cancer (defined as any cancer of Gleason score 7 or greater) in a person on active surveillance for 38 months (range 0.9-134.7months) (Moderate quality evidence from 1 cross-sectional study comprising 72 participants, 95% confidence intervals ranged from slight decrease to very large decrease)
  - A negative MRI/TRUS fusion biopsy leads to a **moderate decrease** in the probability of clinically significant cancer (defined as cancer of Gleason score 6 with greater than 50% involvement in any core) in a person on active surveillance for 38 months (range 0.9-134.7months) (Moderate quality evidence from 1 cross-sectional study comprising 72 participants, 95% confidence intervals ranged from slight decrease to large decrease)

Evidence on **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 multiparametric MRI PIRADS score ≥ 4 leads to a **moderate increase** in the probability of clinically significant cancer in a person diagnosed with low risk prostate cancer within 6 months of initial prostate biopsy (High quality evidence from 1 prospective study comprising 105 participants; 95% confidence intervals range from moderate increase to large increase).
  - A multiparametric MRI PIRADS score ≥ 4 leads to a **very large increase** in the probability of clinical progression (defined as definite extracapsular extension) in a person diagnosed with low risk prostate cancer (High quality evidence from 1 cross-sectional studies comprising 112 participants, 95% confidence intervals ranged from moderate increase to very large increase)
  - A multiparametric MRI PIRADS score ≥ 3 leads to a **large increase** in the probability of clinically significant cancer (defined as suspicious/definite extracapsular extension) in a person diagnosed with low risk prostate cancer (High quality evidence from 1 cross-sectional studies comprising 112 participants, 95% confidence intervals ranged from moderate increase to very large increase)

- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios*
  - A multiparametric MRI PIRADS score < 4 leads to a **very large decrease** in the probability of clinically significant cancer in a person diagnosed with low risk prostate cancer within 6 months of initial prostate biopsy (High quality evidence from 1 cross-sectional study comprising 105 participants, 95% confidence intervals ranged from large decrease to very large decrease)
  - A multiparametric MRI PIRADS score < 4 **does not meaningfully alter** the probability of clinical progression (defined as definite extracapsular extension) in a person diagnosed with low risk prostate cancer (Moderate quality evidence from 1 cross-sectional studies comprising 112 participants, 95% confidence intervals ranged from slight decrease to moderate decrease)
  - A multiparametric MRI PIRADS score <3 leads to a **moderate decrease** in the probability of clinical progression (defined as suspicious/definite extracapsular extension) in a person diagnosed with low risk prostate cancer (Moderate quality evidence from 1 cross-sectional studies comprising 112 participants, 95% confidence intervals ranged from slight decrease to large decrease)
- *Results that indicate a person on active surveillance has an increased probability of pathological disease progression (based on positive likelihood ratios)*:
  - A multiparametric MRI PIRADS score ≥ 3 leads to a **moderate increase** in the probability of pathological disease progression in a person diagnosed with low risk prostate cancer and are on active surveillance for at least a year (Moderate quality evidence from 1 cross-sectional comprising 104 participants, 95% confidence intervals ranged from slight increase to large increase)
- Results that indicate a person on active surveillance has an increased probability of pathological disease progression (based on positive likelihood ratios):
  - A multiparametric MRI PIRADS score <3 **does not meaningfully alter** the probability of pathological disease progression in a person diagnosed with low risk prostate cancer and are on active surveillance for at least a year (Moderate quality evidence from 1 cross-sectional comprising 104 participants, 95% confidence intervals ranged from slight decrease to moderate decrease)

## 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 exclude or identify clinical progression of prostate cancer in people on active surveillance for at least 2 years as expressed by likelihood ratios. The majority of the evidence presented was from studies whose follow up was less than a year and therefore it was highly unlikely that the disease would have progressed within the short follow up period. The committee agreed that in studies with short follow up, any changes in the severity of the cancer were likely to be because it was misclassified at diagnosis rather than because the cancer had progressed.

#### *The quality of the evidence*

All 6 included studies were at either low or moderate risk of bias because they met most of the elements of a good diagnostic cross-sectional study as assessed using the QUADAS tool. One of the included studies was from the United Kingdom. The

studies had very small sample sizes ranging from 18 participants (Chen et al. 2017) to 124 participants (Barzel et al. 2012).

The committee agreed that the evidence partially addressed the review question as two of the studies addressed restaging of prostate after a few weeks or months of diagnosis (Barzel et al. 2012; Chen et al. 2017; Pessoa et al. 2017) and not clinical progression as investigated by Da Rosa et al. (2015) and Feng et al. (2015).

All the studies included participants diagnosed with low risk prostate cancer apart from Feng et al. (2017) who only described participants as "on active surveillance". None of the study participants had ever had an MRI prior to initial diagnosis.

None of the studies could be meta-analysed because they were all different in terms of index test investigated, reference standard used and definitions of restaging or reclassification criteria.

Though the study by Thurtle et al (2018) reported that it used multiparametric MRI, upon assessment the committee concluded that the technology was bi-parametric MRI. The study was not downgraded because that is functional MRI included in the protocol.

Overall, when the evidence was assessed using GRADE, the evidence ranged from very low to high quality. In cases where the study was very low quality this was due to moderate risk of bias of the study and imprecise 95% confidence intervals.

***Benefits and harms***

The committee reflected on the evidence from evidence review D and evidence review E in this update investigating multiparametric MRI in biopsy naïve people who are suspected of prostate cancer and people with at least one negative TRUS biopsy respectively.

In evidence review D the committee made recommendations for clinicians to offer multiparametric MRI as the first-line investigation to people with suspected clinically localised prostate cancer. This was based on 3 studies of which two were from the UK (PROMIS (Ahmed et al. 2017); PRECISION (Kasivisvanathan et al. 2018), and Porpiglia et al. 2017). The committee discussed that as a result of these recommendations, anyone suspected of prostate cancer will be offered multiparametric MRI; however they understood that, there will be a cohort of people who received a diagnosis based on prostate biopsy alone. Some of these people may be on active surveillance.

The committee acknowledged that there is strong evidence (from the PROMIS and PRECISON studies presented in evidence review D), on the efficacy of multiparametric MRI in identifying lesions and this evidence could be extended to be part of the monitoring pathway for those people who are on active surveillance.

Evidence from Pessoa et al. (2017) showed that a positive multiparametric MRI influenced biopsy leads to a moderate increase in the probability of clinically significant cancer in a person diagnosed with low risk cancer within 6 months, resulting in restaging or reclassification of the disease. Evidence from Chen et al. (2017) showed that there is no diagnostic value in carrying out the same investigation in those diagnosed with low risk prostate cancer 8 weeks prior. The participants in both studies had not had a pre-biopsy MRI.

Evidence from Thurtle et al. (2018) showed that a positive multiparametric score of Likert 3 and above leads to a moderate increase in the probability of identifying

pathological progression in people on active surveillance. The study showed that mpMRI was able to identify a change in their prostate cancer at follow up of at least a year.

Based on all the evidence described above, the committee made a “strong” recommendation to offer multiparametric MRI to those people who are enrolled for active surveillance and have not had a pre-biopsy MRI. The committee agreed that multiparametric MRI should be used to either confirm or restage disease in people initially diagnosed with low risk prostate cancer on prostate biopsy alone.

Based on the evidence, the committee recommended clinicians consider multiparametric MRI in those people who have been on active surveillance and have not had a multiparametric MRI before. Evidence from Feng et al. (2015) showed that a positive multiparametric MRI score (defined as PIRADS score ≥3 and >4) has good diagnostic value leading to a large or very large increase in the probability of identifying clinical progression in people on active surveillance. The evidence from Da Rosa (2015) also contributed to the evidence for this recommendation as the study showed that a positive MRI/TRUS fusion biopsy leads to a large increase in the probability of clinically significant cancer (defined as any cancer of Gleason score 7 or greater) in a person on active surveillance for 38 months. Both study populations had not had a pre biopsy MRI prior to being on active surveillance.

The committee also noted that there is a UK study currently underway that will be able to provide evidence to support this review question. However, the completion date and likely publication date is unknown at the time of this review.

The committee considered the evidence from evidence review E: ‘Managing people at risk’ to help amend the suggested active surveillance protocol (table x). They suggested that clinicians should monitor PSA kinetics namely PSA density and PSA velocity because the evidence from review E showed these tests had the best balance between identifying and excluding prostate cancer.

***Cost effectiveness and resource use***

The committee reviewed the included economic evidence. It agreed that the included cost-utility analysis provided partially applicable evidence as it was based on a non-UK study. The committee noted some limitations of the analyses, particularly that the MRI-influenced biopsy every three years was not compared to regimens with different frequencies. In addition, it noted that any biopsy procedures should be triggered by positive findings on screening tests, e.g. PSA density.

The committee agreed that the economic evidence provided by Patel et al. (2018) was not sufficient to influence the recommendations made based on the clinical evidence. It confirmed the positive role of the use of MRI to make prostate biopsy more efficient and this would not have a significant resource impact. Thus, the committee concluded that the clinical evidence is sufficient to underpin its recommendation about considering the MRI-influenced prostate biopsy for people on active surveillance showing positive findings on PSA derivatives tests, e.g. PSA density to identify prostate cancer progression.

# Appendices

## Appendix A – Review protocols

**Review protocol for identifying prostate cancer clinical progression in people with low - intermediate risk cancer**

| ID | Field (based on PRISMA-P | Content |
|---|---|---|
| I | Review question | Which of the following, alone or in combination, constitutes the most clinical and cost-effective pathway for excluding the clinically significant progression of prostate cancer in people with low to intermediate risk (as defined in NICE CG175)<br>• Multiparametric/ functional MRI<br>• TRUS biopsy<br>• Transperineal template biopsy? |
| II | Type of review question | Diagnostic |
| III | Objective of the review | To determine which of the following is the most effective accurate pathway for excluding the clinically significant progression of prostate cancer in people with low to intermediate risk who are on active surveillance:-<br><br>Multiparametric/ functional MRI, TRUS biopsy, Transperineal template biopsy, MRI targeted biopsy |
| IV | Eligibility criteria – population/disease/condition/issue/domain | People with low to intermediate risk prostate cancer (as defined in NICE CG175)<br>• Low risk - <10ng/ML PSA and ≤6 Gleason score and T1-T2a clinical stage<br>• Intermediate risk – 10-20ng/m PSA or 7 Gleason score or T2b Clinical stage |

| | | |
|---|---|---|
| | | Or as defined by the study |
| V | Eligibility criteria – Index tests | • Biparametric/ Multiparametric MRI<br>• MRI guided TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy)<br>• TRUS biopsy alone (*TRUS biopsy also referred to as saturation or extended biopsy)* |
| VI | Eligibility criteria –reference (gold) standard | • Transperineal template biopsy<br>• TRUS biopsy<br>• Radical prostatectomy<br>*TRUS biopsy also referred to as saturation or extended biopsy* |
| VII | Outcomes and prioritisation | Diagnostic accuracy<br>• Sensitivity and specificity<br>• Likelihood ratios<br>If available from studies reporting diagnostic accuracy we will also extract information on:<br>• Adverse events<br>• Health-related quality of life |
| VIII | Eligibility criteria – study design | • Diagnostic cross sectional studies<br>• Systematic reviews of diagnostic cross-sectional studies |
| IX | Other inclusion exclusion criteria | • Non English- language papers<br>• Unable to calculate 2x2 tables |
| X | Proposed sensitivity/sub-group analysis, or meta-regression | • T stage<br>• Gleason score or<br>• PSA levels |

| | | |
|---|---|---|
| XI | Selection process – duplicate screening/selection/analysis | 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. |
| XII | Data management (software) | See appendix B below – section 1.3 |
| XIII | Information sources – databases and dates | See appendix C of relevant chapter<br><br>The committee advised that studies on MRI guided biopsy prior to 2007 would not reflect current practice. They advised a date cut off of 2007. |
| XIV | Identify if an update | Update.<br><br>This is an update of the 2008 clinical guideline, however the 2008 guideline does not identify a specific clinical question.<br><br>**Related recommendations:**<br><br>1.3.49 For men with evidence of biochemical relapse following radical treatment and who are considering radical salvage therapy: |

| | | |
|---|---|---|
| | | • do not offer routine MRI scanning prior to salvage radiotherapy in men with prostate cancer<br><br>• offer an isotope bone scan if symptoms or PSA trends are suggestive of metastases. [2008] |
| XV | Author contacts | Guideline updates team, National Institute for Health and Care Excellence (contact adam.okeefe@nice.org.uk ) |
| XVI | Highlight if amendment to previous protocol | For details please see section 4.5 of Developing NICE guidelines: the manual |
| XVII | Search strategy – for one database | For details please see appendix C of relevant chapter |
| XVIII | Data collection process – forms/duplicate | A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). |
| XIX | Data items – define all variables to be collected | For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables). |
| XX | Methods for assessing bias at outcome/study level | See Appendix B below – see section 1.6.1 |
| 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 1.6.2 |
| XXIII | Meta-bias assessment – publication bias, selective reporting bias | See Appendix B below – see section 1.6.3 and 1.6.5 |
| XXIV | Assessment of confidence in cumulative evidence | See Appendix B below - see section 1.6.3 |
| 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.<br><br>Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual. |
| XXVII | Sources of funding/support | The NICE Guideline Updates Team is an internal team within NICE. |
| XXVIII | Name of sponsor | The NICE Guideline Updates Team is an internal team within NICE. |

| | | |
|---|---|---|
| XXIX | Roles of sponsor | The NICE Guideline Updates Team is an internal team within NICE. |
| XXX | PROSPERO registration number | N/A |

# Appendix B – Methods

## Evidence of effectiveness of interventions

## Diagnostic test accuracy evidence

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

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

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

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

**Table 3: Interpretation of likelihood ratios**

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

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

## Evidence statements

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

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

## Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

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

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

## 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.

### 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 4 below.

**Table 4: Rationale for downgrading quality of evidence for diagnostic questions**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>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.<br>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.<br>Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. |
| Indirectness | Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded.<br>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.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.<br>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. |

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

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

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

### 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.

### Methods for combining inter-rater agreement evidence

The reliability of agreement for diagnostic data between observers was evaluated using the kappa coefficient. The measure calculates the level of agreement in classification. The general rule of thumb to follow is: if there is no agreement among the classification, then kappa ≤0; if there is complete agreement then kappa=1 (Fleiss 1971). The following schema (see Table 5), adapted from the suggestions of Fleiss, was used to interpret the level of agreement in diagnostic classification. Random-effects models (der Simonian and Laird) were fitted for all syntheses in R v3.4.0.

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.

**Table 5: Interpretation of kappa coefficient**

| Value of kappa coefficients | Interpretation |
|---|---|
| $\kappa < 0$ | No agreement |
| $0 < \kappa \leq 0.2$ | Poor agreement |
| $0.2 < \kappa \leq 0.4$ | Fair agreement |
| $0.4 < \kappa \leq 0.7$ | Good agreement |
| $0.7 < \kappa < 1.0$ | Excellent agreement |
| $\kappa = 1.0$ | Complete agreement |

### Modified GRADE for inter-rater agreement evidence

GRADE has not been developed for use with inter-rater agreement; therefore a modified approach was applied using the GRADE framework. Data from all study types was initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

**Table 6: Rationale for downgrading evidence for inter-rater agreement**

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| Risk of bias | Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded.<br>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.<br>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.<br>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. |
| Inconsistency | 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.<br>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.<br>Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.<br>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. |
| Indirectness | 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.<br>N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study.<br>Not serious: If the $I^2$ was less than 33.3%, the outcome was not downgraded.<br>Serious: If the $I^2$ was between 33.3% and 66.7%, the outcome was downgraded one level.<br>Very serious: If the $I^2$ was greater than 66.7%, the outcome was downgraded two levels. |

| GRADE criteria | Reasons for downgrading quality |
|---|---|
| | Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes. |
| Imprecision | If the 95% confidence interval for the kappa coefficient spanned two of the categories in Table 5, it was downgraded one level. If the 95% confidence interval for the kappa coefficient spanned three or more of the categories in Table 5, it was downgraded two levels.<br>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. |

# Appendix C – Literature search strategies

## Search summary

The search strategies are based on the review protocol provided. The MRI/biopsy terms have been taken from the search strategy used in CG175.

## Clinical searches

Source 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)

The clinical searches were conducted in January 2018.

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

| Database: Ovid MEDLINE(R) |
|---|
| 1 exp Prostatic Neoplasms/ |
| 2 Prostatic Intraepithelial Neoplasia/ |
| 3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw. |
| 4 PIN.tw. |
| 5 or/1-4 |
| 6 *Magnetic Resonance Imaging/ |
| 7 (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw. |
| 8 (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw. |
| 9 (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw. |
| 10 (contrast* adj2 (imag* or scan*)).tw. |
| 11 ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostat*).tw. |
| 12 turbo spin echo*.tw. |

| Database: Ovid MEDLINE(R) | |
|---|---|
| 13 | ((diffusion* or weight*) adj2 imag*).tw. |
| 14 | ((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI*) adj4 prostat*).tw. |
| 15 | (Multi-parametric or multiparametric* or biparametric* or bi-parametric*).tw. |
| 16 | *biopsy/ or *image-guided biopsy/ |
| 17 | ((transrectal* or trans-rectal* or transperineal* or trans-perineal*) adj2 (ultrasound* or biops*)).tw. |
| 18 | ((saturat* or extend* or templat*) adj2 (ultrasound* or biops*)).tw. |
| 19 | ((TRUS or TRUSB) adj4 prostat*).tw. |
| 20 | or/6-19 |
| 21 | 5 and 20 |

## Study design filters and limits

A diagnostic filter was appended to the review question above. The MEDLINE filter is presented below. It were translated for use in the MEDLINE In-Process and Embase databases.

An English language limit has been applied.

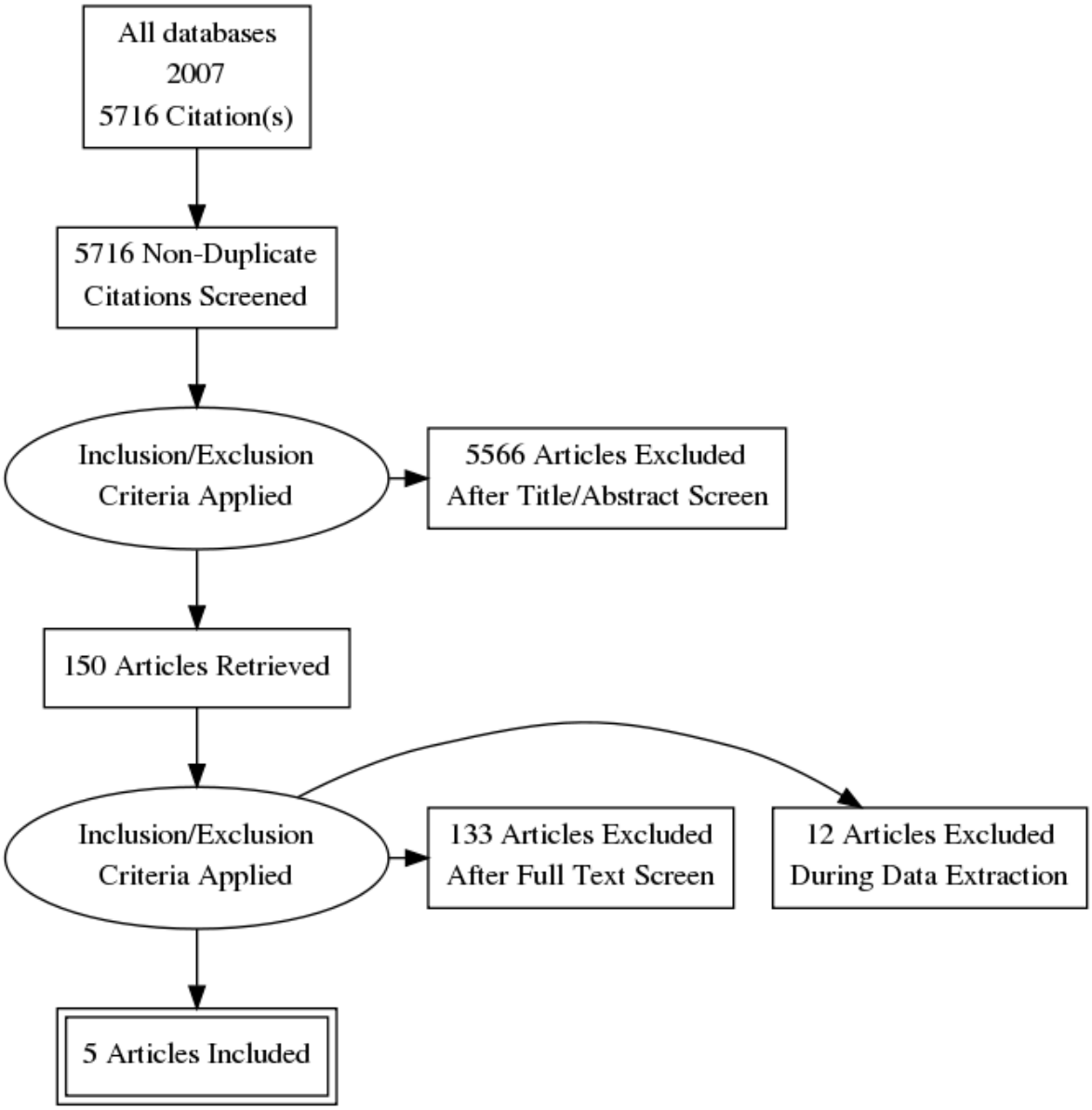
A date limit from 2007 was applied as the committee members were confident we would unlikely find studies on MRI guided biopsy prior to 2007 that reflect current practice.

Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

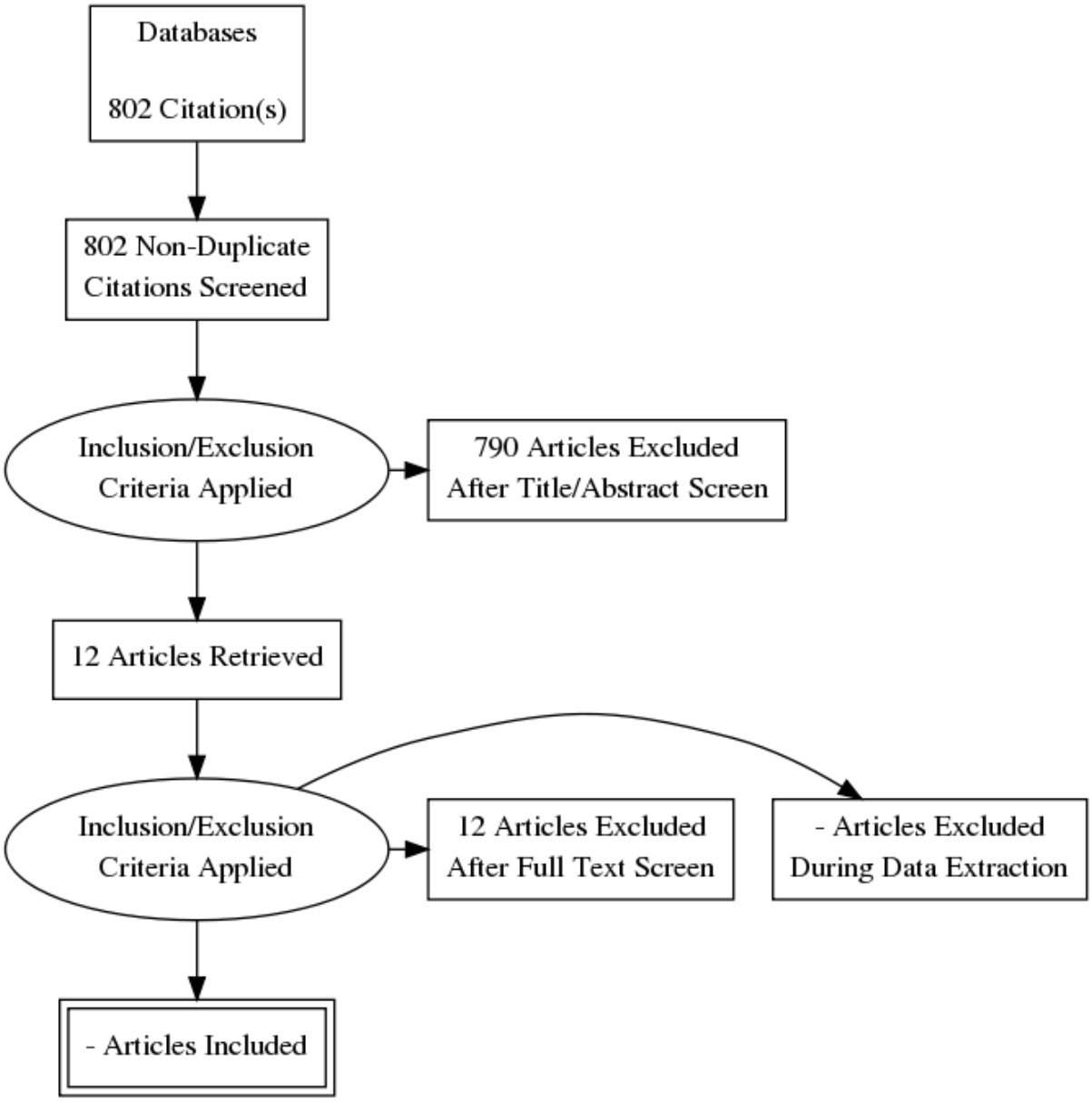
| The MEDLINE diagnostic filter | |
|---|---|
| 1 | (sensitiv: or diagnos:).mp. or di.fs. |
| 2 | Prostate/dg or Prostatic Neoplasms/dg |
| 3 | or/1-3 |

# Appendix D – Clinical evidence study selection

**Clinical evidence –**



**Economic evidence –**



# Appendix E – evidence tables

## Clinical evidence tables

### Identifying prostate cancer clinical progression in people with low - intermediate risk cancer

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| Barzell (2012) | Identifying candidates for active surveillance: An evaluation of the repeat biopsy strategy for men with favourable risk prostate cancer | Study details<br>Study location<br>USA<br>Study setting<br>Hospital<br>Study dates<br>Between 2002 and 2009<br>Sources of funding<br>Department of Health's National institute for Health Research Biomedical Research Centres funding scheme, the Medical Research Council (UK). Pelican cancer foundation, Prostate Action and St Peter's Trust<br><br>Inclusion criteria<br>Men who fulfilled the Epstein low risk definition for prostate cancer<br><br>Exclusion criteria<br>None reported<br><br>Sample characteristics<br>Sample size<br>124 people<br>Mean age (SD)<br>69.4 years (no SD reported)<br>Mean prostate volume (sd)<br>46.3 ml (no SD) | Patient selection<br>Unclear risk of bias<br>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<br><br>Index test<br>Unclear risk of bias<br>Both tests were carried out at the same time.. it is unclear whether the researchers were blind to either test results. The thresholds used were all predetermined<br><br>Reference standard<br>Low risk of bias<br>The reference standard was chosen by the committee and was regarded as gold standard<br><br>Flow and timing<br>Low risk of bias<br>The TRUS and transperineal biopsy was carried out at the same time. All patients received the same reference standard All patients were included in the analysis<br><br>Overall risk of bias<br>Moderate |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | Mean PSA ng/ml<br>0.14 ng/ml (no SD)<br><br>Index test(s)<br>TRUS biopsy<br>repeat biopsy<br><br>Reference standard(s)<br>Transperineal prostate biopsy | Due to uncertainties surrounding patient selection<br><br>Directness<br>Directly applicable |
| Chen (2017) | Outcomes of combination MRI-targeted and transperineal template biopsy in restaging low-risk prostate cancer for active surveillance | Study type<br>Cross-sectional study<br><br>Study details<br>Study location<br>Singapore<br>Study setting<br>No details provided<br>Study dates<br>No dates provided<br>Sources of funding<br>None disclosed<br><br>Inclusion criteria<br>Low risk, low grade, localised prostate cancer<br>Gleason score 6 or less<br>Serum PSA level 10ng/ml or less<br>Clinical stage less than or equal to T2a<br><br>Sample characteristics<br>Sample size<br>19 participants- 18 went through to MRI targeted biopsy<br>%female<br>n/a<br>Mean age (SD) | Patient selection<br>Unclear risk of bias<br>Patient selection details not provided<br><br>Index test<br>Low risk of bias<br>".. The surgeon was blinded to the MRI findings ..." and the reference standard was carried out before the targeted biopsy. The MRI threshold was pre specified using the PIRADS version 1 and 2 depending on the study time period.<br><br>Reference standard<br>Low risk of bias<br>The reference standard matches protocol and is regarded as the "gold standard"<br><br>Flow and timing<br>Low risk of bias<br>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 |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | 65.4 (4.9) years<br>Mean PSA ng/ml<br>7.3 (1.7) ng/ml<br><br>Index test(s)<br>Multiparametric MRI<br>high field mpMRI examination obtained with a 3.0T MRI imaging system using a multichannel pelvic phased array coil. High spatial resolution T2-weighted imaging in the axial, sagittal and coronal planes, diffusion weighted imaging in the axial plane (b values 0-50, 500 and 1000s/mm2) and dynamic contrast-enhanced (DCE) images. Targeted biopsy was then planned and performed by cognitive fusion using the same robotic biopsy platform at the same setting as the systematic template biopsy. PIRADS version 1.o and PIRADS version 2 for studies after December 2014.<br><br>Reference standard(s)<br>Systematic template biopsy<br>performed under general anaesthetic with the surgeon blinded to the MRI findings, using a robotic transperineal biopsy guidance platform. | Overall risk of bias<br>Low<br><br>Directness<br>Directly applicable |
| Da Rosa (2015) | A prospective comparison of MRI-US fused targeted biopsy versus systematic ultrasound-guided biopsy for detecting clinically significant prostate cancer in patients on active surveillance | Study type<br>Cross-sectional study<br><br>Study details<br>Study location<br>Canada<br>Study setting<br>Single institution<br>Study dates<br>From March 2011 to December 2012<br>Sources of funding | Patient selection<br>Unclear risk of bias<br>No patient selection details were provided<br><br>Index test<br>Low risk of bias<br>"...The uro-radiologist was blinded to prior biopsy results and previous pathological findings.." the threshold was predefined, they used a LIKERT scale. |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | No financial support declared<br><br>Inclusion criteria<br>All patient were on active surveillance<br>Referred for biopsy due to rising PSA or appropriate re-biopsy interval according to the AS protocol<br><br>Exclusion criteria<br>None reported<br><br>Sample characteristics<br>Sample size<br>81 participants - 72 included in analysis<br>%female<br>n/a<br>Mean age (SD)<br>64.8 (range 41-79) years<br>Mean PSA ng/ml<br>5.0 (range 1.1-17.6) ng/ml<br>Median months on active surveillance<br>38.0months (range 0.9-134.7)<br><br>Index test(s)<br>MRI-ultrasound fusion biopsy<br>The MRI protocol was - 3.0T MR imaging system, without an endorectal coil, combining axial, sagittal and coronal T2- weighted, diffusion weighted, b values 100, 400, 1000 and dynamic contrast enhanced imaging.<br><br>Reference standard(s)<br>TRUS biopsy | Reference standard<br>Low risk of bias<br>The reference was chosen by the committee as the "gold standard" for this review.<br><br>Flow and timing<br>Low risk of bias<br>the index test and the reference test was carried out by the same operator, however the there was a second operator who was blinded to the location of suspicious lesions on MRI.<br><br>Overall risk of bias<br>Low<br><br>Directness<br>Directly applicable |
| Feng (2015) | Multiparametric magnetic resonance imaging localizes established | Study type<br>Cross-sectional study | Patient selection<br>Unclear risk of bias |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | extracapsular extension of prostate cancer | Study details<br>Study location<br>USA<br>Study setting<br>No details provided<br>Study dates<br>Between January 2010 and July 2014<br>Sources of funding<br>None disclosed<br><br>Inclusion criteria<br>None reported<br><br>Exclusion criteria<br>Patients receiving preoperative androgen deprivation therapy<br><br>Sample characteristics<br>Sample size<br>112 participants<br>%female<br>n/a<br>Mean age (SD)<br>62.8 (7.5) years<br>Mean PSA ng/ml<br>8.2 (7.2) ng/ml<br><br>Index test(s)<br>Multiparametric MRI<br>imaging using 3.0T MRI system equipped with a 12-channel pelvic phased array coil. Anatomic images included T1- and T2 weighted turbo spin echo, acquired in the axial, sagittal and coronal planes. Diffusion weighted imaging was acquired using a standard single-shot echo planar imaging sequence. The orthogonal diffusion directions | Patient selection details not provided. The index test thresholds were predetermined using PIRADS<br><br>Index test<br>Low risk of bias<br>".. All cases were reviewed by a single radiologist with expertise in Prostate MR images..."<br><br>Reference standard<br>Low risk of bias<br>The reference standard matches protocol and is regarded as the "gold standard".<br><br>Flow and timing<br>Unclear risk of bias<br>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<br><br>Overall risk of bias<br>Moderate – as a result of the uncertainties surrounding patients selection<br><br>Directness<br>Directly applicable |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | including a single b0 measurement were acquired at 2 nonzero b values 400 and 800s/mm2.<br><br>Reference standard(s)<br>Radical prostatectomy | |
| Pessoa (2017) | Value of 3-Tesla multiparametric magnetic resonance imaging and targeted biopsy for improved risk stratification in patients considered for active surveillance | Study type<br>Prospective cohort study<br><br>Study details<br>Study location<br>Brazil<br>Study setting<br>No details provided<br>Study dates<br>Between March 2014 and January 2016<br>Sources of funding<br>None declared<br><br>Inclusion criteria<br>Standard Biopsy<br>taken a maximum of 6 months before<br>Low risk, low grade, localised prostate cancer<br>Clinical Stage t1c-t12a cancer<br>Gleason score 6 or less<br>Serum PSA level 10ng/ml or less<br>Life expectancy of >5years<br><br>Exclusion criteria<br>Previous history of prostate biopsy<br>Prostate surgery<br>Had any contraindication to MRI (e.g. claustrophobia, pacemaker, estimated glomerular filtration rate </=50) | Patient selection<br>Unclear risk of bias<br>Patient selection details not provided, the participants were referrals from other centres, it is unclear if the patient selection strategy could have increased risk of bias.<br><br>Index test<br>Unclear risk of bias<br>Every man underwent sampling of 12 systematic sites, independent of mpMRI results, MRI images were then considered and appeared on the screen adjacent to the ultrasound, allowing real-time visual estimation comparison of methods and zones of interest.<br><br>Reference standard<br>Unclear risk of bias<br>The reference standard matches protocol and is regarded as the "gold standard".<br><br>Flow and timing<br>Unclear risk of bias<br>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<br><br>Overall risk of bias<br>Moderate |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | Sample characteristics<br>Sample size<br>105 participants<br>%female<br>N/A<br>Median Age (IQR)<br>67 (48-81) years<br>Median PSA level (IQR) ng/ml<br>7.5 (1.2 - 10.0)<br>Median PSAD (ng/ml/ml)<br>0.11 (0.04 -0.28) ng/ml/ml<br><br>Index test(s)<br>Multiparametric MRI<br>Axial-oblique, fast spin-echo T2-weighted, diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) – MRI on a 16 channel cardiac surface, external phased -array coil 3.0t MRI system with standard widespread recommendation for image acquisition. PIRADS version 1<br><br>Reference standard(s)<br>Confirmatory Biopsy<br>included a standard biopsy and visual estimation-guided TRUS biopsy | as a result of the uncertainties surrounding patients selection and index test results interpretation<br><br>Directness<br>Directly applicable |
| Thurtle (2018) | Progression and treatment rates using an active surveillance protocol incorporating image-guided baseline biopsies and multiparametric magnetic resonance imaging monitoring for men with favourable-risk prostate cancer. | Study type<br>Cross-sectional study<br><br>Study details<br>Study location<br>United Kingdom<br>Study setting<br>Not disclosed<br>Study dates | Patient selection<br>Unclear risk of bias<br>Not specified - any newly diagnosed patients selecting active surveillance as their preferred management.<br><br>Index test<br>Low risk of bias<br>All participants had mpMRI and biopst carried out |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | 2011 onwards<br>Sources of funding<br>None declared<br><br>Inclusion criteria<br>Enrolled in an active surveillance program<br>Men aged 50-80 years with histologically proven prostate cancer<br>Clinical stage T1-T2, PSA <20ng/ml<br>histological Grade Group <2 and <50% overall tumour core involvement<br>Medically fit for radical treatment options (ECOG 0-1)<br>All were treatment naive and first diagnosis of cancer<br>Only men with a clinical follow up of at least 12 months<br><br>Exclusion criteria<br>None reported<br><br>Sample characteristics<br>Sample size<br>145 men<br>Median Age (IQR)<br>64 (IQR 59-68)<br>Median PSA level (IQR) ng/ml<br>6.8 ng/ml (5.2-9.4 ng/ml)<br>Median PSAD (ng/ml/ml)<br>0.13 ng/ml/ml (0.09-0.18)<br>Follow up<br>39 months (range 15-63 months) | Reference standard<br>Low risk of bias<br><br>Flow and timing<br>Low risk of bias<br>All participants had their mpMRI and re-biopsy done as part of the active surveillamce protocol<br><br>Overall risk of bias<br>Moderate<br><br>Directness<br>Directly applicable |

| Short title | Title | Study Characteristics | Quality Assessment |
|---|---|---|---|
| | | Reference standard(s)<br>Systematic biopsy (transperineal or transrectal) | |

## Economic evidence

| Study, population, country and quality | Data sources | Other comments | Strategy | Total Cost (€) | Total Effect (QALYs) | ICER (€/QALY) | Authors' conclusions | Uncertainty |
|---|---|---|---|---|---|---|---|---|
| The Role of MpMRI in AS for Men with Low-risk PCa: A Cost-effectiveness Modeling Study<br><br>**Partially applicable very serious limitations** [a, b, c] | Effectiveness: accuracy data for TRUS, Mp-MRI and MRI-TRUS, obtained from existing literature (Schoots 2015 and PROMIS)<br><br>Cost: healthcare perspective, prices in €, 2016<br><br>Utility: derived from existing literature, applying decrement associated with biopsy that last for 3 weeks. Also, decrement due to AEs associated with RP or RT | A Markov model with a cycle length of 1 year; consisting of 5 health states: Low-risk, low-risk-post-treatment, high-risk, high-risk-post-treatment and death due to PCa or other causes.<br><br>Cost and QALYs discounted by 4 and 1.5% annually<br><br>3 strategies for AS were compared: TRUS every 3 years; MRI-TRUS every 3 years; MRI only every 3 years<br><br>Accuracy data were obtained from studies that addressed different population (people with suspicion of PCa)<br><br>Transition probability from low-risk to high-risk: was not explicitly clear it was derived. | Base case | | | | Mp-MRI, if positive, followed by TRUS every 3 years resulted in greater QALYs and less costs than TRUS only and Mp-MRI only every 3 years to identify high-risk prostate cancer within people with low-risk disease. | Probabilistic model run for 10,000 iterations. Optimal strategy remained the same in 90% of the iterations; the results were robust in one-way sensitivity analysis and scenario analysis. |
| | | | 1 | 5,150 | 18.66 | - | | |
| | | | 2 | 4,848 | 18.67 | Dominant | | |
| | | | 3 | 5,994 | 18.27 | Dominated | | |

| Study, population, country and quality | Data sources | Other comments | Strategy | Total | | ICER (€/QALY) | Authors' conclusions | Uncertainty |
|---|---|---|---|---|---|---|---|---|
| | | | | Cost (€) | Effect (QALYs) | | | |
| a) Techniques used in MRI-targeted TRUS not specified<br>b) Evidence on accuracy data of tests obtained from studies with different population<br>c) Uncertainty in the long-run outcome related to progression rate from low- to high-risk | | | | | | | | |

# Appendix F – GRADE tables

### Identifying prostate cancer clinical progression in people with low - intermediate risk cancer

| No. of studies | Study design | Sample size | Sensitivity (95%CI) | Specificity (95%CI) | Effect size (95%CI) | Risk of bias | Inconsistency | Indirectness | Imprecision | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| **TRUS biopsy- (reference standard: transperineal template mapping biopsy)** | | | | | | | | | | |
| 1 study Barzell (2012) | Cross-sectional | 124 | 0.10 (0.04, 0.21) | 0.93 (0.85, 0.97) | LR- 0.97 (0.87, 1.08) | Serious[1] | N/A | Not serious | Not serious | Moderate |
| | | | | | LR+ 1.43 (0.44, 4.69) | Serious[1] | N/A | Not serious | Very Serious[2] | Very Low |
| **MRI influenced biopsy (reference standard: robotic transperineal template biopsy)** | | | | | | | | | | |
| 1 study Chen (2017) | Cross-sectional | 18 | 0.03(0.01, 0.13) | 0.87 (0.74, 0.94) | LR- 1.12 (0.98, 1.25) | Not serious | N/A | Not serious | Not serious | High |
| | | | | | LR+0.27 (0.06, 1.26) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| **Multiparametric MRI (reference standard: TRUS biopsy) (**people with Clinical Stage t1c-t12a cancer, Gleason score 6 or less Serum PSA level 10ng/ml or less) | | | | | | | | | | |
| 1 study Pessoa (2017) | Cross-sectional | 105 | 0.95 (0.85, 0.98) | 0.79(0.65, 0.88) | LR- 0.07 (0.02, 0.20) | Not serious | N/A | Not serious | Not serious | High |
| | | | | | LR+ 4.46 (2.56, 7.75) | Not serious | N/A | Not serious | Not serious | High |
| **MRI influenced biopsy (reference standard: TRUS Biopsy) (**people with Clinical Stage t1c-t12a cancer, Gleason score 6 or less Serum PSA level 10ng/ml or less) | | | | | | | | | | |
| 1 study Pessoa (2017) | Cross-sectional | 87 | 0.85 (0.70, 0.93) | 0.69 (0.54, 0.80) | LR- 0.22 (0.11, 0.48) | Not serious | N/A | Not serious | Not serious | High |
| | | | | | LR+ 2.71 (1.74, 4.21) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| **MRI/TRUS fusion targeted biopsy (reference standard: TRUS) (people on Active surveillance)** | | | | | | | | | | |
| Reclassification criteria - Any cancer of Gleason score 7 or greater | | | | | | | | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 study Da Rosa (2015) | Cross-sectional | 72 | 0.83(0.52, 0.96) | 0.88 (0.76, 0.94) | LR- 0.19 (0.05, 0.67) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| | | | | | LR+ 7.14 (3.41, 14.98) | Not serious | N/A | Not serious | Not serious | High |
| Reclassification criteria - Gleason score of 6 with >50% involvement in any core | | | | | | | | | | |
| 1 study Da Rosa (2015) | Cross-sectional | 72 | 0.76 (0.54, 0.90) | 0.80 (0.67, 0.89) | LR- 0.30 (0.14, 0.64) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| | | | | | LR+ 3.89 (2.12, 7.14) | Not serious | N/A | Not serious | Not serious | High |
| **Muliparametric MRI (reference standard: Radical prostatectomy)** | | | | | | | | | | |
| Reclassification criteria – suspicious/definite extracapsular extension (mpMRI score ≥3) (participants with clinical prostate stage T1c – T2a) | | | | | | | | | | |
| 1 Study Feng (2015) | Cross-sectional | 112 | 0.72(0.54, 0.86) | 0.90 (0.82, 0.95) | LR- 0.31 (0.17, 0.55) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| | | | | | LR+ 7.51 (3.75, 15.07) | Not serious | N/A | Not serious | Not serious | High |
| Reclassification criteria – definite extracapsular extension (mpMRI PIRADS score ≥4 (participants with clinical prostate stage T1c – T2a) | | | | | | | | | | |
| 1 study Feng (2015) | Cross-sectional | 112 | 0.41 (0.25, 0.60) | 0.99(0.92, 1.00) | LR – 0.59 (0.44, 0.81) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| | | | | | LR+ 34.35 (4.67, 252.69) | Not serious | N/A | Not serious | Not serious | High |
| Muliparametric MRI – pathological progression (reference standard: Systematic biopsies (transperineal or transrectal)) | | | | | | | | | | |
| 1 study Thurtle (2018) | Cross-sectional | 104 | 0.50 (0.29, 0.71) | 0.87 (0.78, 0.93) | LR- 0.58 (0.37, 0.90) | Not serious | N/A | Not serious | Serious[3] | Moderate |
| | | | | | LR+ 3.82 (1.89, 7.72) | Not serious | N/A | Not serious | Serious[3] | Moderate |

1. Moderate risk of bias – due to selection bias – unclear how the study participants were selected, downgraded once
2. 95% confidence interval for likelihood ratio crosses both ends of a defined MID interval – (0.5, 2), downgraded twice
3. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once

# Appendix G – Excluded studies

## Clinical studies

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| Abd-Alazeez (2014) | Can multiparametric magnetic resonance imaging predict upgrading of transrectal ultrasound biopsy results at more definitive histology? | Not possible to calculate a 2x2 table from data presented in the study |
| Abdi (2015) | Multiparametric magnetic resonance imaging enhances detection of significant tumor in patients on active surveillance for prostate cancer | Not possible to calculate a 2x2 table from data presented in the study |
| Ahallal (2016) | Clinical performance of transperineal template guided mapping biopsy for therapeutic decision making in low risk prostate cancer | Study does not contain any relevant index tests |
| Alberts (2017) | Risk-stratification based on magnetic resonance imaging and prostate-specific antigen density may reduce unnecessary follow-up biopsy procedures in men on active surveillance for low-risk prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Anderson (2015) | Age is associated with upgrading at confirmatory biopsy among men with prostate cancer treated with active surveillance | Study does not contain any relevant index tests |
| Arani (2011) | The feasibility of endorectal MR elastography for prostate cancer localization | No reference standard |
| Bains (2014) | Diffusion-weighted magnetic resonance imaging detects significant prostate cancer with high probability | Mixed cancer populations |
| Bianchi (2016) | Multiparametric magnetic resonance imaging and frozen-section analysis efficiently predict upgrading, upstaging, and extraprostatic extension in patients undergoing nerve-sparing robotic-assisted radical prostatectomy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Billing (2015) | Preoperative mp-MRI of the prostate provides little information about staging of prostate carcinoma in daily clinical practice | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Bloch (2007) | Prostate cancer: Accurate determination of extracapsular extension with high-spatial-resolution dynamic contrast-enhanced and T2-weighted MR imaging - Initial results | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | | least 800s/mm2<br>Does not give details of the b values |
| Borkowetz (2015) | Assessment of tumour aggressiveness in tranperineal mri/ultrasound-fusion biopsy in comparison to transrectal systematic prostate biopsy | Conference abstract |
| Borkowetz (2016) | Direct comparison of multiparametric magnetic resonance imaging (MRI) results with final histopathology in patients with proven prostate cancer in MRI/ultrasonography-fusion biopsy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Bosco (2016) | Confirmatory biopsy for the assessment of prostate cancer in men considering active surveillance: Reference centre experience | Not possible to calculate a 2x2 table from data presented in the study |
| Brock (2015) | Fusion of Magnetic Resonance Imaging and Real-Time Elastography to Visualize Prostate Cancer: A Prospective Analysis using Whole Mount Sections after Radical Prostatectomy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Cerantola (2013) | Can 3T multiparametric magnetic resonance imaging accurately detect prostate cancer extracapsular extension? | Study population unclear |
| Chabanova (2011) | Prostate cancer: 1.5 T endo-coil dynamic contrast-enhanced MRI and MR spectroscopy - Correlation with prostate biopsy and prostatectomy histopathological data | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Does not give details of the b values |
| Chamie (2014) | The role of magnetic resonance imaging in delineating clinically significant prostate cancer | Does not contain a population with low risk or intermediate cancer |
| De Rooij (2014) | Accuracy of multiparametric MRI for prostate cancer detection: A meta-analysis | Systematic review- no additional articles identified for inclusion in this review |
| de Rooij (2016) | Accuracy of Magnetic Resonance Imaging for Local Staging of Prostate Cancer: A Diagnostic Meta-analysis | Duplicate reference |
| Dekalo (2017) | High cancer detection rate using cognitive fusion - targeted transperineal prostate biopsies | Does not contain a population with low risk or intermediate |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | | cancer |
| Delongchamps (2011) | Multiparametric MRI is helpful to predict tumor focality, stage, and size in patients diagnosed with unilateral low-risk prostate cancer | Restrospective study looking at participants before their follow up MRI or Biopsy |
| Delongchamps (2015) | Detection of significant prostate cancer with magnetic resonance targeted biopsies - Should transrectal ultrasound-magnetic resonance imaging fusion guided biopsies alone be a standard of care? | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Dianat (2014) | Performance of multiparametric magnetic resonance imaging in the evaluation and management of clinically low-risk prostate cancer | Systematic review- no additional articles identified for inclusion in this review |
| Donati (2014) | Prostate MRI: Evaluating tumor volume and apparent diffusion coefficient as surrogate biomarkers for predicting tumor Gleason score | Study population unclear |
| Eisenberg (2011) | The importance of tumor palpability and transrectal ultrasonographic appearance in the contemporary clinical staging of prostate cancer | No reference standard |
| Flavell (2014) | Abnormal findings on multiparametric prostate magnetic resonance imaging predict subsequent biopsy upgrade in patients with low risk prostate cancer managed with active surveillance | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>B value = 0+600s/mm2 |
| Frye (2017) | Magnetic Resonance Imaging-Transrectal Ultrasound Guided Fusion Biopsy to Detect Progression in Patients with Existing Lesions on Active Surveillance for Low and Intermediate Risk Prostate Cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Gallina (2012) | Unilateral positive biopsies in low risk prostate cancer patients diagnosed with extended transrectal ultrasound-guided biopsy schemes do not predict unilateral prostate cancer at radical prostatectomy | Restrospective study looking at participants before their follow up MRI or Biopsy |
| Girouin (2007) | Prostate dynamic contrast-enhanced MRI with simple visual diagnostic criteria: Is it reasonable? | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| Goeb (2007) | MRI spectroscopy in screening of prostate cancer | Not a relevant study design (crosssectional study) |
| Gondo (2014) | Multiparametric 3T MRI for the prediction of pathological downgrading after radical prostatectomy in patients with biopsy-proven Gleason score 3 + 4 prostate cancer | Study populaton have high risk prostate cancer |
| Gordon (2017) | Cost-effectiveness analysis of multiparametric MRI with increased active surveillance for low-risk prostate cancer in Australia | Health economics paper |
| Guo (2015) | Magnetic resonance imaging on disease reclassification among active surveillance candidates with low-risk prostate cancer: A diagnostic meta-analysis | Systematic review- no additional articles identified for inclusion in this review |
| Gupta (2016) | Multiparametric prostate MRI: focus on T2-weighted imaging and role in staging of prostate cancer | Review article but not a systematic review |
| Haider (2016) | Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer: A Systematic Review | Does not contain a population with low risk or intermediate cancer |
| Hamoen (2018) | Value of Serial Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Imaging-guided Biopsies in Men with Low-risk Prostate Cancer on Active Surveillance After 1 Yr Follow-up | Reference standard in study does not match that specified in protocol |
| Heijmink (2007) | Prostate cancer: Body array versus endorectal coil MR imaging at 3T - Comparison of image quality, localization, and staging performance | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Hoeks (2014) | Value of 3-T multiparametric magnetic resonance imaging and magnetic resonance-guided biopsy for early risk restratification in active surveillance of low-risk prostate cancer: A prospective multicenter cohort study | Reference standard in study does not match that specified in protocol |
| Hwii (2011) | The predictability of T3disease in staging MRI following prostate biopsy decreases in patients with high initial PSA and Gleason score | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Itatani (2014) | Triage of low-risk prostate cancer patients with PSA levels 10 ng/mL or less: Comparison of apparent diffusion coefficient | Does not contain a population with low risk or intermediate |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | value and transrectal ultrasound-guided target biopsy | cancer |
| Jin (2015) | Pathological upgrading in prostate cancer patients eligible for active surveillance: Does prostate-specific antigen density matter? | Study does not contain any relevant index tests |
| Jung (2012) | Local staging of prostate cancer: Comparative accuracy of T2-weighted endorectal MR imaging and transrectal ultrasound | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Kan (2014) | Pre-operative tumor localization and evaluation of extra-capsular extension of prostate cancer: how misleading can it be? | Restrospective study looking at participants before their follow up MRI or Biopsy |
| Kang (2016) | Predictors of pathological upgrading in low-risk prostate cancer patients without hypointense lesions on an apparent diffusion coefficient map of multiparametric magnetic resonance imaging | No reference standard |
| Kasivisvanathan (2013) | Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer | Included a mixed population of suspected prostate cancer and proven prostate cancer with no sub group analysis |
| Katz (2014) | Comparison of transperineal mapping biopsy results with whole-mount radical prostatectomy pathology in patients with localized prostate cancer | Study does not contain any relevant index tests |
| Kim (2014) | Low-risk prostate cancer: The accuracy of multiparametric MR imaging for detection | Not possible to calculate a 2x2 table from data presented in the study<br>The MPMRI modalities were reported separately, unable to combine to see full effect of the MPMRI |
| Kryvenko (2012) | Findings in 12-core transrectal ultrasound-guided prostate needle biopsy that predict more advanced cancer at prostatectomy: analysis of 388 biopsy-prostatectomy pairs | Does not contain a population with low risk or intermediate cancer |
| Kuhl (2017) | Abbreviated biparametric prostate MR imaging in men with elevated prostate-specific antigen | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| Kulkarni (2007) | Clinical predictors of gleason score upgrading: Implications for patients considering watchful waiting, active surveillance, or brachytherapy | Study does not contain any relevant index tests |
| Lai (2017) | Factors predicting prostate cancer upgrading on magnetic resonance imaging-targeted biopsy in an active surveillance population | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>B value not specified |
| Leapman (2017) | Association between a 17-gene genomic prostate score and multi-parametric prostate MRI in men with low and intermediate risk prostate cancer (PCa) | No reference standard |
| Lee (2010) | Is endorectal coil necessary for the staging of clinically localized prostate cancer? Comparison of non-endorectal versus endorectal MR imaging | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Li (2013) | Diagnostic Performance of Contrast Enhanced Ultrasound in Patients with Prostate Cancer. A Meta-Analysis | Study does not contain any relevant index tests |
| Loggitsi (2017) | Multiparametric Magnetic Resonance Imaging of the Prostate for Tumour Detection and Local Staging: Imaging in 1.5T and Histopathologic Correlation | Follow up of less than 4 weeks |
| Ma (2017) | The Role of Multiparametric Magnetic Resonance Imaging/Ultrasound Fusion Biopsy in Active Surveillance | Reference standard in study does not match that specified in protocol |
| Margel (2012) | Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: A prospective cohort study | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Does not give details of the b values |
| Marliere (2014) | The role of MRI-targeted and confirmatory biopsies for cancer upstaging at selection in patients considered for active surveillance for clinically low-risk prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| McCammack (2016) | Restriction spectrum imaging improves MRI-based prostate cancer detection | Reference standard in study does not match that specified in |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | | protocol |
| Meng (2016) | Relationship between Prebiopsy Multiparametric Magnetic Resonance Imaging (MRI), Biopsy Indication, and MRI-ultrasound Fusion-targeted Prostate Biopsy Outcomes | Included a mixed population of suspected prostate cancer and proven prostate cancer with no sub group analysis |
| Min (2012) | Usefulness of a combined approach of T1-weighted, T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging in prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Study comparing MRI protocols |
| Monni (2017) | Magnetic resonance imaging in prostate cancer detection and management: A systematic review | Review article but not a systematic review |
| Moon (2010) | Predictive factors of Gleason score upgrading in localized and locally advanced prostate cancer diagnosed by prostate biopsy | Study does not contain any relevant index tests |
| Mullins (2013) | Multiparametric magnetic resonance imaging findings in men with low-risk prostate cancer followed using active surveillance | Reference standard in study does not match that specified in protocol |
| Muthigi (2017) | Missing the Mark: prostate Cancer Upgrading by Systematic Biopsy over Magnetic Resonance Imaging/Transrectal Ultrasound Fusion Biopsy | Not possible to calculate a 2x2 table from data presented in the study |
| Nahar (2017) | Reclassification Rates of Patients Eligible for Active Surveillance After the Addition of Magnetic Resonance Imaging-Ultrasound Fusion Biopsy: An Analysis of 7 Widely Used Eligibility Criteria | Does not contain a population with low risk or intermediate cancer |
| Nelson (2013) | Repeat prostate biopsy strategies after initial negative biopsy: meta-regression comparing cancer detection of transperineal, transrectal saturation and MRI guided biopsy (Provisional abstract) | Does not contain a population with low risk or intermediate cancer |
| Nogueira (2010) | Focal Treatment or Observation of Prostate Cancer: Pretreatment Accuracy of Transrectal Ultrasound Biopsy and T2-weighted MRI | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Novis (2011) | Clinically low-risk prostate cancer: evaluation with transrectal doppler ultrasound and functional magnetic resonance imaging | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | | at least 1.5T and b value of at least 800s/mm2 |
| Numao (2007) | Improved Accuracy in Predicting the Presence of Gleason Pattern 4/5 Prostate Cancer by Three-Dimensional 26-Core Systematic Biopsy | Reference standard in study does not match that specified in protocol |
| Ouzzane (2015) | Magnetic Resonance Imaging Targeted Biopsy Improves Selection of Patients Considered for Active Surveillance for Clinically Low Risk Prostate Cancer Based on Systematic Biopsies | Does not contain a population with low risk or intermediate cancer |
| Park (2007) | Comparison of phased-array 3.0-T and endorectal 1.5-T magnetic resonance imaging in the evaluation of local staging accuracy for prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Does not give details of the b values and contrast enhancement |
| Park (2010) | The role of endorectal magnetic resonance imaging in predicting extraprostatic extension and seminal vesicle invasion in clinically localized prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Park (2014) | Prostate cancer: Role of pretreatment multiparametric 3-T MRI in predicting biochemical recurrence after radical prostatectomy | Study populaton have high risk prostate cancer |
| Park (2014) | Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Does not give details of the b values |
| Park (2014) | Role of multiparametric 3.0-Tesla magnetic resonance imaging in patients with prostate cancer eligible for active surveillance | Restrospective study looking at participants before their follow up MRI or Biopsy |
| Park (2016) | Prediction of biochemical recurrence after radical prostatectomy with PI-RADS version 2 in prostate cancers: initial results | Study does not contain any relevant index tests |
| Peltier (2016) | Results of a comparative analysis of magnetic resonance imaging-targeted versus three-dimensional transrectal | Does not contain a population with low risk or intermediate |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | ultrasound prostate biopsies: Size does matter | cancer |
| Pepe (2016) | Detection rate for significant cancer at confirmatory biopsy in men enrolled in Active Surveillance protocol: 20 cores vs 30 cores vs MRI/TRUS fusion prostate biopsy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Pepe (2016) | Can MRI/TRUS fusion targeted biopsy replace saturation prostate biopsy in the re-evaluation of men in active surveillance? | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Pepe (2017) | Confirmatory biopsy of men under active surveillance: extended versus saturation versus multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Ploussard (2011) | Prostate cancer antigen 3 score accurately predicts tumour volume and might help in selecting prostate cancer patients for active surveillance | Study does not contain any relevant index tests |
| Ploussard (2013) | Detailed biopsy pathologic features as predictive factors for initial reclassification in prostate cancer patients eligible for active surveillance | Study does not contain any relevant index tests |
| Pokorny (2014) | Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent mr-guided biopsy in men without previous prostate biopsies | Does not contain a population with low risk or intermediate cancer |
| Presti (1996) | Prediction of focal extracapsular extension at radical prostatectomy: Relative merit of transrectal ultrasound, endorectal magnetic resonance imaging, prostate specific antigen, prostate specific antigen density, and systematic biopsy | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Puech (2013) | Prostate cancer diagnosis : Multiparametric mr-targeted biopsy with cognitive and transrectal us-mr fusion guidance versus systematic biopsy-prospective multicenter study | Does not contain a population with low risk or intermediate cancer |
| Radtke (2016) | Further reduction of disqualification rates by additional MRI-targeted biopsy with transperineal saturation biopsy compared with standard 12-core systematic biopsies for the selection of prostate cancer patients for active surveillance | Not possible to calculate a 2x2 table from data presented in the study |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| Radtke (2016) | Reduced disqualification rates when MRI-targeted transperineal fusion biopsies are used instead of standard 12-core systematic biopsies for selection of prostate cancer patients for active surveillance | Duplicate reference |
| Raventos (2010) | Preoperative prediction of pathologically insignificant prostate cancer in radical prostatectomy specimens: the role of prostate volume and the number of positive cores | Study does not contain any relevant index tests |
| Recabal (2016) | The Efficacy of Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Risk Classification for Patients with Prostate Cancer on Active Surveillance | Not possible to calculate a 2x2 table from data presented in the study |
| Renard-Penna (2017) | Role of prostate MRI, TRUS fusion biopsies and new markers in the diagnostic strategy of prostate cancer | Study not reported in English |
| Rosenkrantz (2012) | Prostate cancer foci detected on multiparametric magnetic resonance imaging are histologically distinct from those not detected | No reference standard |
| Rosenkrantz (2013) | Utility of diffusional kurtosis imaging as a marker of adverse pathologic outcomes among prostate cancer active surveillance candidates undergoing radical prostatectomy | No reference standard |
| Russo (2015) | Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard | Reference standard in study does not match that specified in protocol |
| Sahibzada (2016) | Validating multiparametric MRI for diagnosis and monitoring of prostate cancer in patients for active surveillance | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Satasivam (2016) | Can Confirmatory Biopsy be Omitted in Patients with Prostate Cancer Favorable Diagnostic Features on Active Surveillance? | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Schoots (2015) | Magnetic resonance imaging in active surveillance of prostate cancer: A systematic review | Systematic review- no additional articles identified for inclusion in this review |
| Schoots (2015) | Magnetic Resonance Imaging-targeted Biopsy May Enhance the Diagnostic Accuracy of Significant Prostate Cancer Detection Compared to Standard | Study population is biopsy naive |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | Transrectal Ultrasound-guided Biopsy: A Systematic Review and Meta-analysis | |
| Schoots (2017) | Role of MRI in low-risk prostate cancer: Finding the Wolf in sheep's clothing or the sheep in Wolf's clothing? | Review article but not a systematic review |
| Schulman (2017) | The Contemporary Role of Multiparametric Magnetic Resonance Imaging in Active Surveillance for Prostate Cancer | Systematic review- no additional articles identified for inclusion in this review |
| Scott (2015) | Is transperineal prostate biopsy more accurate than transrectal biopsy in determining final Gleason score and clinical risk category? A comparative analysis | Not a relevant study design (crosssectional study) |
| Scott (2017) | The role of magnetic resonance image guided prostate biopsy in stratifying men for risk of extracapsular extension at radical prostatectomy | Conference abstract |
| Siddiqui (2013) | Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy | Included a mixed population of suspected prostate cancer and proven prostate cancer with no sub group analysis |
| Siddiqui (2015) | Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Siddiqui (2015) | Clinical implications of a multiparametric magnetic resonance imaging based nomogram applied to prostate cancer active surveillance | Study does not contain any relevant index tests Assessing a nomogram |
| Simmons (2014) | The PICTURE study - prostate imaging (multi-parametric MRI and Prostate HistoScanningTM) compared to transperineal ultrasound guided biopsy for significant prostate cancer risk evaluation | Does not contain a population with low risk or intermediate cancer |
| Starobinets (2017) | Characterization and stratification of prostate lesions based on comprehensive multiparametric MRI using detailed whole-mount histopathology as a reference standard | Conference abstract |
| Syer (2017) | The diagnostic accuracy of high b-value diffusion- and T2-weighted imaging for the detection of prostate cancer: a meta-analysis | Does not contain a population with low risk or intermediate cancer |
| Taira (2013) | Transperineal template-guided mapping biopsy as a staging procedure to select patients best suited for active surveillance | Study does not contain any |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| | | relevant index tests |
| Tan (2015) | Characteristics of detected and missed prostate cancer foci on 3-T multiparametric MRI using an endorectal coil correlated with whole-mount thin-section histopathology | Does not contain a population with low risk or intermediate cancer<br>Mixed cancer populations |
| Thestrup (2016) | Biparametric versus multiparametric MRI in the diagnosis of prostate cancer | Reference standard in study does not match that specified in protocol |
| Thoeny (2014) | Metastases in normal-sized pelvic lymph nodes: detection with diffusion-weighted MR imaging | Not a relevant study design (crosssectional study)<br>Non randomised control trial |
| Thompson (2015) | Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer | Not possible to calculate a 2x2 table from data presented in the study |
| Toner (2015) | Magnetic resonance imaging for prostate cancer: Comparative studies including radical prostatectomy specimens and template transperineal biopsy | Systematic review- no additional articles identified for inclusion in this review |
| Toner (2017) | Multiparametric magnetic resonance imaging for prostate cancer-a comparative study including radical prostatectomy specimens | Not a relevant study design (crosssectional study)<br>Comparative study |
| Tosoian (2016) | Active Surveillance of Prostate Cancer: Use, Outcomes, Imaging, and Diagnostic Tools | Review article but not a systematic review |
| Tran (2017) | Magnetic Resonance Imaging-Ultrasound Fusion Biopsy During Prostate Cancer Active Surveillance | Reference standard in study does not match that specified in protocol |
| Tsivian (2017) | Assessing clinically significant prostate cancer: Diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology | Does not contain a population of people with suspected/low risk/intermediate prostate cancer |
| Turkbey (2010) | Prostate cancer: Value of multiparametric MR imaging at 3 T for detection - Histopathologic correlation | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| van As (2009) | A Study of Diffusion-Weighted Magnetic Resonance Imaging in Men with Untreated Localised Prostate Cancer on Active Surveillance | Not possible to calculate a 2x2 table from data presented in the study |
| Vargas (2011) | Diffusion-weighted endorectal MR imaging at 3 T for prostate cancer: Tumor detection and assessment of aggressiveness | Not possible to calculate a 2x2 table from data presented in the study<br>Comparison was between 2 readers and did not provide values for 2x2 calculations |
| Vargas (2012) | Magnetic resonance imaging for predicting prostate biopsy findings in patients considered for active surveillance of clinically low risk prostate cancer | Does not contain a population with low risk or intermediate cancer |
| Vargas (2012) | Performance characteristics of MR imaging in the evaluation of clinically low-risk prostate cancer: A prospective study | Not possible to calculate a 2x2 table from data presented in the study |
| Viana (2017) | The accuracy and validation of multiparametric magnetic resonance imaging (MPMRI) using PI-RADS V2 in disease upgrading on re-biopsy among patients with low-risk prostate cancer on active surveillance (AS)-a Brazilian perspective | Conference abstract |
| von Below (2017) | Additional value of magnetic resonance-targeted biopsies to standard transrectal ultrasound-guided biopsies for detection of clinically significant prostate cancer | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2<br>Does not give details of the b values |
| Vos (2016) | Role of serial multiparametric magnetic resonance imaging in prostate cancer active surveillance | MRI protocol does not satisfy the following criteria - diffusion weighted, contrast enhanced, at least 1.5T and b value of at least 800s/mm2 |
| Wang (2017) | Determination of the Role of Negative Magnetic Resonance Imaging of the Prostate in Clinical Practice: Is Biopsy Still Necessary? | Does not contain a population with low risk or intermediate cancer |
| Washington (2012) | Transrectal ultrasonography-guided biopsy does not reliably identify dominant cancer location in men with low-risk prostate cancer | Restrospective study looking at participants before their follow up MRI or Biopsy |

| Short Title | Title | Reason for Exclusion |
|---|---|---|
| Woo (2018) | Diagnostic Performance of Magnetic Resonance Imaging for the Detection of Bone Metastasis in Prostate Cancer: A Systematic Review and Meta-analysis | Study populaton have high risk prostate cancer |
| Yoo (2018) | A novel biopsy-related parameter derived from location and relationship of positive cores on standard 12-core trans-rectal ultrasound-guided prostate biopsy: a useful parameter for predicting tumor volume compared to number of positive cores | Study not investigating progression or restaging of participants |
| Yoshida (2015) | Information of prostate biopsy positive core: does it affect MR detection of prostate cancer on using 3T-MRI? | Not possible to calculate a 2x2 table from data presented in the study |
| Zakian (2016) | Prostate MRSI predicts outcome in radical prostatectomy patients | Study population unclear |
| Zhang (2007) | Role of Endorectal Coil Magnetic Resonance Imaging in Treatment of Patients with Prostate Cancer and in Determining Radical Prostatectomy Surgical Margin Status: Report of a Single Surgeon's Practice | Study does not contain any relevant index tests |

## Economic studies

| Short Title | Title | Reason for exclusion |
|---|---|---|
| Venderink et al. 2017 | Cost-Effectiveness Comparison of Imaging-Guided Prostate Biopsy Techniques: Systematic Transrectal Ultrasound, Direct In-Bore MRI, and Image Fusion | Not using the trans-perineal mapping biopsy as a reference |
| Willis et al 2015 | A review of economic evaluations of diagnostic strategies using imaging in men at risk of prostate cancer | Review reporting already identified studies |
| Pahwa et al 2017 | Cost-effectiveness of MR Imaging-guided Strategies for Detection of Prostate Cancer in Biopsy-Naive Men | Not using the trans-perineal mapping biopsy as a reference |
| Loeb et al 2017 | Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions | Men diagnosed with localised PC. Not using the trans-perineal mapping biopsy as a reference |
| Gordon et al 2017 | Cost-effectiveness analysis of multiparametric MRI with increased active surveillance for low-risk prostate cancer in Australia | Men diagnosed with localised PC. Not using the trans-perineal mapping biopsy as a reference |
| Do Rooij et al 2014 | Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate | Not using the trans-perineal mapping biopsy as a reference |

| Short Title | Title | Reason for exclusion |
|---|---|---|
| | cancer: a modelling study from a health care perspective | |
| Cerantola et al 2016 | Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer | Not using the trans-perineal mapping biopsy as a reference |
| Mowatt et al 2013 | The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation | Different population (patients with previous negative biopsy) |
| Hovels et al 2009 | Cost-effectiveness of MR lymphography for the detection of lymph node metastases in patients with prostate cancer | population and comparator out of the scope (MR Lymphography for the Detection of Lymph Node Metastases in Patients with Prostate Cancer |
| Roth et al 2015 | Cost-Effectiveness of a Biopsy-Based 8-Protein Prostate Cancer Prognostic Assay to Optimize Treatment Decision Making in Gleason 3 + 3 and 3 + 4 Early Stage Prostate Cancer | Comparators out of the scope (PCA3) |
| Faria et al 2018 | Optimising the diagnosis of prostate cancer in the era of multiparametric magnetic resonance imaging: a cost-effectiveness analysis based on the Prostate MR Imaging Study (PROMIS) | different population: People suspected to be having prostate cancer |
| Nicholson et al 2015 | The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation | Comparators out of the scope (PCA3) |

# Appendix H – References

## Clinical studies - included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# Appendix I– Research recommendations

| Question | What is the most clinically and cost effective pathway for excluding the clinically significant progression of prostate cancer in people with low to intermediate risk |
|---|---|
| Population | People with low-to-intermediate risk prostate cancer |
| Intervention | mpMRI, TRUS biopsy, transperineal biopsy |
| Comparator | Transperineal template (mapping) biopsy |
| Outcomes | Sensitivity<br>Specificity<br>Positive and negative likelihood ratios<br>Adverse events<br>QoL measures |
| Study design | Diagnostic cross sectional |
| **Potential criterion** | **Explanation** |
| Importance to patients, service users or the population | The committee agreed that active surveillance is an important option for people with low to intermediate risk prostate cancer, but that it was vital as part of that process to monitor people for clinically significant progression so that they can be offered timely radical treatment. It also commented that managing peoples anxieties and the impact that monitoring has on their quality of life are also key factors in monitoring for progression. |
| Relevance to NICE guidance | Evidence in this area will enable future committees to make more concrete recommendations about frequency and type of monitoring that should be used. |
| Current evidence base | The evidence used in the current guideline is reasonably poor. Few studies used a gold standard comparator (since this would not occur in a normal clinical pathway). |
| Equality | No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people. |
| Feasibility | There is a large enough population of people on surveillance and monitoring regimes, carrying out a trial in this areas should be feasible |