Appendix

Appendix 1: Search terms

Ovid - Medline

1. exp prostatic neoplasms/

2. (cancer adj3 (prostate or prostatic)).tw.

3. (carcinoma adj3 (prostate or prostatic)).tw.

4. (neoplas$ adj3 (prostate or prostatic)).tw.

5. (malignan$ adj3 (prostate or prostatic)).tw

6. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw

7. 1 or 2 or 3 or 4 or 5 or 6

8. Prostate-Specific Antigen/

9 (prostate specific antigen or prostate-specific antigen or psa) tw

10. Mass screening/

11. (Screen$ or test$) tw

12. 8 or 9 or 10 or 11

13. exp “costs and cost analysis”/

14. (model adj3 (economic or cost)).tw.

15. (cost adj3 (effect$ or util$)).tw.

16. (economic adj3 (anal$ or eval$)).tw.

17. (natural history model) tw

18. (screen$ model$) tw

19. (disease progression model$) tw

20. 13 or14 or 15 or 16 or 17 or 18 or 19

21. 7 and 12 and 20

22. limit 12 to yr=”2006-Current”

Ovid - EMBASE

1. prostatic neoplasms [not a MESH term]

2. exp prostate tumor/ [broader than cancer]

3. (cancer adj3 (prostate or prostatic)).tw.

4. (carcinoma adj3 (prostate or prostatic)).tw.

5. (neoplas$ adj3 (prostate or prostatic)).tw.

6. (malignan$ adj3 (prostate or prostatic)).tw

7. (prostat$ adj3 (neoplasm$ or cancer or carcinoma or tumo?r$ or malignan$)).tw

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. Prostate-Specific Antigen/

10 (prostate specific antigen or prostate-specific antigen or psa) tw

11. Mass screening/

12. (Screen\* or test\*) tw

13. 9 or 10 or 11 or 12

14. exp Economic evaluation/

15. (model adj3 (economic or cost)

16. (cost adj3 (effect$ or util$))

17. (economic adj3 (anal$ or eval$)

18. (natural history model) tw

19. (screen$ model$) tw

20. (disease progression model$) tw

21. 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 8 and 13 and 21

23. limit 12 to yr=”2006-Current”

Cochrane – NHS EED

#1 MeSH descriptor: [Prostatic Neoplasms]

#2 (prostat\* NEAR/3 (neoplasm\* or cancer or carcinoma or tumor\* or tumour\* or malignan\*)):

#3 screen\* or test\*

#4 MeSH descriptor: [Mass screening]

#5 (prostate specific antigen or prostate-specific antigen or psa) tw

#6 Prostate-Specific Antigen/

#7 #1 or #2

#8 #3 or #4 or #5 or #6

#9 #7 and #8

#10 limit publication year from 2006 to 2016, in Economic Evaluations

Cochrane - HTA

#1 MeSH descriptor: [Prostatic Neoplasms]

#2 (prostat\* NEAR/3 (neoplasm\* or cancer or carcinoma or tumor\* or tumour\* or malignan\*)):

#3 screen\* or test\*

#4 MeSH descriptor: [Mass screening]

#5 (prostate specific antigen or prostate-specific antigen or psa) tw

#6 Prostate-Specific Antigen/

#7 #1 or #2

#8 #3 or #4 or #5 or #6

#9 #7 and #8

#10 limit publication year from 2006 to 2016, in Technology Assessments

Appendix 2: Data extraction form

Data extraction form for systematic review of model-based economic evaluation methods in prostate cancer screening.

|  |  |
| --- | --- |
| **Title** |  |
| **Author** |  |
| **Year** |  |
| **Country** |  |
| **Study objective** |  |
| **Strategies/tests compared** |  |
| **Threshold for a positive result** |  |
| **Frequency of testing/screening** |  |
| **Starting/stopping age** |  |
| **Types of biopsy** |  |
| **Types of treatment** |  |
| **Population – age/ethnicity/prevalence of prostate cancer** |  |
| **Outcome measure** |  |
| **Economic evaluation type** |  |
| **Cost-effectiveness result** |  |
| **Model type** |  |
| **Justification for model type** |  |
| **Model structure (Stage or grade progression)** |  |
| **Evidence source/s for natural history pathway** |  |
| **Cycle Length** |  |
| **Justification for cycle length** |  |
| **Time horizon** |  |
| **Justification for time horizon** |  |
| **Sensitivity analysis (methods for incorporating uncertainty)** |  |
| **Evidence base for health state utility values** |  |
| **Evidence base for costs** |  |
| **Data on accuracy of tests** |  |
| **Software used** |  |
| **Is overdiagnosis/overtreatment reported? If so, how?** |  |
| **VOI (EVPPI or EVSI)** |  |

## Appendix 3: Tables

*Table 1 Definitions of biomarkers used in included studies*

|  |  |
| --- | --- |
| **Biomarker** | **Definition** |
| Prostate Health Index (PHI) | blood biomarker calculated by a test analyser from the combination of total PSA (tPSA), free PSA (fPSA), and [-2]proPSA assays. It is used to calculate the probability of PCa and as an aid in distinguishing PCa from benign prostatic conditions for men with a borderline PSA test (e.g. PSA 2-10 ng/mL or 4-10 ng/mL) and non-suspicious digital rectal examination.(25) |
| SelectMDx (SelectMDx; MDxHealth, Inc., Irvine, CA, USA) | urinary molecular biomarker-based risk score developed to identify patients that are at risk of harbouring high-grade PCa (Gleason score ≥7).(26) This risk score is based on the urinary homeobox C6 (HOXC6) and distal-less homeobox 1 (DLX1) mRNA signature in combination with serum PSA level, PSA density, and other clinical risk factors such as age, prior cancer-negative biopsies, DRE, and family history |
| Urinary Proteome Analysis for PCa diagnosis (UPA-PC) | based on capillary electrophoresis mass spectrometry (CE/MS) and allows proteome analyses of prostatic secretions in first stream urine (first 10–15 mL urine fraction) to distinguish patients with positive PSA and/or DRE with PCa from those without PCa. The test simultaneously determines 12 biomarkers combined as a PC-specific multi-biomarker profile.(27) |
| 4Kscore® Test (OPKO Diagnostics, LLC) | incorporates measured blood levels of four kallikrein proteins: total PSA, free PSA, intact PSA, and human kallikrein 2 plus clinical information (age, DRE findings, and a history of prior negative biopsy result) into an algorithm to calculate an individual man’s percentage risk (< 1% to > 95%) of having Gleason score ≥ 7 if a prostate biopsy were to be performed.(28) |
| ExoDx Prostate (IntelliScore) (EPI) | urine exosome gene expression test, which utilizes exosomal RNA expression levels of three genes to predict the likelihood of having high-grade PCa of Grade Group 2 or greater.(29) |
| PCA3 | a segment of noncoding messenger ribonucleic acid (mRNA) from chromosome 9q21–22 that is overexpressed by more than 95% of all PCas tested (30). |

*Table 2. Definitions of biopsy methods used in included studies*

|  |  |
| --- | --- |
| **Biopsy method** | **Definition** |
| Standard | Transrectal ultrasound guided |
| Template mapping | Accurately characterises disease status by sampling the entire prostate every 5 mm (4) |
| Fusion | the patient undergoes a standard transrectal ultrasound guided biopsy but MRI targets from a preceding MRI scan are digitally “fused” to the ultrasound images so that additional cores can also be taken from those locations under ultrasound visualization (33) |
| Combined | both standard and targeted fusion biopsies are performed during a single biopsy session (25) |
| Cognitively guided | the patient undergoes a standard transrectal ultrasound guided biopsy, but the operator performs a biopsy on the basis of his or her knowledge of the location of the lesion at MR imaging (27) |
| In-gantry/In-bore | involves obtaining tissue samples with direct MR imaging guidance while the patient is in the MR imaging gantry and allows direct visualization of the MR imaging target and the needle at the same time (33) |
| Magnetic resonance spectroscopy imaging (MRSI) | Further to imaging of water and lipids, which is normally performed with MRI, MRS is a technique that provides detail on protons of molecules other than water and lipids. It can give quantitative information on the  presence and quantity of metabolites in the prostate which can be used to estimate the presence and aggressiveness of cancer in  prostate tissue (31) |
| Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) | dynamically measures a bolus pass of an intravenously administrated MR contrast agent through the prostate. Has been shown to be of use in detection and staging of PC within a multiparametric protocol (31) |
| Diffusion-weighted magnetic resonance imaging (DW-MRI) | evaluates the microscopic mobility of water molecules in  tissue. In addition to its value in the detection of cancer DW-MRI has also been shown to be a promising marker of tumour aggressiveness (31) |

*Table 3. Reported accuracy of tests compared in studies*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Test** | **sensitivity** | **type of cancer** | **specificity** | **type of cancer** | **Source** |
| Dijkstra et al 2017(19) | SelectMDx | 0.957 | high grade | 0.336 | low grade | Two prospective multicentre studies in the Netherlands in men who were scheduled for prostate biopsies, based on elevated PSA levels (≥3 ng/ml), abnormal DRE, or a family history of PCa (n=619)(33) |
| SelectMDx |  |  | 0.608 | no cancer |  |
| Bouttell et al 2019(17) | PHI cut off 25 | 0.887 | any grade | 0.365 | any grade | Prospective cohort study of Chinese men with PSA 4-10 ng/mL and non-suspicious DRE (n=569)(34) |
| PHI cut off 35 | 0.613 | any grade | 0.775 | any grade |  |
| PHI cut off 55 | 0.129 | any grade | 0.974 | any grade |  |
| Sathianathen et al 2018(22) | TRUS guided biopsy | 0.46 | low grade |  |  | Taken from de Rooij CEA(30) |
| TRUS guided biopsy | 0.67 | high grade |  |  | biopsy simulation study (38) |
| PHI | 0.883 | low grade | 0.294 | no cancer | US multi-center, double-blind, case-control clinical trial in men with no history of PCa, non-suspicious DRE and pre-study PSA of 1.5–11.0 ng/mL (n=1372)(39) |
| PHI | 0.914 | high grade |  |  |  |
| MRI | 0.680 | low grade | 0.51 | no cancer |  |
| MRI | 0.880 | high grade |  |  |  |
| 4k score | 0.816 | low grade | 0.3801 | no cancer | US Multi-institutional Prospective Trial in men referred for biopsy (n=1012)(40) |
| 4k score | 0.948 | high grade |  |  |  |
| Select MDx | 0.830 | low grade | 0.4 | no cancer | Two prospective multicentre studies in the Netherlands in men who were scheduled for prostate biopsies, based on elevated PSA levels (≥3 ng/ml), abnormal DRE, or a family history of PCa (n=619)(33) |
| Select MDx | 0.910 | high grade |  |  |  |
| EPI | 0.800 | low grade | 0.3918 | no cancer | Prospective multicenter study in the US in men with with PSA levels of 2 to 20 ng/mL (n=255)(41) |
| EPI | 0.919 | high grade |  |  |  |
| MRIGB | 0.440 | low grade |  |  |  |
| MRIGB | 0.910 | high grade |  |  |  |
| Govers et al 2018(20) | SelectMDx | 0.957 | high grade | 0.61 | NR | Two prospective multicentre studies in the Netherlands in men who were scheduled for prostate biopsies, based on elevated PSA levels (≥3 ng/ml), abnormal DRE, or a family history of PCa (n=619)(33) |
|  | 0.660 | low grade |  |  |  |
| Heijnsdijk et al 2016(16) | PSA test | 0.790 | T1 Gleason 2-6 |  |  | ERSPC trial (n=42,376)(35) |
|  | 0.990 | T3 Gleason 8-10 |  |  |  |
| Biopsy | 0.900 |  |  |  |  |
| Schiffer et al 2012(21) | UPA-PC | 0.86 |  | 0.59 |  | Prospective study carried out in Germany of men with suspicious PSA and/or DRE (n=211)(21) |
| Biopsy | 0.70 |  | 1 |  |  |
| Barnett et al 2018(25) | Standard Biopsy | 0.8 |  |  |  | Retrospective analysis of 7643 needle biopsies carried out in the US(42) |
| Targeted fusion biopsy | 0.770 | high grade | 0.68 | high grade | Prospective cohort study of men with elevated PSA or abnormal DRE undergoing both targeted and standard biopsy concurrently at the National Cancer Institute in the US (n=1003)(37) |
| Combined biopsy | 0.850 | high grade | 0.49 | high grade |  |
| PI-RADS > 3 | 0.965 | clinically significant | 0.597 | clinically significant | Prospective study of men who presented for transperineal biopsy after mpMRI in one UK institution (n=201)(36) |
| PI-RADS > 4 | 0.789 | clinically significant | 0.789 | clinically significant |  |
| Pahwa et al 2017(26) | MR Imaging | 0.760 |  | 0.88 |  | Taken from de Rooij CEA(30) |
| Standard Biopsy | 0.460 |  |  |  |  |
| MR Cognitive biopsy | 0.780 | clinically significant |  |  | Two retrospective studies, one of 178 men and another of 54 men both undergoing MRI due to elevated PSA levels in Japan (43, 44) |
| MR Cognitive biopsy | 0.200 | clinically insignificant |  |  | Systematic review and meta-analysis of 16 studies including 1926 men(45) |
| MR fusion biopsy | 0.800 | clinically significant |  |  | Retrospective analysis of men who underwent prebiopsy mpMRI followed by MRI fusion targeted biopsy in one US institution (n=452)(46) |
| MR fusion biopsy | 0.510 | clinically insignificant |  |  | Systematic review and meta analysis of 16 studies including 1926 men(45) |
| MR guided in-gantry biopsy | 0.920 | clinically significant |  |  | Single-institution, prospective study of biopsy-naive men referred to a urologist with elevated PSA in Australia (n=223)(47) |
| MR guided in-gantry biopsy | 0.210 | clinically insignificant |  |  | Systematic review and meta analysis of 16 studies including 1926 men(45) |
| All biopsy procedures |  |  | 1 |  | Assumption |
| Venderink et al 2017 (28) | mpMRI | 0.930 | clinically significant | 0.21 | clinically significant | Prospective cohort study of UK men with clinical suspicion of PCa who underwent mpMRI followed by TPM (n=129)(48) |
| mpMRI |  |  | 0.28 | any cancer |  |
| MRI-TRUS fusion | 0.770 | clinically significant |  |  | Prospective cohort study of men with elevated PSA or abnormal DRE undergoing both targeted and standard biopsy concurrently at the National Cancer Institute in the US (n=1003)(37) |
| MRI-TRUS fusion | 0.500 | clinically insignificant |  |  |  |
| MRI-TRUS fusion |  |  | 1 | any cancer | Assumption |
| TRUS guided biopsy | 0.530 | clinically significant |  |  | Prospective cohort study of men with elevated PSA or abnormal DRE undergoing both targeted and standard biopsy concurrently at the National Cancer Institute in the US (n=1003)(37) |
| TRUS guided biopsy | 0.550 | clinically insignificant |  |  |  |
| TRUS guided biopsy |  |  | 1 | any cancer | Assumption |
| de Rooij et al 2014(30) | TRUS guided biopsy | 0.456 |  | 0.88 |  | Sensitivity: Single institution retrospective study (n=438), Single institution prospective study (n=100), Single institution prospective study (n=54), Single institution prospective study (n=71) (49-51) (52)  Specificity: Single institution prospective study (n=64)(53) |
| mpMRI | 0.740 |  | 0.88 |  | Meta-analysis of seven studies including 526 patients(54) |
| MRGB | 0.900 |  | 1 |  | Assumption |
| Mowatt et al 2013(31) | TRUS guided biopsy | 0.832 |  | 1 |  | Prospective study of Italian patients suspected of harbouring PCa after a first negative biopsy (n=340)(55) |
| T2-MRI | 0.86 |  | 0.55 |  | Systematic review and meta-analysis of 15 studies in 620 patients(31) |
| MRS | 0.92 |  | 0.76 |  | Systematic review and meta-analysis of 10 studies in 438 patients(31) |
| DCE-MRI | 0.79 |  | 0.52 |  | Systematic review and meta-analysis of 3 studies in 209 patients(31) |
| T2-MRI or MRS | 0.96 |  | 0.31 |  | Systematic review and meta-analysis of 8 studies in 316 patients(31) |
| T2-MRI or DCE-MRI | 0.88 |  | 0.14 |  | Systematic review and meta-analysis of 3 studies in 209 patients(31) |