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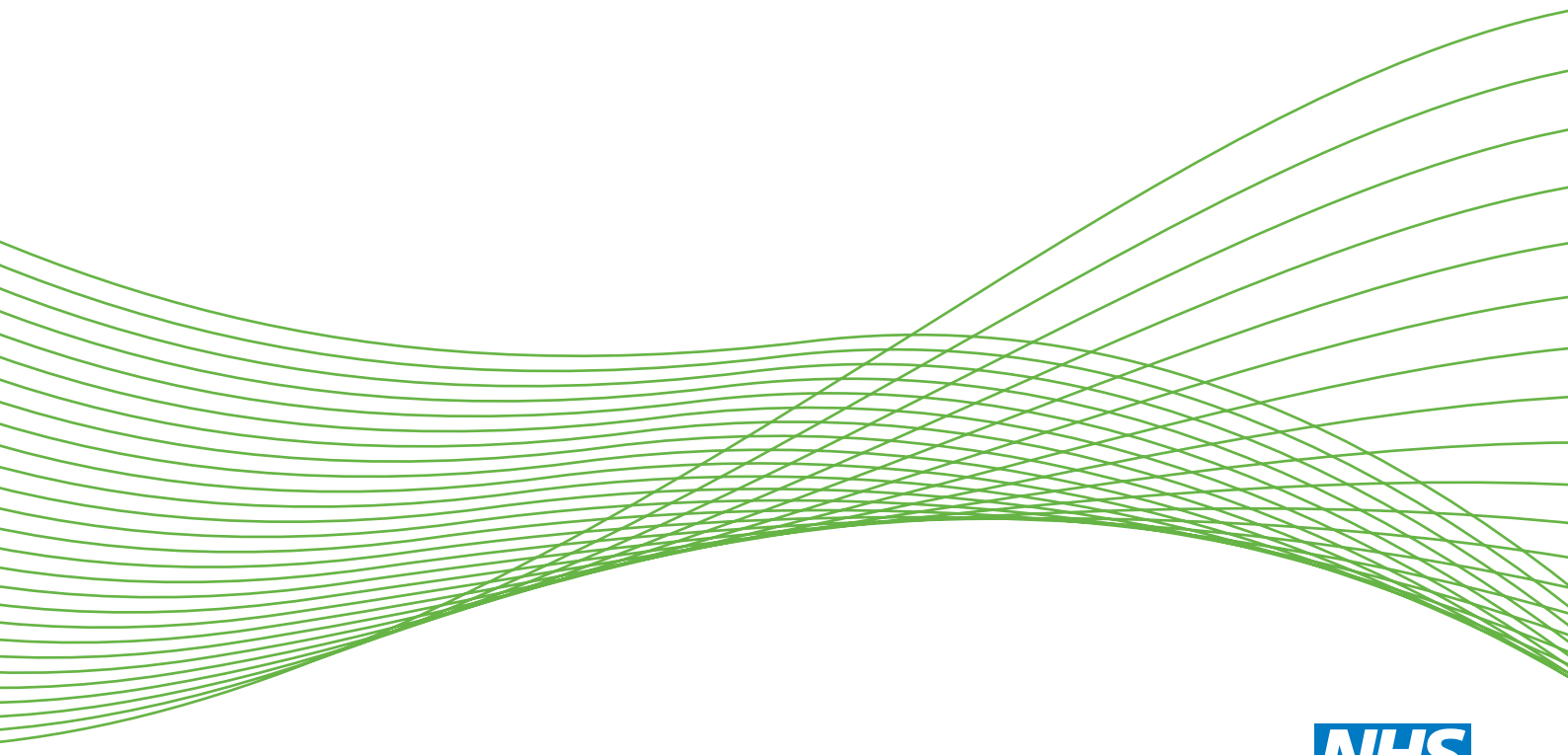

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The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation

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Abstract

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

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Background: In the UK, prostate cancer (PC) is the most common cancer in men. A diagnosis can be confirmed only following a prostate biopsy. Many men find themselves with an elevated prostate-specific antigen (PSA) level and a negative biopsy. The best way to manage these men remains uncertain.

Objectives: To assess the diagnostic accuracy of magnetic resonance spectroscopy (MRS) and enhanced magnetic resonance imaging (MRI) techniques [dynamic contrast-enhanced MRI (DCE-MRI), diffusion-weighted MRI (DW-MRI)] and the clinical effectiveness and cost-effectiveness of strategies involving their use in aiding the localisation of prostate abnormalities for biopsy in patients with prior negative biopsy who remain clinically suspicious for harbouring malignancy.

Data sources: Databases searched – MEDLINE (1946 to March 2012), MEDLINE In-Process & Other Non-Indexed Citations (March 2012), EMBASE (1980 to March 2012), Bioscience Information Service (BIOSIS; 1995 to March 2012), Science Citation Index (SCI; 1995 to March 2012), The Cochrane Library (Issue 3 2012), Database of Abstracts of Reviews of Effects (DARE; March 2012), Medion (March 2012) and Health Technology Assessment database (March 2012).

Review methods: Types of studies: direct studies/randomised controlled trials reporting diagnostic outcomes. Index tests: MRS, DCE-MRI and DW-MRI. Comparators: T2-weighted magnetic resonance imaging (T2-MRI), transrectal ultrasound-guided biopsy (TRUS/Bx). Reference standard: histopathological assessment of biopsied tissue. A Markov model was developed to assess the cost-effectiveness of alternative MRS/MRI sequences to direct TRUS-guided biopsies compared with systematic extended-cores TRUS-guided biopsies. A health service provider perspective was adopted and the recommended 3.5% discount rate was applied to costs and outcomes.

Results: A total of 51 studies were included. In pooled estimates, sensitivity [95% confidence interval (CI)] was highest for MRS (92%; 95% CI 86% to 95%). Specificity was highest for TRUS (imaging test) (81%; 95% CI 77% to 85%). Lifetime costs ranged from £3895 using systematic TRUS-guided biopsies to £4056 using findings on T2-MRI or DCE-MRI to direct biopsies (60-year-old cohort, cancer prevalence 24%). The base-case incremental cost-effectiveness ratio for T2-MRI was < £30,000 per QALY (all cohorts). Probabilistic sensitivity analysis showed high uncertainty surrounding the incremental cost-effectiveness of T2-MRI in moderate prevalence cohorts. The cost-effectiveness of MRS compared with T2-MRI and TRUS was sensitive to several key parameters.

Limitations: Non-English-language studies were excluded. Few studies reported DCE-MRI/DW-MRI. The modelling was hampered by limited data on the relative diagnostic accuracy of alternative strategies, the natural history of cancer detected at repeat biopsy, and the impact of diagnosis and treatment on disease progression and health-related quality of life.

Conclusions: MRS had higher sensitivity and specificity than T2-MRI. Relative cost-effectiveness of alternative strategies was sensitive to key parameters/assumptions. Under certain circumstances T2-MRI may be cost-effective compared with systematic TRUS. If MRS and DW-MRI can be shown to have high sensitivity for detecting moderate/high-risk cancer, while negating patients with no cancer/low-risk disease to undergo biopsy, their use could represent a cost-effective approach to diagnosis. However, owing to the relative paucity of reliable data, further studies are required. In particular, prospective studies are required in men with suspected PC and elevated PSA levels but previously negative biopsy comparing the utility of the individual and combined components of a multiparametric magnetic resonance (MR) approach (MRS, DCE-MRI and DW-MRI) with both a MR-guided/-directed biopsy session and an extended 14-core TRUS-guided biopsy scheme against a reference standard of histopathological assessment of biopsied tissue obtained via saturation biopsy, template biopsy or prostatectomy specimens.

Study registration: PROSPERO number CRD42011001376.

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Contents

Glossary

Atypical small acinar proliferation A diagnosis of 'atypical small acinar proliferation' signifies an unusual cellular appearance. Atypical small acinar proliferation is not, in general, considered a pre-malignant condition, but is an indication for repeat biopsy.

Benign prostatic hyperplasia Non-malignant increase in number of cells in the prostate.

Case series Descriptive study of a group of people with the same disease or the same treatment. This type of study cannot determine how people with the disease compare with those without the disease or those who are treated differently.

Case–control study This type of study compares a group of people who have the disease and a group who do not have it.

Central zone Located at the centre of the prostate. Surrounds the ejaculatory ducts.

Clinical T staging Four categories for describing the local extent of a prostate tumour, ranging from T1 to T4. T1 represents localised tumours with no spread, whereas T4 represents tumours that have spread.

Comparator The best diagnostic test currently available.

Cross-sectional study A study in which data are collected at one point in time and relationships between factors are explored.

Diagnostic odds ratio The ratio of the odds of testing positive in those with the disease relative to the odds of testing positive in those without the disease.

Direct head-to-head study A study in which people receive both index and comparator tests and the tests are therefore evaluated in the same participants.

False-negative/true-negative/false-positive/true-positive In terms of diagnostic accuracy, indicators of index test results compared with the reference standard: negative index test, positive reference standard/negative index test, negative reference standard/positive index test, negative reference standard/positive index test, positive reference standard, respectively.

Gleason score A system of grading prostate cancer tissue based on how it looks under a microscope. Gleason scores range from 2 to 10 and signify the likelihood of a tumour spreading. Lower Gleason scores mean that the cancer tissue is similar to normal prostate tissue and the tumour is less likely to behave aggressively; higher Gleason scores mean that the cancer tissue is very different from normal tissue and the tumour is more likely to behave aggressively.

(High-grade) prostatic intraepithelial neoplasia An abnormality of prostate cells. Associated with a finding of prostate cancer on repeat biopsies.

Hypoechoic In ultrasonography, describes areas of abnormally low echoes due to pathological changes in tissue density. Hypoechoic lesions are commonly found to be malignant.

Index- or reference test-directed biopsy This refers to the method used to identify suspicious areas prior to biopsy, i.e. where one or more index tests are used to identify cancer-suspicious areas for use in a subsequent biopsy.

Index- or reference test-guided biopsy This refers to the method used at the time of obtaining tissue samples, i.e. where the specified test is used to locate previously identified cancer-suspicious areas as part of the biopsy procedure.

Index test The diagnostic test that is being evaluated.

Isoechoic In ultrasonography, describes similarity between two or more tissues. Isoechoic lesions are less likely than hypoechoic lesions to be malignant.

Likelihood ratio A description of how many times more likely it is that a person with the disease will receive a particular test result than a person without the disease.

Meta-analysis The quantitative pooling of data from two or more studies.

Negative predictive value The proportion of those with negative test results who do not have the disease.

Nomogram A prognostic indicator incorporating multiple risk variables to produce mathematical models that predict the likelihood of disease recurrence or progression.

Observational study A study in which people are observed without input from the researchers.

Peripheral zone Located around the outside of the prostate gland, next to the rectum.

Positive predictive value The proportion of those with positive test results who actually have the disease.

Prostate-specific antigen A protein manufactured by the prostate which aids the liquefaction of semen and is released and detectable in the bloodstream in a number of conditions related to the prostate.

Randomised controlled trial A study in which people are randomly allocated to receive – or not receive – a particular treatment or intervention. This is said to be the best study type to determine effectiveness of a treatment.

Reference standard The best available method for establishing the presence or absence of the disease.

Sclerotic Hard or hardening (of tissue).

Sensitivity The proportion of those who actually have the disease and who are correctly identified with positive test results.

Specificity The proportion of those who actually do not have the disease and who are correctly identified with negative test results.

TNM staging system This describes the local extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of metastasis (M stage).

Transition zone Located in the interior of the prostate. Surrounds the proximal urethra.

List of abbreviations

ADC	apparent diffusion coefficient
AIF	arterial input function
ASAP	atypical small acinar proliferation
ASCO	American Society of Clinical Oncology
CC/C	choline-plus-creatine–citrate ratio
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CT	computed tomography
CZ	central zone
DCE-MRI	dynamic contrast-enhanced magnetic resonance imaging
DOR	diagnostic odds ratio
DRE	digital rectal examination
DW-MRI	diffusion-weighted magnetic resonance imaging
EAU	European Association of Urology
EBRT	external beam radiotherapy
ED	erectile dysfunction
EQ-5D	European Quality of Life-5 Dimensions
GP	general practitioner
HGPIN	high-grade prostatic intraepithelial neoplasia
HIFU	high-intensity focused ultrasound
HRG	Healthcare Resource Group
HSROC	hierarchical summary receiver operating characteristic
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
LHRH	luteinising hormone-releasing hormone
LR	likelihood ratio
MeSH	medical subject heading
MR	magnetic resonance
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
MRSI	magnetic resonance spectroscopy imaging
N/A	not available
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
NPV	negative predictive value
PC	prostate cancer
PIN	prostatic intraepithelial neoplasia
PPV	positive predictive value
PSA	prostate-specific antigen
PZ	peripheral zone
QoL	quality of life
QUADAS-2	quality assessment of diagnostic accuracy studies, version 2
RCR	Royal College of Radiologists
ROC	receiver operating characteristic
SD	standard deviation
SROC	summary receiver operating characteristic
T2-MRI	T2-weighted magnetic resonance imaging
TAR	technology assessment report

TNM	tumour, node, metastasis staging system
TRUS	transrectal ultrasonography
TRUS/Bx	transrectal ultrasound-guided biopsy
TZ	transition zone
UI	urinary incontinence
UTI	urinary tract infection

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

In the UK, prostate cancer (PC) is the most common cancer in men. Many men find themselves with the dilemma of having an elevated prostate-specific antigen (PSA) level and a negative prostate biopsy, and the best way for doctors to manage these patients remains uncertain. The strategy of further repeat biopsies for these men remains controversial, with uncertainties surrounding the optimal number of cores, which area of the prostate to target, and imaging modality for guidance. This has led to the introduction of new imaging techniques. Conventional standard (T2-weighted) magnetic resonance imaging (T2-MRI) can be performed with add-on modalities, including three-dimensional magnetic resonance spectroscopy (MRS), dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted MRI (DW-MRI).

Objectives

This review aims to assess the diagnostic accuracy of MRS and enhanced MRI techniques (DCE-MRI, DW-MRI) and the clinical effectiveness and cost-effectiveness of strategies involving their use in aiding the localisation of prostate abnormalities for biopsy in patients with prior negative biopsy in whom there remains a clinical suspicion that they are harbouring malignancy.

Methods

Electronic databases searched included MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, Bioscience Information Service (BIOSIS), Science Citation Index (SCI), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Medion, Health Technology Assessment database, conference abstracts from the American Society for Clinical Oncology (ASCO) and current research registers. Searches were carried out from 1995 to March 2012. Types of studies considered were direct studies or randomised controlled trials reporting absolute numbers of true- and false-positives and true- and false-negatives, allowing the calculation of sensitivity, specificity or predictive values. The population was men with suspected PC and elevated PSA level but previously negative biopsy. Index tests were MRS, DCE-MRI and DW-MRI, and comparator tests were standard T2-MRI and transrectal ultrasonography (TRUS). The reference standard was histopathological assessment of biopsied tissue obtained via transrectal needle biopsy, saturation biopsy, transperineal template biopsy or from prostatectomy specimens.

Two reviewers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were subsequently obtained for assessment. Data extraction was undertaken by one reviewer and checked by a second. Two reviewers independently assessed the risk of bias of the diagnostic studies using a modified version of the QUADAS-2 (quality assessment of diagnostic accuracy studies, version 2) instrument.

The results of the individual studies were tabulated and sensitivity, specificity and their 95% confidence intervals (CIs) presented for each test or combination of tests at both patient and biopsy level. The presence of heterogeneity was assessed by visual examination of pairs of forest plots of sensitivity and specificity. Separate summary receiver operating characteristic (SROC) curves were derived for different levels of analysis. Meta-analysis models were fitted using hierarchical SROC (HSROC) curves. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios for each model were reported as median and 95% CI. An indirect comparison of tests was also undertaken.

An economic model was developed to assess the cost-effectiveness of using alternative MRS/MRI sequences to direct TRUS-guided biopsies (TRUS/Bx), compared with the standard practice of relying on systematic extended TRUS-guided biopsies (in patients with a previous negative biopsy). The alternative diagnostic pathways were embedded in a Markov model simulating the progression of undiagnosed cancer and the downstream impact of diagnosis and treatment on survival and health-related quality of life (QoL). Costs incorporated in the model included the costs associated with obtaining the final diagnosis (cancer/no cancer), management of biopsy complications, cancer staging, cancer treatment, and the management of complications resulting from cancer treatment. Survival benefits of diagnosis were captured through the application of relative risk parameters reflecting the benefit of appropriate treatment by stage of underlying cancer. Health-state utilities associated with cancer stage and the occurrence of treatment complications were incorporated in the model to estimate quality-adjusted life-years (QALYs). Experimental strategies were compared incrementally with standard practice in terms of their incremental cost per life-year and QALY gained.

Results

Number and quality of studies

Fifty-one studies (39 full text and 12 abstracts) were included, involving over 10,000 men. Only full-text studies were assessed for risk of bias, the majority of which were considered to have a low risk of bias for the patient selection (74%, 29/39), index test (100%, 39/39) and flow and timing (92%, 36/39) domains. In the reference standard domain, the majority of studies (64%, 25/39) were considered at high risk of bias owing to a lack of follow-up.

Summary of benefits and risks

In meta-analyses of the individual tests, sensitivity was highest for MRS at 92% (95% CI 86% to 95%), followed by T2-MRI at 86% (95% CI 74% to 93%) and DCE-MRI at 79% (95% CI 69% to 87%), whereas specificity was highest for TRUS (used as an imaging test) at 81% (95% CI 77% to 85%), followed by MRS at 76% (95% CI 61% to 87%). In pooled estimates for combinations of tests, sensitivity was highest for 'MRS or T2-MRI' at 96% (95% CI 90% to 98%) followed by 'DCE-MRI or T2-MRI' at 88% (95% CI 80% to 96%), whereas specificity was highest for 'MRS and T2-MRI' at 74% (95% CI 65% to 84%). Only one small study involving 43 patients reported DW-MRI, with sensitivity of 100% (specificity not reported). The results of the indirect comparison broadly reflected those of the meta-analyses of the individual tests and combinations of tests.

Summary of costs

The base-case analysis showed average discounted lifetime costs to range between £3895 using systematic TRUS-guided biopsies and £4056 using positive findings on either T2-MRI or DCE-MRI to determine and direct biopsies (60-year-old cohort, cancer prevalence 24%). The corresponding figures for the same strategies in a 70-year-old cohort were £3199–3660. Using T2-MRI to direct biopsies represented the least costly approach in low-prevalence (10%) cohorts.

Summary of cost-effectiveness

Survival and QALY differences between strategies were very small but these favoured more sensitive approaches. Under base-case parameter values and assumptions (with underlying cancer prevalence 24%), the incremental cost-effectiveness ratio (ICER) for T2-MRI was < £30,000 per QALY in comparison with systematic extended-cores TRUS/Bx (all cohorts) and T2-MRI was found to dominate extended-cores TRUS/Bx in low-prevalence cohorts. However, probabilistic sensitivity analysis demonstrated a high degree of uncertainty surrounding the incremental cost-effectiveness of T2-MRI compared with extended-cores TRUS/Bx in the moderate prevalence cohorts. The cost-effectiveness of MRS compared with T2-MRI was less favourable under base-case assumptions, although its ICER did fall to < £30,000 compared with extended-cores TRUS/Bx in the moderate prevalence 60-year-old cohort, and also compared with T2-MRI-directed

biopsy in the high-prevalence 60-year-old cohort. The ICER for MRS, or any of the other more sensitive strategies, did not fall to < £30,000 in any of the 70-year-old cohorts under base-case assumptions.

Sensitivity analyses

Base-case findings were found to be highly sensitive to a number of uncertain parameters and assumptions. The cost-effectiveness of using MRS to direct biopsies was found to be particularly sensitive to the cost of prostate biopsies relative to the cost of obtaining a MRS sequence. When the cost of obtaining biopsies was raised by ~£115 relative to the cost of MRS, MRS-directed biopsy was found to dominate extended-cores TRUS/Bx in all of the cohorts, and its ICER dropped to < £30,000 in comparison with the T2-MRI-directed approach in the moderate- and high-prevalence 60-year-old cohorts (although it remained > £30,000 in all of the 70-year-old cohorts). The cost-effectiveness of MRS was also crucially sensitive to its modelled ability to discriminate between low- and moderate-/high-risk cancer. When all of its false-negative findings were modelled to occur in patients with low-risk disease, its cost-effectiveness improved substantially in the moderate- and high-prevalence 60-year-old cohorts, although its ICERs remained less favourable in the 70-year-old cohorts. Factors undermining the cost-effectiveness of MRS included the application of lower disease progression rates and lower relative risk reductions associated with diagnosis and treatment. Although a lack of available evidence precluded its inclusion in our base-case analysis, if DW-MRI could be shown to perform similarly to MRS in terms of diagnostic accuracy, it would probably be favoured over MRS for its lower cost.

Discussion

Strengths, limitations of the analyses and uncertainties

In terms of strengths, a comprehensive literature search was undertaken. A HSROC model was used, which takes account of the trade-off between true/false-positives and models between-study heterogeneity. Pooled estimates were performed at both patient and biopsy level and an indirect comparison of tests was undertaken. In terms of limitations, non-English-language studies were excluded. Few studies reported DCE-MRI or DW-MRI or included a period of follow-up as part of the reference standard. The index and comparator tests were not independent of the reference standard.

In terms of uncertainties, where studies reported an 'equivocal' results category, this was classed with positive rather than negative results, increasing sensitivity and decreasing specificity, whereas the reverse would have been the case if 'equivocal' had been classed with negative results. There was only limited evidence available of the ability of MRS and other MRI techniques to detect clinically significant disease. In studies reporting MRS or other MRI techniques a systematic TRUS/Bx was also undertaken and in most of these studies it was unclear how this contributed to sensitivity and specificity values reported.

Generalisability of the findings

All studies included in the pooled estimates reported men with suspected PC and elevated PSA level but previously negative biopsy, and therefore these findings would be broadly generalisable to patients meeting the above criteria. However, in one study the spectrum of patients was not representative (all had atypical small acinar proliferation). In two studies imaging was MR-guided (rather than TRUS-guided), a method not generally used in the UK. Six studies reporting TRUS-guided systematic biopsies were large screening studies, which is not representative of how men are detected with PC in the UK.

Conclusions

Implications for service provision

Given the level of uncertainty surrounding several key model inputs, it is difficult to arrive at definitive conclusions on the cost-effectiveness of using different MRS/MRI sequences to aid the localisation of

prostate abnormalities for biopsy. However, our modelling suggests that, under certain circumstances, T2-MRI may be considered cost-effective in comparison with systematic TRUS/Bx, and if MRS and DW-MRI can be shown to have high sensitivity for detecting moderate-/high-risk cancer, while negating the need for patients with no cancer or low-risk disease to undergo biopsy, then their use could represent a cost-effective approach to diagnosis.

The introduction of MRS and other MRI techniques (T2-MRI, DCE-MRI, DW-MRI) for evaluation of men with negative TRUS/Bx but in whom there remains suspicion of cancer would have a range of implications for the NHS. These would arise primarily because of a shift in the test–treatment pathway for this group, with changes in the method of making diagnosis resulting in changes to the types of patients being treated, offered patient options and timings of treatments. This would have consequential effects on service provision, costs and training. If urological and/or radiological services were to undertake targeted biopsies of MRS-/MRI-suspicious regions then extra provision would be required for this. A new generation of equipment and software would be needed to enable accurate, documentable biopsies to be obtained from all regions of the prostate. If MRS/MRI identified more patients with localised disease with intermediate and high risk of progression then this would increase the proportion of patients considered eligible for radical therapies. If MRS or MRI detected few patients with low risk of disease progression then fewer patients in this category would undergo perhaps inappropriate radical therapies. Thus, the total number of patients undergoing radical therapies would be appropriately decreased, requiring a rebalancing of resources currently allocated to surgical and radiation therapy services. Furthermore, if MRS or MRI contributed to the more accurate classification of patients with a low risk of progression, this would lead to an increase in the proportion of appropriately selected patients who are likely to undergo 'active surveillance', helping to mitigate the current high dropout rate of this approach. The implications for the follow-up of active surveillance patients would include repeated PSA testing, repeated interval biopsies and follow-up clinics (much of this work is protocol driven and could be nurse practitioner led). Taken together, earlier, more accurate diagnoses and more appropriate treatments of PC may improve patient outcomes by reducing treatment-related morbidity, improving survival and, in the longer term, reducing the requirement for end-of-life and palliative care services. There would be cost implications of these service reconfigurations and for changes in treatment patterns mentioned above. Implementation would also result in the need for further training of all staff involved in delivering care to patients with PC.

Suggested research priorities

Prospective studies are required in men with suspected PC in whom PSA level is elevated but a previous biopsy has been negative, comparing the utility of the individual and combined components of a multiparametric magnetic resonance (MR) approach (MRS, DCE-MRI and DW-MRI) with both a MR-guided or -directed biopsy session and an extended 14-core TRUS/Bx scheme against a reference standard of histopathological assessment of biopsied tissue obtained via saturation biopsy, template biopsy or prostatectomy specimens. A follow-up time of 12 months should form part of the reference standard. Investigations of DW-MRI should be encouraged, as it is already gaining widespread acceptance in the clinic owing to its relatively easy use. These studies should also report the sensitivity of the tests in detecting clinically significant disease (Gleason score of ≥ 7 and/or volume > 0.5 ml). In addition to diagnostic outcomes, adverse event data and impact of the tests on subsequent physician attitudes to patient management should also be obtained, as well as cost-effectiveness data including impact of testing on health-related QoL.

Uncertainties surrounding cost-effectiveness could be significantly reduced by future research focusing on generating comparable estimates of (1) the sensitivity of MRI-/MRS-directed and systematic approaches to TRUS/Bx (using a robust and common reference standard); (2) the prospective sensitivity or specificity of MRS or MRI sequences for detecting different grades of localised disease in the repeat biopsy setting; and (3) the full economic costs of MRI sequences and systematic approaches to TRUS/Bx based on different numbers of cores.

Further, with the survival and QALY differences between strategies being so small, and of questionable clinical significance, the choice between strategies might be better informed by patient or public preferences for process of care factors to which the standard QALY model may be insensitive. Scope exists to carry out preference elicitation studies to identify and value the key factors influencing patients' preferences for alternative diagnostic, monitoring, and subsequent treatment pathways.

Study registration

This study is registered as PROSPERO CRD42011001376.

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Chapter 1 Background

Description of health problem

Brief statement describing the health problem

The diagnosis of prostate cancer (PC) is based on a combination of measuring the serum prostate-specific antigen (PSA) level, performing a digital rectal examination (DRE) to palpate the prostate, and a prostate biopsy. Men with an elevated PSA level and/or abnormal DRE undergo a prostate biopsy, which is normally performed using a transrectal probe guided by greyscale ultrasound [or transrectal ultrasound-guided biopsy (TRUS/Bx)]. The prostate biopsy procedure is associated with some morbidity,[1] including risk of infection, discomfort during the procedure, blood in urine (i.e. haematuria), rectal bleeding, blood in semen (i.e. haematospermia), risk of precipitating acute urinary retention, and perineal pain afterwards. In some cases, the TRUS/Bx will not show cancer and a repeat biopsy may be necessary. The strategy of repeat biopsies remains controversial, with TRUS/Bx-based protocols often resulting in high adverse effect profiles[2] or low diagnostic accuracy. In order to overcome some of the current limitations, new imaging modalities and technologies such as magnetic resonance spectroscopy (MRS) and enhanced magnetic resonance imaging (MRI) techniques have been introduced. This present review was tasked with evaluating MRS and enhanced MRI techniques in aiding the localisation of prostate abnormalities for biopsy in men with suspected PC and elevated PSA level but previously negative biopsy, from the perspective of the NHS.

Aetiology and pathology

The prostate is located in the pelvis, lying below the bladder and encompassing the prostatic urethra (*Figure 1*). In a normal young adult male the gland is approximately 3 cm long and weighs approximately 20 g.[3] Histologically, the prostate consists of glandular epithelial cells and fibromuscular stroma, and is surrounded by a capsule. There are three glandular regions: peripheral zone (PZ), central zone (CZ) and transition zone (TZ).[4] The vast majority of PCs originate from glandular epithelial cells; hence, they are adenocarcinomas. Up to 70% of cancers arise in the PZ, 15–20% arise in the CZ, and 10–15% arise in the TZ.[5] The aetiology of PC remains controversial, although several risk factors have been identified. The most important risk factors include family history, ethnicity (especially men of black African, African American or black Caribbean ancestry[6]) and increasing age.

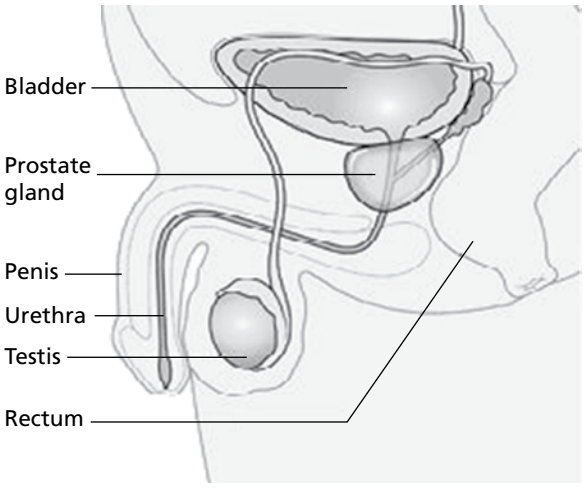


FIGURE 1 Location of the prostate. Taken from CancerHelp UK, the patient information website of Cancer Research UK: http://cancerhelp.cancerresearchuk.org.

Cancer spread occurs by three possible routes: direct (or local) spread to the rectum or bladder, spread through the lymphatic channels to the pelvic lymph nodes, or spread through the blood vessels to solid organs, especially bone. Clinically, the extent of spread can be classified as localised (i.e. confined to the prostate gland), locally advanced (i.e. spread outside the capsule of the prostate gland), metastatic (i.e. distantly spread from site of origin) or hormone refractory (i.e. when the cancer becomes unresponsive to hormonal manipulation).

Epidemiology and prognosis

In the UK, PC is the commonest cancer in men and the second most common cause of cancer death in men after lung cancer.[7] Each year around 35,000 men in the UK are diagnosed with PC and more than 10,000 men die from it.[7] At the end of 2006, the number of men in the UK still living with the disease up to 10 years after diagnosis was estimated at 181,463.[7]

The prognosis of patients with PC depends on several factors, especially stage of disease (i.e. extent of spread), grade of disease (i.e. histological assessment of aggressiveness, measured by the Gleason sum score), PSA level, and extent and volume of disease determined by biopsy. Since the advent of PSA testing, there has been a gradual stage migration towards the earlier stages of the disease, such that the majority of men (i.e. 80%) with PC are diagnosed when the disease is at the localised stage.[8] It has been estimated that, of asymptomatic men in whom PC is detected by prostate biopsy following PSA measurement, around 50% do not require active treatment.[9] Nearly half of patients with clinically diagnosed organ-confined disease have extraprostatic disease pathologically, whereas one-third of patients with clinically diagnosed extraprostatic disease have organ-confined disease pathologically.[10,11] With the introduction of MRI in clinical management of PC, these numbers are very likely to change.[12]

Impact of health problem

Many men find themselves with the dilemma of having a persistently elevated PSA level, or persistent suspicion of cancer, and a negative biopsy. There are two possible explanations: either cancer has been missed (i.e. false-negative) or there is no cancer (i.e. true-negative). This situation can be a source of considerable uncertainty and anxiety for patients, families and friends, resulting in reduced QoL. Some patients may have friends or relatives who have PC, which may further increase anxiety. In part, anxiety is caused by a perceived delay in diagnosis and subsequent treatment.[13–15]

Most men in whom there is suspicion of cancer but a previous biopsy was negative are asymptomatic. Symptoms occur when a tumour causes the prostate gland to enlarge to a significant degree or cancer spreads to areas beyond the prostate. A range of symptoms can result, including increased frequency of urination, problems starting or stopping urination, a painful burning sensation or blood in urine.[16]

From a health-care services perspective, a significant amount of time and resources are directed at managing men with a suspicion of cancer but negative biopsy. These men are usually monitored either 3- or 6-monthly with PSA tests. Significant numbers of men will undergo further biopsies, either immediately or subsequently. For these men there is a risk of the diagnosis being delayed, possibly leading to disease progression (and hence compromising cure), increased morbidity and the need for more costly services.

Measurement of disease

Diagnosis of prostate cancer

Men with an elevated PSA level and/or abnormal DRE undergo a prostate biopsy, which is normally performed using TRUS/Bx. Some men with negative biopsies will require a repeat biopsy, either immediately [owing to suspicious features on histology, such as atypical small acinar proliferation (ASAP)] or subsequently (owing to a further rise in PSA, persistently raised PSA or rapidly rising PSA).[17] Achieving a diagnosis at repeat biopsy can be challenging either because they have an enlarged central prostate gland due to benign prostatic hyperplasia or because cancer is present in locations difficult to biopsy.[18] Recently,

promising alternatives have emerged, which include MRS and enhanced MRI techniques. Lesions identified on MRS/MRI are sampled either by MRI-directed biopsy (tissue obtained under direct MRS/MRI imaging) or by TRUS guidance (TRUS/Bx used to identify and biopsy suspicious lesions on MRS/MRI).

Staging

Staging is performed to determine the extent of disease spread. Information from staging is essential, because it influences treatment decisions and affects prognosis.

Pre-treatment imaging staging of PC is usually individualised according to risk stratification based on clinical parameters that are predictive of the likelihood of extraprostatic disease. These clinical parameters normally include pre-treatment PSA level and rate of rise or doubling time, Gleason score, clinical T staging and volume of disease detected on biopsy. Imaging potentially improves these general estimates of risk by specifically identifying lesions with anatomical abnormalities. The most commonly used imaging modalities for staging of PC are MRI, computed tomography (CT), isotope bone scan and positron emission tomography.

Staging can be divided into local, regional and distant categories. Local staging is usually performed by DRE and MRI; regional staging is performed by either CT or MRI; and distant staging is performed by CT, bone scanning and plain bone radiography. In addition, measurement of PSA level in the blood[19–21] and Gleason sum score[22] can also yield useful information regarding stage. Pathological staging determines the actual extent of spread (i.e. if it is either confined to, or spread outwith, the prostate gland, or if resected lymph nodes have cancer) through histological examination. The staging system most commonly used is the tumour, node, metastasis (TNM) staging system.[23] This describes the local extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of metastasis (M stage).

Grading

Grading is the histological assessment of cancer tissue to determine its aggressiveness. This is done on either biopsy tissue, resected tissue (e.g. from transurethral resection of prostate) or surgical specimens. Pathologists usually assign a grade from 1 to 5 to the most common tumour pattern observed and then a second 1–5 grade to the next most common tumour pattern. The Gleason score is the sum of these two grade assignments.[24] This scoring system describes a score between 2 and 10, with '2' being the least aggressive and '10' being the most aggressive,[25] although most pathologists now group scores 1–6 as Gleason 6.[26]

Use of nomograms to predict treatment outcomes

Nomograms are a means of predicting the probability of important outcomes following treatment using pre-treatment variables as predictors. For PC, several nomograms exist, which predict various outcomes following treatment for men with localised PC, based on pre-treatment variables such as PSA, clinical stage and Gleason score. The outcomes predicted include the probability of biochemical disease recurrence following curative treatment (Kattan nomograms[21,27,28] and the D'Amico nomogram[29]) and the probability of various pathological stages following surgery (Partin tables[30]). These nomograms may be used by clinicians and health-care professionals with patients and their families to facilitate decision-making. Use of some of these nomograms has enabled the stratification of men with localised PC into risk groups according to their risk of biochemical recurrence if they were treated with radical treatment, such as radical prostatectomy or external beam radiotherapy (EBRT) (*Table 1*).[31] Studies have shown the added value of MRS and/or MRI in enhancing the value of normograms.[32–34]

Monitoring of disease following treatment

Men who have undergone curative treatments are monitored via PSA measurements, to ensure eradication of disease. Patients who develop disease recurrence will have gradual rises in their PSA level (i.e. biochemical recurrence). In addition, men with suspected local recurrence (i.e. in the pelvis) may be imaged with either MRI or CT scans, or undergo TRUS-guided prostate biopsy to confirm local disease

TABLE 1 Risk stratification for men with localised PC

Risk	PSA (ng/ml)		Gleason score		Clinical stage
Low	<10	*and*	≤6	*and*	T1–T2a
Intermediate	10–20	*or*	7	*or*	T2b–T2c
High	>20	*or*	8–10	*or*	T3–T4

recurrence. However, the benefit of these investigations remains controversial.[17] Patients with more rapid rises in PSA level may have disease outside of the pelvis and more extensive investigations are performed, including a bone scan.

Current service provision

Management of disease

Management of localised prostate cancer

A range of treatment options exist for men with localised PC, ranging from active surveillance for low-risk disease, whereby treatment is deferred until the cancer progresses or becomes more aggressive, to minimally invasive treatments that ablate a part of the prostate [such as high-intensity focused ultrasound (HIFU) and cryotherapy] and to immediate curative treatments (including invasive treatments such as radical prostatectomy, radiation treatment or brachytherapy).[35] Curative treatments may result in significant side effects, including urinary incontinence (UI), erectile dysfunction (ED) or troublesome urinary symptoms.[36]

Based on current National Institute for Health and Care Excellence (NICE) guidance,[9] *Table 2* outlines the alternative treatment modalities recommended by PC stage at time of diagnosis. It has been noted that the vast majority of patients identified from second biopsies have localised cancer and few fall into

TABLE 2 Treatment/surveillance options for patients with newly diagnosed PC

	Cancer stage (risk stratification)					
Treatment options	Localised (low risk)	Localised (intermediate risk)	Localised (high risk)	Locally advanced	Metastatic	Hormone refractory
Watchful waiting	✓	✓	✓			
Active surveillance	✓[a]	✓				
Prostatectomy	✓	✓[a]	✓[a]			
EBRT	✓	✓[a]	✓[a]			
Brachytherapy	✓	✓				
Cryotherapy						
HIFU						
EBRT + neoadjuvant/ adjuvant hormone therapy				✓		
Hormone therapy (first, second lines)				✓	✓	
Chemotherapy						✓

a Indicates recommended treatment option for stage.

the high-risk group.[2,37,38] Based on routinely collected data on hospital episodes in Scotland (Dr Karina Laing, MSc in Surgical Sciences thesis, University of Edinburgh, May 2012, personal communication), it is estimated that the majority of patients with localised disease receive active surveillance (40%), radical prostatectomy (35%) or EBRT (25%) in the first year following diagnosis.

Management of locally advanced prostate cancer

The vast majority of patients with locally advanced PC will undergo potentially curative hormone manipulation [castration, luteinising hormone-releasing hormone (LHRH) agonists or antagonists] for a minimum of 2 years plus radiotherapy. In the UK, for radical radiotherapy, most men receive 72 grays (Gy) in 36–37 fractions.

A small percentage of men may undergo radical prostatectomy for previously unsuspected T3 disease, T3 disease with severe lower urinary tract symptoms or patient preference where radiotherapy is contraindicated or problematic. Some will be cured by their surgery but those who are not will mostly be offered adjuvant radiotherapy. Men who would not benefit from radical treatment because of comorbidities are usually offered immediate or deferred hormone manipulation.

Management of metastatic disease

Patients who are initially diagnosed with metastatic disease receive first-line treatment with hormone manipulation. When first-line treatment fails, second-line hormone manipulation with the addition of an anti-androgen is usually initiated. If this is unsuccessful, those who are fit enough are offered chemotherapy. If unsuitable for chemotherapy, or after unsuccessful chemotherapy, third-line hormonal treatment may be initiated. Timing of third-line hormonal treatment, with respect to chemotherapy, varies throughout the UK and may change with the introduction of abiraterone (Zytiga®, Janssen Biotech).[39]

Current service cost

It is difficult to estimate current PC diagnosis costs in the UK owing to limitations in the reporting of biopsies carried out as outpatient procedures. However, the number of new PC cases diagnosed in 2009 was 40,841. If we assume that approximately 25%[40] of these cancers were detected by repeat TRUS-guided needle biopsies, and the cancer detection rate is approximately 25%,[14,38] then it is not unreasonable to assume that approximately 41,000 repeat biopsies were performed in the UK in 2009. The 2009–10 NHS reference cost for the Healthcare Resource Group (HRG) to which needle biopsy of the prostate maps (LB27Z, outpatient procedure) was £212.[41] This would suggest an absolute lower limit for the cost of repeat prostate biopsies to the NHS of ~£8.7M in 2009. In reality, this will be higher as a significant proportion of biopsies will have been reimbursed as day-case activity, and commissioning practice may vary by location. Given the limitations of outpatient reporting, it is difficult to ascertain exactly what this proportion is.

Considering the impact of diagnosing localised disease, the estimated first-year costs of receiving treatment under the modalities reported in *Table 2* are presented in *Table 3* (see *Chapter 5* for details).

TABLE 3 Estimated average first-year treatment costs per patient identified with cancer through repeat biopsy

Treatment modality	First-year costs per patient[a] (£)	Proportion receiving treatment modality	Weighted cost of treatment (£)
Active surveillance	284	0.40	113.46
Radical prostatectomy	4650	0.35	1627.44
EBRT	4809	0.25	1202.21
Total			2943.10

a See *Chapter 5* for details of cost estimates.

Assuming again that 25% (10,205) of cancers diagnosed in the UK each year are identified through repeat biopsies, and that all are treated with these modalities in the proportions derived from routine Scottish data, then the approximate first-year costs to the NHS of treating this cohort would equate to approximately £30M.

Variation in services and/or uncertainty about best practice

A degree of variation has been brought about by government targets, meaning that in some centres patients undergo a standard T2-weighted magnetic resonance imaging (T2-MRI) of the prostate prior to biopsy for lesion detection and staging purposes (the latter just in case a cancer is eventually found). The MRI before biopsy strategy in some centres is done so that the wait for a staging MRI after biopsy is removed. Most centres still perform their staging MRI post biopsy at around 3–6 weeks to allow time for post-biopsy haemorrhage to resolve but this may lead to breaches in national targets.

There are a number of different diagnostic pathways for patients who have an initial negative biopsy. If histopathological assessment indicates suspicion of cancer or abnormalities, most centres would proceed to a further biopsy, either a repeat 10- to 12-core TRUS/Bx or extended 14–16 core. Some centres would perform a pre-biopsy MRI, enhanced MRI techniques or MRS, to assist in targeting larger lesions. Where available, some centres may also use TRUS-guided transperineally obtained template biopsies, or TRUS-guided transrectally obtained saturation biopsies, dependent upon physician preference, the latter usually after a second negative TRUS/Bx.

Further variation in services will depend upon:

- local policy
- interpretation of national policy (MRI pre biopsy in some centres)
- access to prostate biopsy services
- access to MRI, enhanced MRI and MRS facilities
- access to template biopsy equipment.

Relevant national guidelines, including National Service Frameworks

The 2008 NICE PC guideline[9] states that men with high-risk localised and locally advanced PC who are being considered for radical treatment should have pelvic imaging with either MRI or CT, if MRI is contraindicated. Qualifying statement: 'there is evidence from observational studies to support making this recommendation'. Furthermore, 'MRS is not recommended for men with PC except in the context of a clinical trial'. Qualifying statement: 'there is no evidence to support routine use of MRS'.

The Prostate Cancer Risk Management Programme in 2006 issued guidance for prostate biopsies recommending a 10- to 12-core scheme at first biopsy, which samples the mid-lobe PZ and the lateral PZ only (NHS Cancer Screening Programmes. *Undertaking a transrectal ultrasound guided biopsy of the prostate*. 2006. URL: www.cancerscreening.nhs.uk/prostate/pcrmp-guide-1.html). Directed cores should also be sampled from any hypoechoic areas identified during the procedure. Anterior/TZ samples may be appropriate at a repeat biopsy. However, no comments were made on the number of cores on repeat biopsies or any other methods of guiding the biopsy protocol.

The European Association of Urology (EAU) guidelines state[17] 'if clinical suspicion for prostate cancer persists in spite of negative prostate biopsies, MRI may be used to investigate the possibility of an anterior located prostate cancer, followed by TRUS or MRI-guided biopsies of the suspicious area'.

The European Society of Urogenital Radiology (ESUR) guidelines for MRI in PC,[42] issued in April 2012, recommend that when TRUS biopsy is negative, and an interval rise in PSA justifies further investigation, enhanced MRI using the 'detection protocol' must be applied before further TRUS/Bx. In this context, the detection protocol consists of T2-MRI, diffusion-weighted magnetic resonance imaging (DW-MRI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), with MRS being an option.

The UK Royal College of Radiologists (RCR) guidelines[43] recommend the use of MRI for staging known PC. The use of MRI to detect PC is indicated only in specific circumstances, making the comment that 'MRI is capable of detecting prostatic carcinoma when clinical suspicion is high but transrectal US-guided biopsy negative. Focal areas of abnormal signal can be targeted for biopsy or repeat biopsy under ultrasound guidance'. Guidance published in 2006 by the RCR outlined in detail the usage of MRI in PC emphasising T2-MRI. DCE-MRI and MRS were mentioned as techniques that could be useful for staging, therapy planning and for detecting recurrent disease. The 2006 RCR guidance is currently being updated under the Cancer Staging Proforma Reporting Project (CASPAR),[44] which is a pilot programme to test the design and utility of proforma-based reporting for a number of cancers. The CASPAR PC imaging proforma provides guidance on the use of T2-MRI, DW-MRI and DCE-MRI (Dr Gina Brown, Project Lead, 27 February 2012, personal communication). No mention is made of the clinical utility of MRS in this setting. The RCR in its guidance does not detail a strategy for evaluating patients with negative TRUS biopsy.

Description of technologies under assessment

Summary of technologies (index tests)

This review is concerned with three technologies: MRS, DCE-MRI and DW-MRI.

Magnetic resonance spectroscopy

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. MRS makes use of the slight differences in chemical environment of protons attached to small metabolites present in the tissue or organ of interest. Signals of the different protons in these molecules are presented in a spectrum, in which the position on the *x*-axis is representative for the exact so-called chemical shift of the protons at hand (*which* molecule), and the intensity on the *y*-axis represents the amount of that particular proton pool present *(how much* of that molecule is present). In this way, MRS can give quantitative information on the presence and quantity of metabolites in the prostate. Magnetic resonance spectroscopy imaging (MRSI) does the same, but also provides this information according to spatial location of spectra superimposed on an imaginary two- or three-dimensional grid over the prostate.

In the prostate, three-dimensional MRSI is the current standard of doing spectroscopy, providing spectra of the whole organ with a spatial resolution in the order of 0.5 cc.[45–47] In the prostate the relative concentrations of four metabolites are routinely detectable:

1. citrate, an intermediate of the Krebs cycle, which accumulates in the luminal space of healthy prostate tissue
2. choline, free and phosphorylated choline compounds, which are involved in the phospholipid metabolism of the cell, elevated in cancer tissue
3. creatine, involved in the energy metabolism of cells
4. polyamines (spermine, spermidine and more), accumulating in the luminal space.

As the chemical shifts of choline, polyamines and creatine do not differ greatly, these resonances cannot always be separated, and are therefore incorporated into one clinically useful biomarker for the presence of PC: the choline (+ polyamines) + creatine to citrate ratio (CC/C). After spectral fitting of the different metabolites, this CC/C ratio can be calculated and used either qualitatively[48] or quantitatively[49] in the so-called standardised threshold approach[50,51] to estimate the presence and aggressiveness of cancer in prostate tissue.[52]

Differences in the concentrations of these metabolites between normal and malignant prostate tissues allow for increasing the accuracy of staging among less-experienced readers, and decreasing interobserver variability.[53] Furthermore, correlations have been demonstrated between the metabolic signal pattern

and a pathological Gleason score, suggesting the potential for a non-invasive assessment of tumour aggressiveness.[52,54]

Dynamic contrast-enhanced magnetic resonance imaging

Dynamic contrast-enhanced MRI is a fast T1-weighted imaging technique that dynamically measures a bolus pass of an intravenously administrated MR contrast agent through the prostate. For its nutrient and oxygen supply, a tumour forms new vessels made through the process of neoangiogenesis. In tumour tissue these vessels are often leaky or incomplete, which makes it easier for a contrast agent to extravasate into the extravascular extracellular space. In this extracellular space, the gadolinium-based contrast agent increases the signal intensity of T1-weighted images. In this way, tissues with increased perfusion and vessel leakage stand out with respect to normally perfused tissue, which enhances less.

Three-dimensional DCE-MRI measures the time course of the contrast agent passing through the prostate by repeatedly acquiring three-dimensional T1-weighted images at high temporal resolution (in the order of seconds), providing a signal enhancement curve for every voxel of the three-dimensional MRI data sets. These time-curves can be described semiquantitatively or modelled into pharmacokinetic parameters, which gives either descriptive measures of the enhancement curve (start of enhancement, wash-in gradient, maximum enhancement, time to peak, washout gradient, area under the gadolinium curve, etc.) or model parameters (forward leakage rate, washout rate constant and leakage space) usual after the fitting to a pharmacokinetic model.[55] For an accurate assessment of the model parameters, an arterial input function (AIF) is required that describes the shape of the contrast bolus arriving at the prostate. The semiquantitative parameters do not need such an AIF. Tumour tissue in the prostate is characterised by increased pharmacokinetic parameters compared with healthy tissue. Unfortunately, especially in the TZ of older men, benign diseases such as proliferative benign prostatic hyperplasia or prostatitis also show marked enhancement after contrast agent administration, making DCE-MRI less specific in the TZ of the prostate. Very recently, recommendations have been published on how this technique can best be used.[56]

Dynamic contrast-enhanced MRI has been shown to be of use in detection and staging of PC within a multiparametric protocol[57–59] and is especially useful in follow-up after treatment, when normal prostate anatomy is either not present[60] or disturbed after radiotherapy.[61]

Diffusion-weighted magnetic resonance imaging

Diffusion-weighted MRI is a technique that evaluates the microscopic mobility of water molecules in tissue. Impeded water movements within cellularly dense tissues, such as tumours, appear as high-signal regions on diffusion-weighted images and as darker signals on apparent diffusion coefficient (ADC) maps. In glandular spaces (healthy prostate luminal spaces) or large extracellular spaces, water motion is less impeded, leading to larger signal attenuation (low signal on diffusion-weighted images) and to higher ADC values. In addition to its value in the detection of cancer,[62,63] DW-MRI has also been shown to be a promising marker of tumour aggressiveness, with good correlation between ADC values and Gleason score in the PZ of the prostate.[64]

Current usage in the NHS

As a result of the aforementioned guidelines (see *Relevant national guidelines, including National Service Frameworks*, above), MRI is widely used to evaluate the stage of PC in the UK. Most centres have 1.5-T (tesla) scanners, although 3-T machines are found in major teaching hospitals and more recently have appeared in non-teaching hospitals. Endorectal coil usage is found only at selected centres. Most centres use T2-MRI and DW-MRI routinely for PC imaging, although the quality of DW-MRI is variable on currently installed equipment in many centres. Centres with a high volume of PC referrals do perform DCE-MRI in selected patients, including patients with prior negative TRUS/Bx and for suspect locally recurrent disease. There are very few centres in the UK with prostate MRS experience. Systematic proforma reporting is beginning to appear at selected expert centres but this is likely to expand more widely once the findings and recommendations of joint RCR/National Cancer Intelligence Network (NCIN) CASPAR project (see *Relevant national guidelines, including National Service Frameworks*, above) are implemented nationwide.

Anticipated costs associated with the intervention

The anticipated costs associated with the use of MRS/MRI in the diagnostic pathway will depend on the specific sequences used. Diagnostic imaging scans of the prostate using T2-MRI, DW-MRI and MRS all map to the HRG RA01Z (Magnetic Resonance Imaging Scan, one area, no contrast), whereas sequences involving the use of DCE-MRI map to RA03Z (Magnetic Resonance Imaging Scan, one area, pre and post contrast). The national average NHS reference costs for RA01Z and RA03Z were £174 and £229, respectively, in 2009–10.[41] If all 41,000 patients in our estimated annual cohort undergoing a repeat biopsy were to receive an MRI scan prior to biopsy (0.4 with pre and post contrast, 0.6 without) then this would equate to a cost of approximately £8M to the NHS. If it is assumed that the results of MRI are used to direct TRUS biopsies in patients with a visible lesion, while those with no visible lesion receive a systematic TRUS/Bx instead, then this £8M represents the additional cost to the NHS of using MRI compared with using TRUS alone to guide biopsies. Of course there would be anticipated benefits in terms of improved detection rates, reduced need for further biopsies and timely intervention. An alternative way of using MRS/MRI could be to use it to safely filter out patients with no visible lesion, such that biopsy costs and associated complications would be reduced at the population level. Both these models for its use are explored in the chapter on cost-effectiveness. Although the reference costs used in the above calculations broadly reflect the cost to the NHS of commissioning different types of MRI, they do not capture more subtle differences in costs between different MRI sequences. For this reason we have carried out some bottom-up costing of the sequences and combinations of them to inform the cost-effectiveness analysis reported in *Chapter 5*.

Comparator tests

Standard (T2-weighted) magnetic resonance imaging

T2-weighted MR images are usually obtained in two to three planes, with axial and coronal planes being the minimum. The axial T2-weighted MRI sequence must cover the entire prostate and seminal vesicles with section thicknesses of 3–4 mm. An endorectal coil (ERC) is not an absolute requirement for T2-MRI performed on 1.5-T or 3-T scanners but a pelvic phased-array external coil with a minimum of 16 channels is required to produce high-quality images. T2-weighted MRI provides the best depiction of the prostate's zonal anatomy, seminal vesicles and the prostatic capsule. T2-MRI is mostly used for PC staging but also has some utility for lesion detection and localisation.

It is not recommended that T2-MRI should be used on its own for detection and localisation; it should, in general, be used with other enhanced MRI or MRS techniques because their combined use improves both sensitivity and specificity.[42] PC typically manifests as a round or ill-defined, low-signal-intensity focus in the PZ on T2-MRI. However, various conditions [such as prostate intraepithelial neoplasia, prostatitis (infection or inflammation), haemorrhage, glandular atrophy, scars from previous infections and biopsies, and post-treatment changes] can mimic cancer on T2-MRI in the PZ. The high frequency of non-cancer prostate conditions and their ability to affect T2-MRI appearances accounts for the high sensitivity but low specificity of T2-MRI for tumour detection and localisation.

Tumours located in the TZ are more challenging to detect on T2-MRI, as the signal intensity characteristics of the normal TZ and cancer usually overlap.[65] TZ tumour often is shown as a homogeneous signal mass, with indistinct margins with lenticular shapes if anteriorly located.

High-grade PCs tend to be larger, more infiltrative and to have lower signal intensity than low-grade cancers on T2-MRI, which makes high-grade disease easier to detect.[66,67] T2-MRI can be ineffective for detecting low-risk PC (small volume disease or sparse variants of Gleason 3 + 3 cancer) because of imaging overlaps with non-cancer conditions mentioned above.

Transrectal ultrasound guided prostate biopsy

The main role of TRUS is to direct biopsies in order to obtain a systematic sampling of the prostate gland rather than to target specific lesions, because of the unreliability of greyscale ultrasonography to visualise cancer.[68,69] A systematic TRUS biopsy simply means that the cores are obtained in an organised manner. Template biopsy is a type of systematic biopsy, and uses a grid-based method to guide the random core biopsies. A saturation biopsy aims to sample the entire prostate and would routinely use 20 or more cores. It should be noted that these techniques are not performed in a targeted manner but rather randomly, albeit in a systematic fashion.

It is unclear how repeat biopsies should be performed.[70] The standard approach would be to repeat the biopsies transrectally under TRUS guidance, increasing the number of cores, and including samples from other zones.

As the majority of cancers arise from the PZ of the gland, initial biopsies are targeted at this area.[17] The sensitivity and specificity of TRUS-guided prostate biopsies in diagnosing cancer vary depending on several factors, including the threshold of PSA level used to justify a biopsy, the area of the prostate targeted, and the number of prostate tissue cores. Although the patient-level diagnostic accuracy is increased by increasing the number of tissue cores,[71] this strategy invariably results in more side effects.

Transrectal ultrasound prostate biopsy is usually performed under local anaesthetic as an outpatient procedure. Due to the risk of sepsis from the procedure a dose of antibiotic is administered prior to the procedure, with one to three doses supplied to the patient postoperatively. The patient is commonly positioned in the left lateral position. The scans are performed with either an end- or side-fire transrectal probe scanning between 7.5 and 9 MHz. A disposable guide is attached over the probe prior to its placement in the rectum. Scans are performed in the transverse and longitudinal direction, sometimes simultaneously.

Transperineal biopsies are typically performed under a short general anaesthetic. Where the patient has a rectum and an anus, a transrectal probe is then introduced to either guide the biopsy needle freehand or, in the case of template biopsies, a grid is placed over the perineum and the ultrasound transducer is placed into the rectum via a housing that keeps the probe in the correct position. Biopsies are then taken using the template with standard 18-gauge needle from predetermined sections of the gland. These can then be processed separately to allow a map of the disease to be built up. Biopsies performed in this way allow the anterior and apical portions of the gland, which are more difficult to target on transrectal biopsies, to be sampled more easily. Where the patient has no rectum the biopsies can be guided using a transabdominal probe.

Care pathways

In developing the care pathways, we used a combination of current clinical guidelines and expert opinion to devise alternative diagnostic and treatment pathways for the economic modelling reported in *Chapter 5*. The general diagnostic pathway is outlined in *Figure 2*.

The options for patients following a previous negative biopsy are divided into standard pathways and experimental pathways. For the purposes of this review the use of any MRI sequence to direct TRUS/Bx is considered experimental, whereas the use of systematic TRUS-guided biopsies is considered standard practice. Under standard practice, the options for patients with a previous negative biopsy are to monitor PSA and other measures predictive of PC, perform a further standard cores biopsy (10–12 cores based on expert clinical opinion) if there is a technical reason to do so, or perform an extended-cores biopsy for patients where suspicion of PC remains. For the purposes of the economic modelling carried out in *Chapter 5*, we take patients selected for a repeat biopsy as the starting point for the analysis, and for this

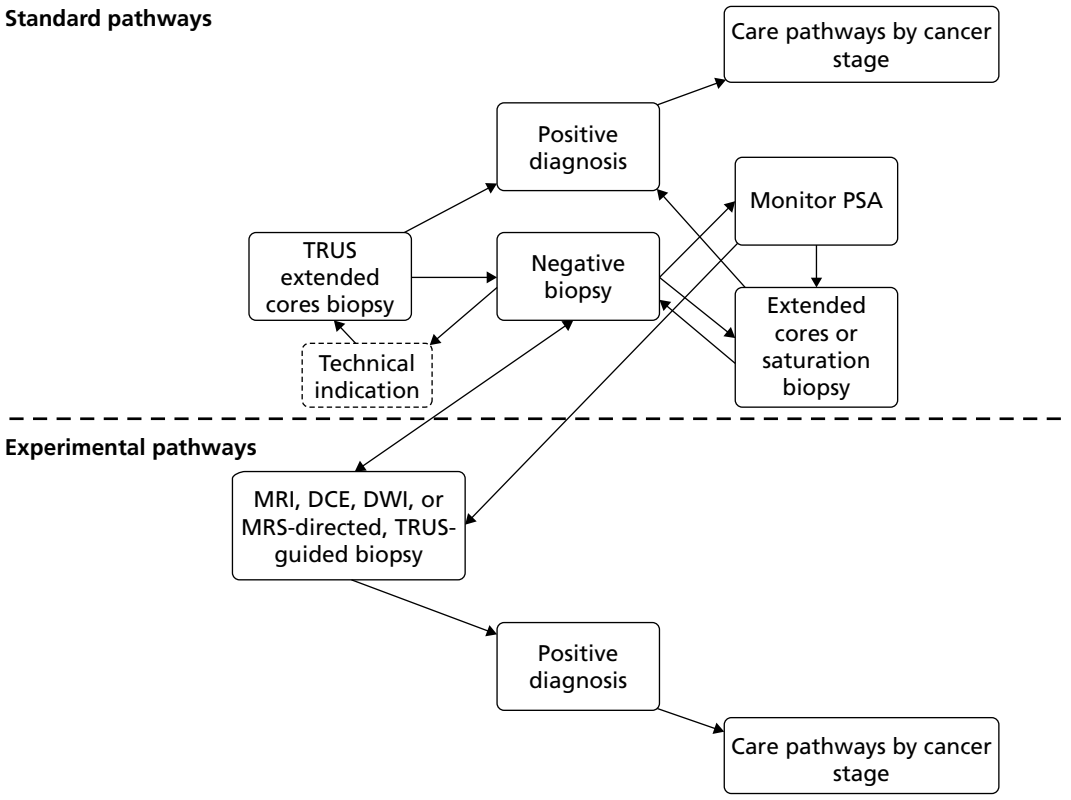


FIGURE 2 General diagnostic pathway.

cohort the consensus among clinical experts on our team was that a systematic extended-cores biopsy (14–16 cores) would be the appropriate comparator under standard practice. The use of MRS/MRI to direct TRUS/Bx at this stage offers the alternative experimental approach.

Following a negative result from a second biopsy, patients can remain cycling within the diagnostic pathway, with further monitoring of PSA and further repeat biopsies. Clinical opinion within the research team was that, in the case of patients selected for a third biopsy, a systematic saturation biopsy would probably be performed at this stage. Thus, the economic modelling applied the simplifying assumption that any patients with underlying cancer missed by the second biopsy would have persistently elevated PSA level and would progress to a TRUS-guided saturation biopsy within 12 months. This last procedure is considered the reference standard for the presence of PC. For those patients with no underlying cancer (disease negative on a reference standard), the assumption was made that PSA monitoring would continue indefinitely and that no further biopsies would be undertaken unless incident cancer developed. Although this may seem clinically unrealistic, the proportion of patients with no cancer and their downstream management would probably remain constant between the experimental and control arms of the model following the index repeat biopsy. Hence, their subsequent treatment, outcomes and costs would not influence the decision problem in hand, of whether or not MRS/MRI should be used in men with a previous negative biopsy to direct the next biopsy, i.e. we do not model the ongoing use of MRI to direct all further repeat biopsies in men who remain negative following their initial MRI-directed TRUS/Bx.

Following a positive diagnosis from any biopsy procedure, staging and subsequent treatment is implemented in line with the current guidance by stage and grade of cancer present (see *Table 3*). The Markov model developed to simulate the progression of undiagnosed and diagnosed cancer, and its subsequent treatment by stage and grade, is described in detail in *Chapter 5*.

Chapter 2 Definition of the decision problem

Decision problem

The purpose of this review is to assess the diagnostic accuracy of MRS, DCE-MRI and DW-MRI and the clinical effectiveness and cost-effectiveness of strategies involving their use in men with suspected PC and elevated PSA level but previously negative biopsy.

Interventions

As data allow, the following tests are considered, alone or in combination:

- MRS-guided biopsy
- DCE-MRI-guided biopsy
- DW-MRI-guided biopsy.

In addition, the above tests are considered in combination with standard (T2-weighted) MRI. In situations when both tests are required to be positive for the combination to be positive, the test combination is linked by 'and'. When only one of the tests is required to be positive for the combination to be positive, the test combination is linked by 'or'.

Population including subgroups

The population concerned is men with suspected PC and elevated PSA level of up to 20 ng/ml but previously negative biopsy.

The setting considered is secondary or tertiary care.

Where data allow, a subgroup of participants with prostatic intraepithelial neoplasia (PIN) and ASAP diagnosed at first biopsy is considered.

Relevant comparators

The comparator tests considered are:

- standard (T2-weighted) MRI
- TRUS.

Reference standard

The reference standard is histopathological assessment of biopsied tissue. Tissue samples may be obtained by transrectal needle biopsy, saturation biopsy, transperineal template biopsy or from prostatectomy specimens.

A maximum follow-up time of 12 months was incorporated into the reference standard. This was to distinguish between tumours missed by the index/comparator test (detected before 12 months) and interval tumours that were not missed (detected after 12 months).

Outcomes

The following outcomes are considered:

- Diagnostic performance of MRS, DCE-MRI and DW-MRI in the localisation of abnormalities of the prostate.

These outcomes are considered at both patient-level and biopsy level, where data allow.

The reported Gleason score of the patients diagnosed with PC is presented to assess if index/comparator tests detect different grades of tumour.

In studies reporting the above outcome, the following outcomes are also considered, if reported:

- altered treatment as a result of the tests
- acceptability of the tests
- interpretability of the tests
- effect of testing on QoL (disease-specific and generic instruments)
- adverse effects of testing.

Key issues

There are several key issues. First, does a single test or a combination of tests provide the greatest diagnostic accuracy and cost-effectiveness? MRS, DCE-MRI, DW-MRI or standard (T2-weighted) can be used in combination. If a combination of tests is used, is greatest benefit derived when both tests are required to be positive or when only one test is required to be positive? Second, are there patient groups for which MRS, DCE-MRI and DW-MRI are more effective, for example patients who are diagnosed with PIN or ASAP on initial biopsy? Third, does MRS, DCE-MRI or DW-MRI detect more clinically significant tumours?

Two significant challenges are worth noting. First, the reference standard (histopathological assessment of biopsied tissue) is linked with one of the comparator tests (TRUS). Most studies use TRUS to obtain histopathological samples. TRUS can be used to either obtain a systematic, predefined set of biopsies (TRUS/Bx) and/or identify suspicious areas. When TRUS is used in a systematic, predefined manner, a template is usually used and areas in the prostate are not diagnosed as 'normal' or 'abnormal'. Therefore, diagnostic outcomes cannot be measured. However, when TRUS is used to identify 'abnormal' areas and a subsequent biopsy obtained, diagnostic outcomes can be measured. A number of studies combine these two uses of TRUS; suspicious lesions are biopsied and subsequently a systematic, predefined set of biopsies is obtained. The situation is further complicated because there is variation in the number and pattern of cores obtained on systematic biopsy.

Second, there is no widely accepted definition of 'guided', 'directed' and 'targeted'. After a lesion is identified on MRS, DCE-MRI, DW-MRI or standard T2-MRI, biopsies can subsequently be obtained using a MRI compatible device or TRUS/Bx. For the purposes of this review, the term 'MRI-guided' is used when biopsies are obtained using a MRI compatible device. The term 'MRI-directed TRUS-guided' is used when lesions are identified using MRI, but biopsies are obtained using TRUS.

Overall aims and objectives of assessment

This review assessed the diagnostic accuracy of MRS, DCE-MRI and DW-MRI and the clinical effectiveness and cost-effectiveness of strategies involving their use in men with suspected PC and elevated PSA level but previously negative biopsy. Subsidiary questions to be addressed relating to these techniques included:

- In which patient group are they most clinically effective?
- Can they identify cases where PC is present but further procedures are unnecessary?
- Does their use lead to changes in patient management?

Chapter 3 Methods for reviewing diagnostic accuracy

Methods were in accordance with the protocol, which is presented in *Appendix 1*.

Identification of studies

Comprehensive electronic searches were conducted to identify reports of published studies. Highly sensitive search strategies were designed including appropriate subject headings and text word terms relating to PC, biopsy and the tests under consideration. Searches were restricted to years from 1995 onwards, reflecting the time of introduction of the tests, and non-English-language publications were excluded. MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE, BIOSIS, Science Citation Index (SCI) and the Cochrane Controlled Trials Register (CENTRAL) were searched for primary studies, while the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), MEDION and the Health Technology Assessment (HTA) databases were searched for reports of evidence syntheses. Recent conference abstracts (2009–11) from the American Society of Clinical Oncology (ASCO) meetings were also searched. The date of the last searches was March 2012.

Reference lists of all included studies were scanned in order to identify additional potentially relevant reports. The expert panel provided details of any additional potentially relevant reports. Ongoing studies were identified through searching Current Controlled Trials (CCT), Clinical Trials, WHO International Clinical Trials Registry Platform (ICTRP) and NIH Reporter. Full details of the search strategies used are detailed in *Appendix 2*.

Inclusion and exclusion criteria

Types of studies

For diagnostic accuracy of MRS, DCE-MRI and DW-MRI the following types of studies were included:

- direct (head-to-head) studies in which index test(s), comparator test(s) and reference standard test were done independently in the same group of people
- randomised controlled trials in which people were randomised to the index and comparator test(s) and all received the reference standard test.

In the event that there was insufficient evidence from direct and randomised studies, we considered undertaking indirect (between-study) comparisons by meta-analysing studies that compared each single test or combination of tests with the reference standard test, and making comparisons between meta-analyses of the different tests. However, this type of study design is less reliable than direct studies as differences in diagnostic accuracy are susceptible to confounding factors between studies. The following types of studies were considered:

- Observational studies, including case series, in which the sample is created by identifying all people presenting at the point of testing (without any reference to the test results).
- Case–control studies in which two groups are created, one known to have the target disease and one known not to have the target disease, where it is reasonable for all included to go through the tests. We excluded case–control studies comparing severely diseased people with very healthy control

subjects or studies excluding people with other urological disease such that the spectrum of disease and non-disease was unlike that to be encountered in practice.

The following types of report were excluded:

- reviews, editorials and opinions
- case reports
- reports investigating technical aspects of a test
- non-English-language reports.

Types of participants

The types of participants considered were men with suspected PC and elevated PSA level but previously negative biopsy. Studies were also included in which the participants with previously negative biopsy had elevated PSA level and/or abnormal DRE. Studies whose populations included subgroups of men meeting these criteria were also included. Studies that included men diagnosed with ASAP or high-grade prostatic intraepithelial neoplasia (HGPIN) were included. The setting considered was secondary or tertiary care.

Index tests

The index tests considered were MRS, DCE-MRI or DW-MRI, alone or in combination.

Given sufficient data, we planned to undertake sensitivity analysis around when the studies took place, to assess the effects of changes in the technology over time. This was possible only for MRS and T2-MRI.

Comparator tests

The comparator tests considered were standard (T2-weighted) MRI and transrectal ultrasound (TRUS) guided prostate biopsy (greyscale only).

Reference standard

The reference standard considered was histopathological assessment of biopsied tissue. Tissue samples could be obtained by transrectal needle biopsy, saturation biopsy, transperineal template biopsy or from prostatectomy specimens.

A follow-up time of 12 months was specified in the protocol as part of the reference standard. The reason for this was to help distinguish between tumours missed by the index/comparator tests (subsequently detected within this 12-month period) and interval tumours that were not missed (and subsequently detected after the 12-month follow-up period). However, few studies reported a follow-up, and this criterion was relaxed to allow those that did not report a period of follow-up but otherwise met the remaining inclusion criteria to be included in the review.

Types of outcomes

Studies had to report the diagnostic performance of MRS, DCE-MRI or DW-MRI in the localisation of abnormalities of the prostate. In included studies, outcomes relating to altered treatment as a result of the tests, acceptability of the tests, interpretability of the tests, effect of testing on QoL and adverse effects of testing were also considered.

All included studies reported relevant and interpretable data including the absolute numbers of true-positives, false-positives, false-negatives and/or true-negatives, or provided information allowing their calculation such that at least one indicator of diagnostic performance [i.e. sensitivity, specificity, predictive values or likelihood ratio (LR)] was calculable. In addition to studies that reported patient-level analysis, we also considered those that reported only a biopsy-level analysis on the basis that these might also provide potentially useful information.

Data extraction strategy

Two reviewers (from MC, JF, KR, PS) independently screened the titles (and abstracts if available) of all reports identified by the search strategy. Full-text copies of all studies deemed to be potentially relevant were obtained and two reviewers (from MC, JF, GM, KR, PS) independently assessed them for inclusion. Any disagreements were resolved by consensus or arbitration by a third party.

A data extraction form was developed and piloted. One reviewer extracted details of study design, participants, index, comparator and reference standard tests and outcome data, and a second reviewer checked the data extraction. Any disagreements were resolved by consensus.

Critical appraisal strategy

Two reviewers (from MC, JF, GM, KR) independently assessed the risk of bias and applicability concerns of all included full-text diagnostic studies using the updated quality assessment of diagnostic accuracy studies (QUADAS-2) checklist. The original QUADAS checklist was developed for use in systematic reviews of diagnostic studies[72] and was designed to be adapted to make it more applicable to a specific review topic. QUADAS was developed through a formal consensus method and was based on empirical evidence. Following anecdotal reports and feedback which suggested problems with QUADAS, the QUADAS-2 tool was developed. QUADAS-2 consists of four key domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow of patients through the study and timing of the index test(s) and reference standard. Each domain is assessed in terms of the risk of bias. The first three domains are also assessed for concerns regarding their applicability in terms of whether (1) the participants and setting; (2) the index test, its conduct or interpretation; and (3) the target condition as defined by the reference standard match the question being addressed by the review.

For this review, QUADAS-2 was modified to make it more appropriate for assessing the quality of studies of tests for detecting PC. Domains 1 (patient selection) and 4 (flow and timing) were retained in their entirety. The title of Domain 2 was amended to 'index & comparator test(s)' to accommodate all the specified tests. One item was added to the risk of bias section of Domain 2 to assess whether or not tests that required subjective interpretation were interpreted by a suitably experienced person. Two items were added to the risk of bias section of Domain 3 (reference standard) to assess whether or not (1) the results of the reference standard test were interpreted by a suitably experienced person and (2) a follow-up was included in the reference standard. The modified tool consisted of 14 items.

Prior to completing the QUADAS-2 tool some decision rules were agreed between reviewers. In general, if a particular point was not mentioned in a paper, then the relevant signalling item was marked as 'unclear'. Responses to the risk of bias and applicability questions were based upon the three or four relevant signalling questions; in each case, the majority response to signalling questions dictated the overall risk of bias or applicability response. There were some exceptions to this. For the Domain 1 (patient selection) applicability item 'Is there concern that the included patients do not match the review question?', the primary criterion was previously negative biopsy, followed by elevated PSA level. The item was classed as 'Low' if all patients had a previously negative biopsy and >10% of the sample had elevated PSA level. For Domain 2 [index & comparator test(s)], responses of 'yes' to the 'Were the index test results interpreted without knowledge of the results of the reference standard?', 'not available (N/A)' to the item 'If a threshold was used, was it pre-specified?', and 'unclear' to the item 'For a test requiring subjective interpretation, was it interpreted by someone experienced in interpreting such tests?' were classed as 'low' risk of bias. For the Domain 2 applicability item, studies that explicitly did not image or analyse the entire prostate were classed as high concern for applicability. Otherwise, it was assumed that the entire prostate had been imaged and analysed, and studies were classed as low concern for applicability on this item. For Domain 3 (reference standard), a 'no' response to the item 'Were the reference standard results interpreted without knowledge of the index test?' and histopathological specimens which had

been labelled (as suspicious or not) led to risk of bias being classed as 'high', regardless of responses to the remaining signalling items. In addition, a 'no' response to the item 'Was a follow-up included in the reference standard?' led to an automatic classification of high risk of bias. Risk of bias for the Domain 4 (flow and timing) item 'Were all patients included in the analysis?' was classed as 'low' if the proportion of participants included in the analysis was ≥90%.

Each item was worded so that a rating of 'Yes' was always optimal in terms of methodological quality. Any disagreements were resolved by consensus or arbitration by a third party. A sample QUADAS-2 checklist used in this review is presented in *Appendix 3*.

Methods of data synthesis

Data from each study were summarised in a 2×2 table of true-positive (TP), false-positive (FP), false-negative (FN) and true-negative (TN) according to the type of test and whether the primary study analysis was based on patient or biopsy level. These 2×2 tables were then entered into RevMan 5 software (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). All statistical analyses and graphical plots were undertaken in RevMan.

The sensitivity, specificity and their 95% confidence intervals (CIs) were calculated for each 2×2 table and presented for each test or combination of tests at both patient- and biopsy-level analysis. We investigated the presence of heterogeneity by visual examination of pairs of forest plots of sensitivity and specificity.

Sensitivity describes the proportion of those with disease who have positive test results, whereas specificity is the proportion of those without disease who have negative test results. A positive predictive value (PPV) describes the proportion of those with positive test results who have the disease, whereas a negative predictive value (NPV) is the proportion of those with negative test results who do not have the disease. A positive LR describes how many more times more likely it is that a person with disease will receive a positive test than a person without disease, whereas a negative LR describes how many more times more likely it is that a person with disease will receive a negative test result than a person without disease. A diagnostic odds ratio (DOR) is a single indicator of test performance and is the ratio of the odds of testing positive in those with the disease relative to the odds of testing positive in those without the disease. It can be calculated from the sensitivity and specificity values. The DOR summarises the results into a single indicator of test performance; however, information contained in sensitivity and specificity is lost and in particular a DOR cannot distinguish between tests with high sensitivity and low specificity and vice versa.

We undertook meta-analysis, where adequate data were available, using METADAS macro[73] to fit hierarchical summary receiver operating characteristic (HSROC) models in SAS. HSROC models including random effects terms for variation in accuracy and threshold between studies, and non-symmetrical underlying receiver operating characteristic (ROC) curves, were fitted. The average operating point for each test was identified on each curve, and average sensitivities and specificities computed. Comparisons between tests were made by adding a covariate for test type to the accuracy and threshold parameters assuming a common underlying shape.

The comparative analysis was between all tests with three or more studies with relevant data. Comparative analysis consisted of uncontrolled/indirect comparison where all tests with relevant data were compared by adding covariates for a test type to the threshold and accuracy assuming a common underlying shape. A second comparative analysis of paired design where patients received both tests was also conducted.

Given sufficient evidence, we planned to undertake sensitivity analysis to assess the impact of the different number of biopsy cores taken (<10 cores and ≥10 cores) on the accuracy of the tests. However, there was insufficient evidence to undertake such an analysis.

Chapter 4 Assessment of diagnostic accuracy

This chapter is structured as follows. The next section (see *Quantity of research available*, below) provides information on the quantity of research available, including characteristics and risk of bias of the included studies. The section *Results: assessment of diagnostic accuracy* reports the diagnostic accuracy results: individual index and comparator tests (see *Magnetic resonance spectroscopy*, *Dynamic contrast-enhanced magnetic resonance imaging*, *Diffusion-weighted magnetic resonance imaging*, *T2-weighted magnetic resonance imaging* and *Transrectal ultrasonography*); studies directly comparing two or more tests (see *Studies directly comparing tests*); combinations of tests (see *Studies reporting combinations of tests*) and indirect comparison of tests (see *Indirect comparison*). Meta-analyses are included where appropriate and feasible, and patient- and biopsy-level analyses are reported separately. Information on false-positives is provided in *False-positive results* and information on the detection of clinically significant disease is provided in *Detection of clinically significant disease*. The section *Results: assessment of non-diagnostic outcomes* provides information on non-diagnostic outcomes, followed by a chapter summary (see *Summary*).

Quantity of research available

Number and type of studies included

Appendix 4 lists the 51 studies, published in 65 reports (41 full-text papers[57,74–113] and 24 abstracts[114–137]) that were included in the review of diagnostic accuracy. *Figure 3* shows a flow diagram outlining the screening process, with reasons for exclusion of full-text papers.

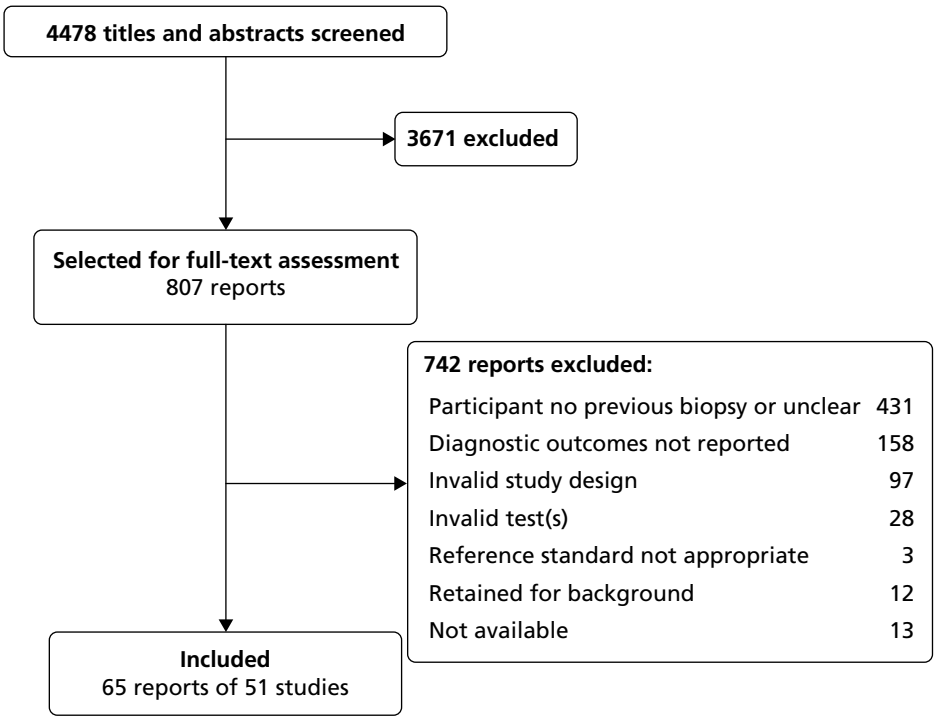


FIGURE 3 Screening process.

Number and type of studies excluded

A list of full-text papers that were excluded along with the reasons for their exclusion is given in *Appendix 5*. These reports were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test, reference standard or outcomes reported.

Characteristics of the included studies

Appendix 6 displays the characteristics of the 51 included studies. *Table 4* presents summary information for the included studies. There were 39 full-text papers.[57,74–84,86–93,95–113] Twenty-seven studies involved consecutive samples.[57,74,76,78,79,81,84,86,87,89–93,95,97,100,101,104–106,108,111,112,118,127,133] Twenty-four studies did not report this information.[75,77,80,82,83,88,96,98,99,102,103,107,109,110,113,115–117,120,126,130,134,136,137] There were 41 prospective studies[57,74–76,79–84,86,88–90,92,93,95,99–101,103–106,108,109,111–113,115–118,120,126,127,130,133,134,136,137] and 10 retrospective studies.[77,78,87,91,96–98,102,107,110]

Fourteen studies included a follow-up in the reference standard: Campodonico *et al.*[77] and Ukimura *et al.*[107] did not report the length of follow-up; Hoeks *et al.*[87] reported follow-up of 5 months; Lin *et al.*[91] reported a total follow-up of 18 months with only the initial 12 months taken into account for the present review; Lopez-Corona *et al.*[92] reported follow-up of up to 97 months; Pepe *et al.*[97] reported follow-up of up to 22 months; Philip *et al.*[98] reported follow-ups of 3 and 6 months; Quinlan *et al.*[102] reported follow-up of up to (a mean of) 50 months; Yanke *et al.*[110] reported a mean period of 30 months between first and last biopsy. Djavan *et al.*, Keetch *et al.*, Pinsky *et al.*, Roehl *et al.* and Zackrisson *et al.* reported population-based screening studies in which participants with negative biopsies were followed up every 6 or 8 weeks, 6 months, 12 months, 6 months and 2 years, respectively.[81,88,99,103,113]

Eighteen studies[74,76,79,84,95,100,101,104–106,108,111,115,117,118,120,130,134] reported diagnostic test accuracy for MRS (alone or in combination with other tests). Twelve studies[78,84,86,87,89,90,95,100,104,105,109,133] reported diagnostic test accuracy for DCE-MRI (alone or in combination with other tests). Eleven studies[84,86,87,89,96,100,104,109,116,126,133] reported diagnostic test accuracy for DW-MRI (alone or in combination with other tests). Twenty-six studies[57,74,76,78,79,82,84,86,87,89,90,100,104,106,108,109,112,116–118,126,127,130,134,136,137] reported diagnostic test accuracy for T2-MRI (alone or in combination with other tests). Twenty-two studies[57,75,77,80,81,83,88,91–93,96–99,102,103,107,110,111,113,120,136] reported diagnostic test accuracy for TRUS (alone or in combination with other tests).

Seven studies[82,84,86,87,104,108,109] involved MRI-guided biopsies and 44 studies[57,74–81,83,88–93,95–103,105–107,110–113,115–118,120,126,127,130,133,134,136,137] involved TRUS-guided biopsies.

Of the 18 studies[84,104,112,115,117,120,130] that involved MRS, seven did not report a threshold for a positive test. Four studies[74,79,100,118] reported a threshold of the CC/C ratio of >0.86. Two studies[95,105] used a threshold of CC/C >0.80. Two studies[101,106] reported a threshold of CC/C ratio more than three standard deviations (SDs) above the mean healthy value. Bhatia *et al.*[76] reported using the mean healthy CC/C to adjust a primary score to obtain a final voxel score. Wefer *et al.*[134] reported abnormal metabolism as areas with four or more voxels with a CC/C ratio more than two SDs. Wetter *et al.*[108] used a threshold of CC/C >0.6.

Twelve studies were undertaken in the USA,[75,88,90,92,99,103,107,110,127,130,134,136] eight in Italy,[77,79,95,97,105,106,118,133] six in Germany,[57,82,84,89,104,108] four each in France[74,78,100,137] and the Netherlands,[80,86,87,109] three in Republic of Korea,[96,116,126] two each in Singapore,[111,112] Spain[115,117] and Turkey[83,93] and one each in Brazil,[101] Ireland,[102] Sweden,[113] Taiwan, Province of China,[91] Thailand,[76] Islamic Republic of Iran[120] and the UK.[98] One multicentre study was undertaken in Austria, Belgium, France and Poland.[81]

The 51 diagnostic studies enrolled 92,588 participants, with 10,264 included in the analysis. In 18 studies, the number of participants analysed was less than the number of participants enrolled. Of these, six[81,88,97,99,103,113] were large-scale screening studies in which only some of the participants matched the inclusion criteria of this review and were reported separately. The differences between the numbers enrolled (86,749) and the much smaller numbers matching the inclusion criteria for this review (5771)

TABLE 4 Summary of the characteristics of the diagnostic accuracy studies

Characteristic	No.	No. of studies
Patients		
Enrolled[a]	92,588	50
Analysed	10,264	51
Age (years)		
Median (range) of means	63.5 (60.3 to 68.1)	24 (47%)
Median (range) of medians	66 (62 to 69)	7 (14%)
Other format/not reported	–	20 (39%)
Baseline PSA (ng/ml)		
Median (range) of means	10.8 (6.4 to 16)	17 (33%)
Median (range) of medians	10 (5.5 to 19.5)	8 (16%)
Other format/not reported	–	26 (51%)
Participants at initial biopsy with		
ASAP	217 (2%)	4 (8%)
HGPIN	199 (2%)	5 (10%)
Test results reported		
MRS	772 (8%)	18 (35%)
DCE-MRI	1094 (11%)	12 (23%)
DW-MRI	1021 (10%)	11 (22%)
T2-MRI[b]	1615 (16%)	26 (51%)
TRUS	8105 (79%)	22 (43%)
Biopsy guidance		
T2-MRI	538 (5%)	7 (14%)
TRUS	9726 (95%)	44 (86%)
Prostate size (cc)		
Median (range) of means	53.9 (42.5 to 59.3)	4 (8%)
Median (range) of medians	54.9 (41 to 67)	3 (6%)
Other format/not reported	–	44 (86%)

a No. of participants enrolled not reported by Comet-Batlle.

b Studies that used T2-MRI in combination with other MRI modalities, but did not report results for T2-MRI not included in these totals.

in these six studies[81,88,97,99,103,113] largely accounted for the difference in numbers between those enrolled and those analysed shown in *Table 4*. In five studies,[57,105,108,127,136] not all participants had a previous negative biopsy (those with a previous negative biopsy were reported separately). Two studies[84,86] involved participants withdrawing because of comorbidities. The study by Destefanis *et al.*[118] was an ongoing study in which not all enrolled participants had reached the point of analysis. Hoeks *et al.*[87] analysed only participants who underwent a follow-up MR-guided biopsy. The study by Panebianco *et al.*[95] involved analysing urine samples, not all of which were successful. In the study by Testa *et al.*,[106] data from four

participants were not analysed because of poor MRS quality. Yakar *et al.*[109] analysed only participants in whom scanning revealed cancer-suspicious regions.

Across 24 studies reporting mean age,[57,74–76,78–82,86,92,93,95,96,98–100,105–107,112,120,136,137] the median (range) of means was 63.5 years (60.3 to 68.1 years). Seven studies[84,87,90,101,104,108,109] reported median values for age and the median (range) of medians was 66 years (62 to 69 years). Eight studies[77,83,89,97,102,111,126] reported age in other formats. Twelve studies[88,91,103,113,115–118,127,130,133,134] did not report this information.

Across 17 studies[57,74–76,78,79,81,82,92,93,95,96,100,101,106,120,136] reporting mean baseline PSA, the median (range) of means was 10.8 ng/ml (6.4 to 16 ng/ml). Eight studies[80,84,86,87,90,104,108,109] reported median baseline PSA levels, the median (range) of medians being 10 ng/ml (5.5 to 19.5 ng/ml). Eleven studies[83,88,89,97,99,102,105,110,111,112,126] reported baseline PSA in other formats. The remaining 15 studies did not report baseline PSA levels.

At initial biopsy, four studies[75,90,110,118] reported a total of 217 participants with ASAP and five studies[75,79,83,90,110] reported a total of 199 participants with HGPIN. In the study by Destefanis *et al.*,[118] all participants had been diagnosed with ASAP on enrolment.[118] One study[96] included three participants (out of 43 participants analysed) with a history of radiation therapy for PC.

Four studies[75,78,81,106] reported mean prostate size, with the median (range) of means being 53.9 cc (42.5 to 59.3 cc). Three studies[87,90,104] reported median prostate size, with the median (range) of medians being 54.9 cc (41 to 67 cc). Seven studies[79,80,83,126,105,110,111] reported prostate size in other formats. The remaining 37 studies did not report prostate size.

Eight studies[57,76,82,88,91,103,108,113] reported six or fewer cores taken in the previous biopsy scheme. Eleven studies[74,77,80,81,86,93,96,97,105,116,126] reported between 8 and 12 cores taken in the previous biopsy scheme. Eskicorapci *et al.*[83] and Yuen *et al.*[111] reported six or 10 cores, and Yanke *et al.*[110] reported 6 or 12 cores taken in the previous biopsy scheme. Twenty-nine studies[75,78,79,84,87,89,90,92,95,98–102,104,106,107,109,112,115,117,118,120,127,130,133,134,136,137] did not report this information.

Risk of bias of the included studies

All 39 full-text papers were assessed using a modified version of the QUADAS-2 tool containing 14 items. *Figure 4* presents a summary of the results for the risk of bias and concerns for applicability QUADAS-2 domains across the 39 full-text papers. *Appendix 7* presents results of risk of bias and applicability concerns for the individual studies.

The majority of studies were considered to have a low risk of bias for the patient selection (74%, 29/39), index test (100%, 39/39) and flow and timing (92%, 36/39) domains. The 10 studies for which risk of bias for patient selection was unclear did not report exclusion criteria or whether or not the sample was consecutive.[75,77,82,83,88,96,98,102,103,110] Three studies (8%) were considered at high risk of bias for the flow and timing domain; patients did not all receive a reference standard and all patients were not included in the analysis.[57,87,109] In two studies (5%) patients did not all receive the same reference standard.[87,109]

In the reference standard domain, the majority of studies (64%, 25/39) were considered at high risk of bias, although the risk of bias for the remaining 14 (36%) studies was considered unclear. All 25 studies were classed as high risk of bias in this domain owing to having no follow-up included in the reference standard.[57,74–76,78–80,82–84,86,89,90,93,95,96,100,101,104–106,108,109,111,112] Five of these studies[78,83,89,93,101] also involved the reference standard not being interpreted without knowledge of the index test. None of the 14 studies[77,81,87,88,91,92,97–99,102,103,107,110,113] that did include a follow-up in the reference standard reported whether or not the reference standard was interpreted without knowledge of results of the index test. In addition, 13 (33%) studies[77,81,88,91,92,97–99,102,103,107,110,113] did not report whether or not the reference standard was interpreted by an experienced person.

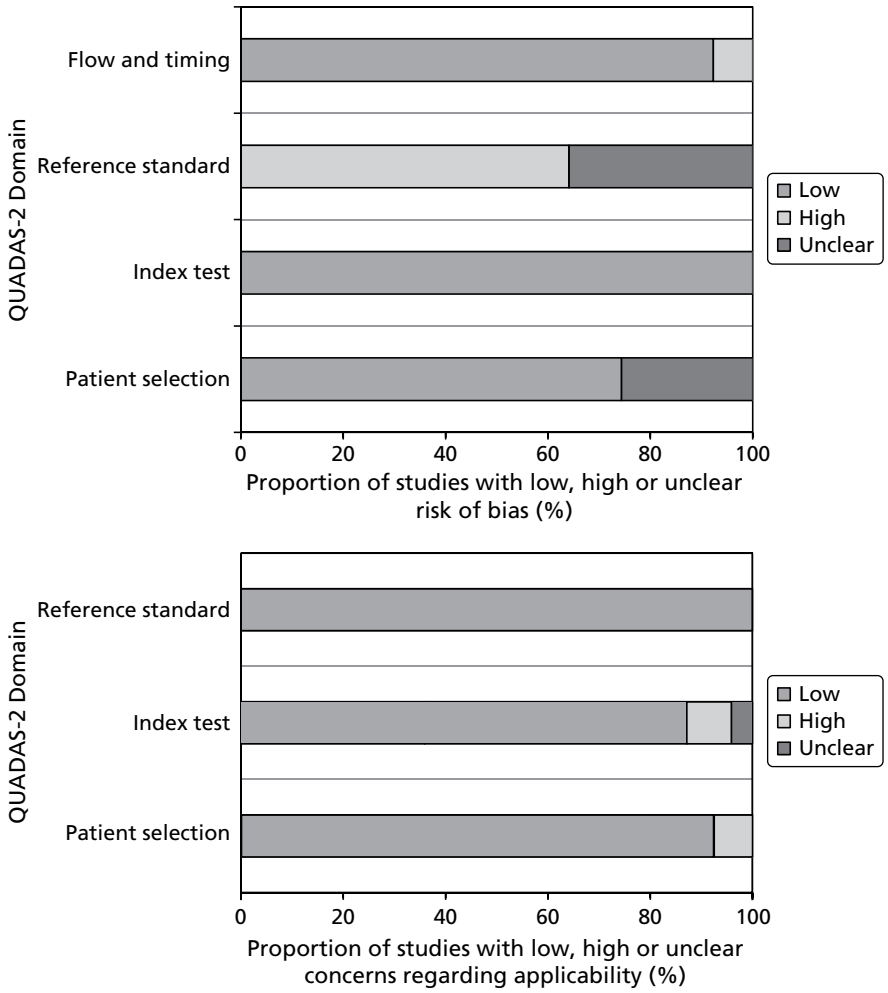


FIGURE 4 Summary of risk of bias and applicability domains.

All 39 studies had low concern for applicability for the reference standard domain and the majority had low concerns for applicability for the patient selection domain (95%, 37/39). The study by Labanaris *et al.*[89] was classed as high concern for applicability for patient selection due to specification of the inclusion criteria as 'one of the following' (p. 66), which may have resulted in some participants having a suspicious DRE but not a raised PSA level.[89] The study by Yanke *et al.*[110] was also classed as high concern in this domain as patient preference was one of the inclusion criteria. Thus, patients with normal PSA levels and DRE may have opted to have a biopsy, albeit all had undergone a previous negative biopsy.[110]

A majority of studies had low concern for applicability for the index test domain (87%, 34/39). One study[76] was classed as unclear in this domain as both normal and equivocal index tests were categorised as negative for malignancy.[76] There was therefore the possibility that some test results classed as equivocal may ultimately have been positive. Four studies[79,100,101,111] for which there was high concern for applicability for the index test did not report findings relating to the entire prostate; three studies[79,100,111] involved the PZ only and one study[101] did not include the central gland.

Results: assessment of diagnostic accuracy

Individual study results are presented in *Appendix 8*.

Magnetic resonance spectroscopy

Patient-level analysis

Ten studies[74,76,79,101,105,106,108,112,115,120] involving 438 patients reported the diagnostic accuracy of MRS and provided sufficient information for inclusion in a meta-analysis. All used a (10- or 12-core) TRUS-guided approach plus additional targeted cores on MRS equivocal or suspicious areas, apart from the study by Wetter *et al.*,[108] which used a MRI-guided approach. Four studies reported the CC/C ratio used as the cut-off for a positive test result, which ranged from >0.6[108] to >0.86.[79]

Across the studies the median (range) prevalence of PC was 34.5% (9.5% to 48.9%). The number of previous biopsy sessions the participants had undergone ranged from one[105] to two to six.[101] Most studies reported that participants had undergone one to three, or one to four, previous biopsy sessions. The number of cores extracted in the previous biopsy session ranged from six[76,108] to (a mean of) 16.[106]

The studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains. All studies were judged to have a high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for the patient selection, index test and reference standard domains, apart from, for the index test domain, Cirillo *et al.*[79] (only PZ assessed) and Prando *et al.*[101] (central gland not assessed).

Figure 5 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 92% (86% to 95%) and 76% (61% to 87%), respectively.

All of the studies reported sensitivity of ≥88% apart from Yuen *et al.*[112] (71%). Yuen *et al.*[112] suggested that contributory factors to the low sensitivity reported might have been (1) difficulties in ensuring the correspondence of TRUS biopsy spatial accuracies to suspicious areas on MRS and (2) that MRS did not cover the entire PZ of the gland. The studies by Prando *et al.*[101] and Testa *et al.*[106] reported low specificity (both 44%). Prando *et al.*[101] reported results either when a voxel score of 4 or 5, or just 5, was used as a cut-off for a positive test result. The results using the cut-off of 4 or 5 were included in the pooled estimates. However, if the results using a cut-off of just 5 had been used this would have increased the specificity to 84% but reduced the sensitivity from 100% to 70.6%. Testa *et al.*[106] suggested that the low specificity in their study was probably determined by the lower CC/C ratio used (actual value not reported) compared with cut-offs used by other studies.

A sensitivity analysis comparing pooled estimates of the results of earlier studies (pre 2007) with those of studies published more recently (2007 onwards) found no significant differences between the two subgroups. The pooled (95% CI) estimates for sensitivity and specificity were pre 2007, 93% (80% to 98%) and 71% (43% to 89%); 2007 onwards, 91% (84% to 95%) and 79% (60% to 90%) (see *Appendix 9*).

Biopsy-level analysis

Six studies[76,79,100,101,106,112] reported the diagnostic accuracy of MRS at biopsy or other non-patient-level analysis and provided sufficient information for inclusion in a meta-analysis. *Figure 6* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The units of analyses reported by the studies included biopsy,[76] site,[79] segment,[100] region[106] and core.[112] The pooled (95% CI) estimates for sensitivity and specificity were 66% (46% to 82%) and 89% (86% to 92%), respectively.

Testa *et al.*[106] also reported region-based analysis separately for the PZ (sensitivity 64.9%, specificity 85.8%) and the TZ (sensitivity 72.2%, specificity 93.2%).

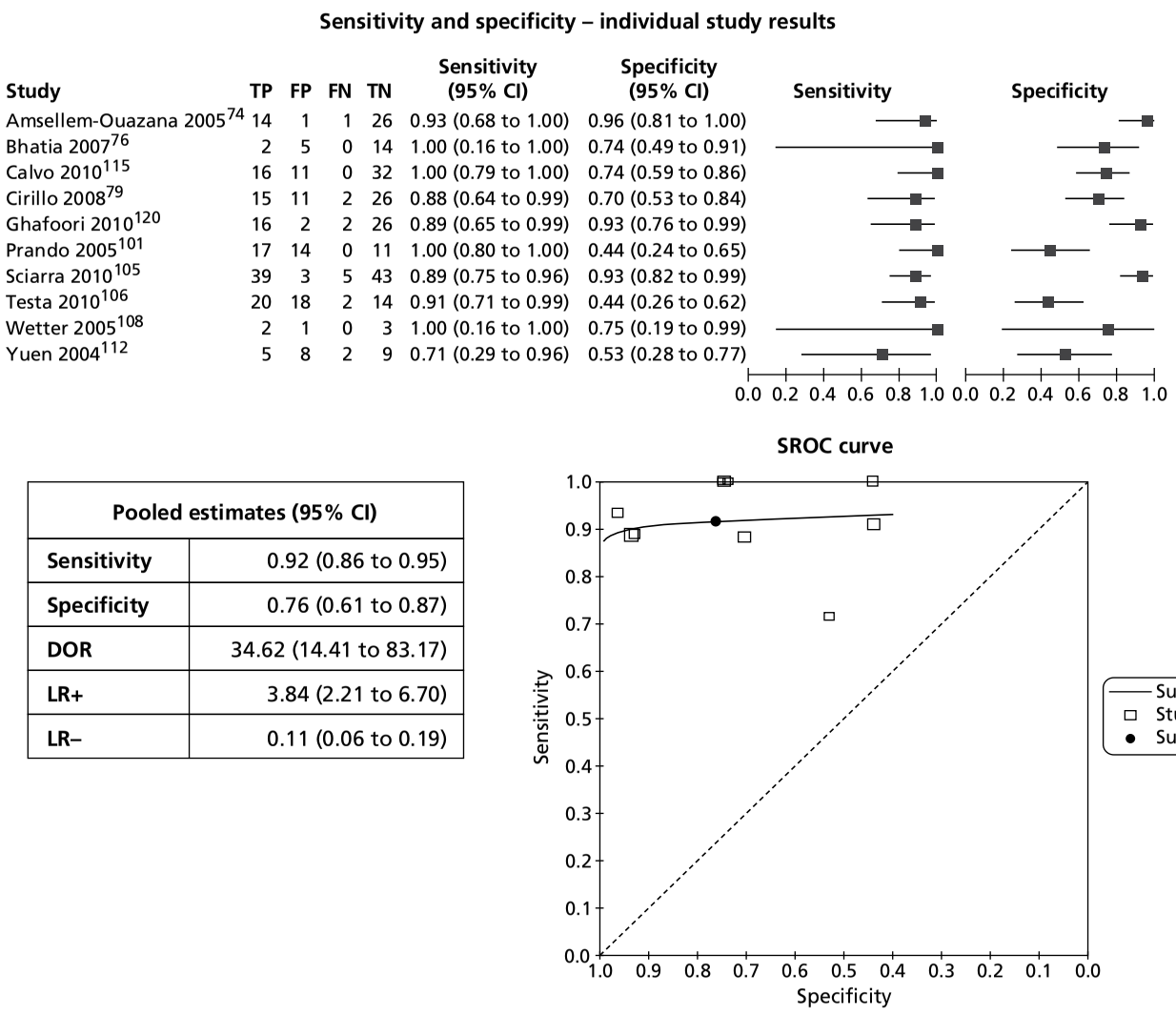
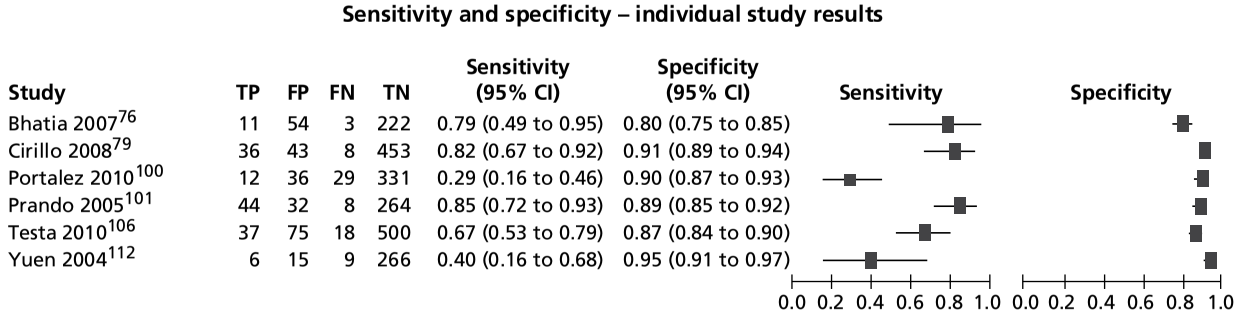


FIGURE 5 Magnetic resonance spectroscopy – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.



Pooled estimates (95% CI)	
Sensitivity	0.66 (0.46 to 0.82)
Specificity	0.89 (0.86 to 0.92)
DOR	16.62 (7.81 to 35.40)
LR+	6.25 (4.57 to 8.55)
LR–	0.38 (0.22 to 0.65)

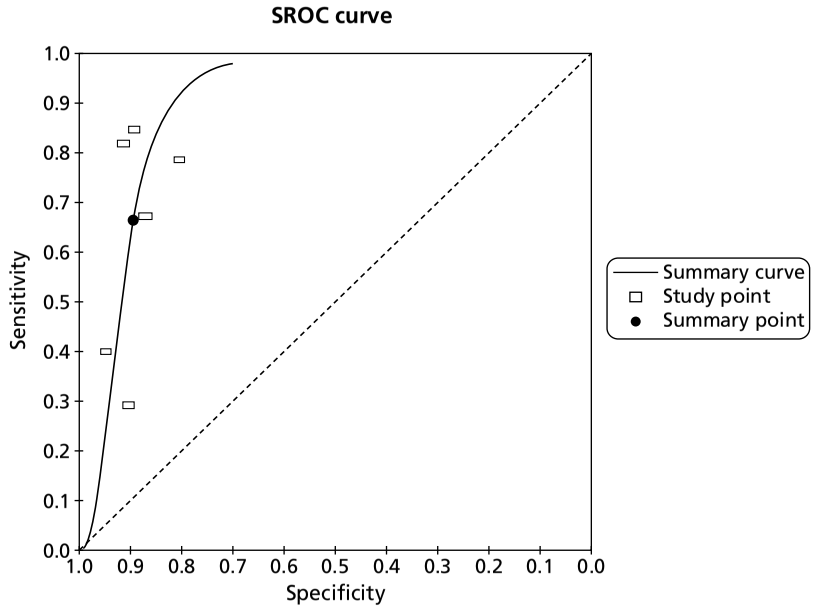


FIGURE 6 Magnetic resonance spectroscopy – biopsy-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

Dynamic contrast-enhanced magnetic resonance imaging

Patient-level analysis

Three studies[78,90,105] involving 209 patients reported the diagnostic accuracy of DCE-MRI and provided sufficient information for inclusion in a meta-analysis. All used a (10-core or at least 12-core) TRUS-guided approach plus additional targeted cores from suspicious areas on the imaging test.

Across the studies the median (range) prevalence of PC was 48.9% (24.7% to 53.8%). The number of previous biopsy sessions the participants had undergone ranged from one[105] to one to twelve.[90] The number of cores extracted in the previous biopsy session was 10,[105] and (a mean of) 12.6,[78] although this information was not reported by Lattouf *et al.*[90] The studies were judged to have low risk of bias and applicability concerns for all domains, apart from the reference standard domain where all three were judged to be at high risk of bias due to a lack of follow-up.

Figure 7 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 79% (69% to 87%) and 52% (14% to 88%), respectively. Compared with the other two studies, the study by Sciarra *et al.*[105] reported high specificity (91%). This study actually reported sensitivity of 84.6% and specificity of 82.3%; however, using the actual 2×2 data presented in the paper led to a calculation of 79.5% for sensitivity and 91.3% for specificity, and these were the data used in the pooled estimates. However, there was no obvious explanation for the large difference in specificity values between this study and the other two studies.

Biopsy-level analysis

Four studies[78,100,105,133] reported the sensitivity and/or specificity of DCE-MRI at biopsy or other non-patient-level analysis (*Table 5*). Across these studies the median (range) sensitivity and specificity was 64.0% (29.3% to 80.0%) and 83.5% (76.7% to 93.5%), respectively.

Diffusion-weighted magnetic resonance imaging

Patient-level analysis

One study, by Park *et al.*,[96] reported a patient-level analysis for DW-MRI. This study, involving 43 patients, employed an MRI-directed, TRUS-guided approach, with at least two cores from suspicious DW areas followed by a 6-, 8- or 10-core biopsy. The study reported a sensitivity of 100% (specificity not reported).

Biopsy-level analysis

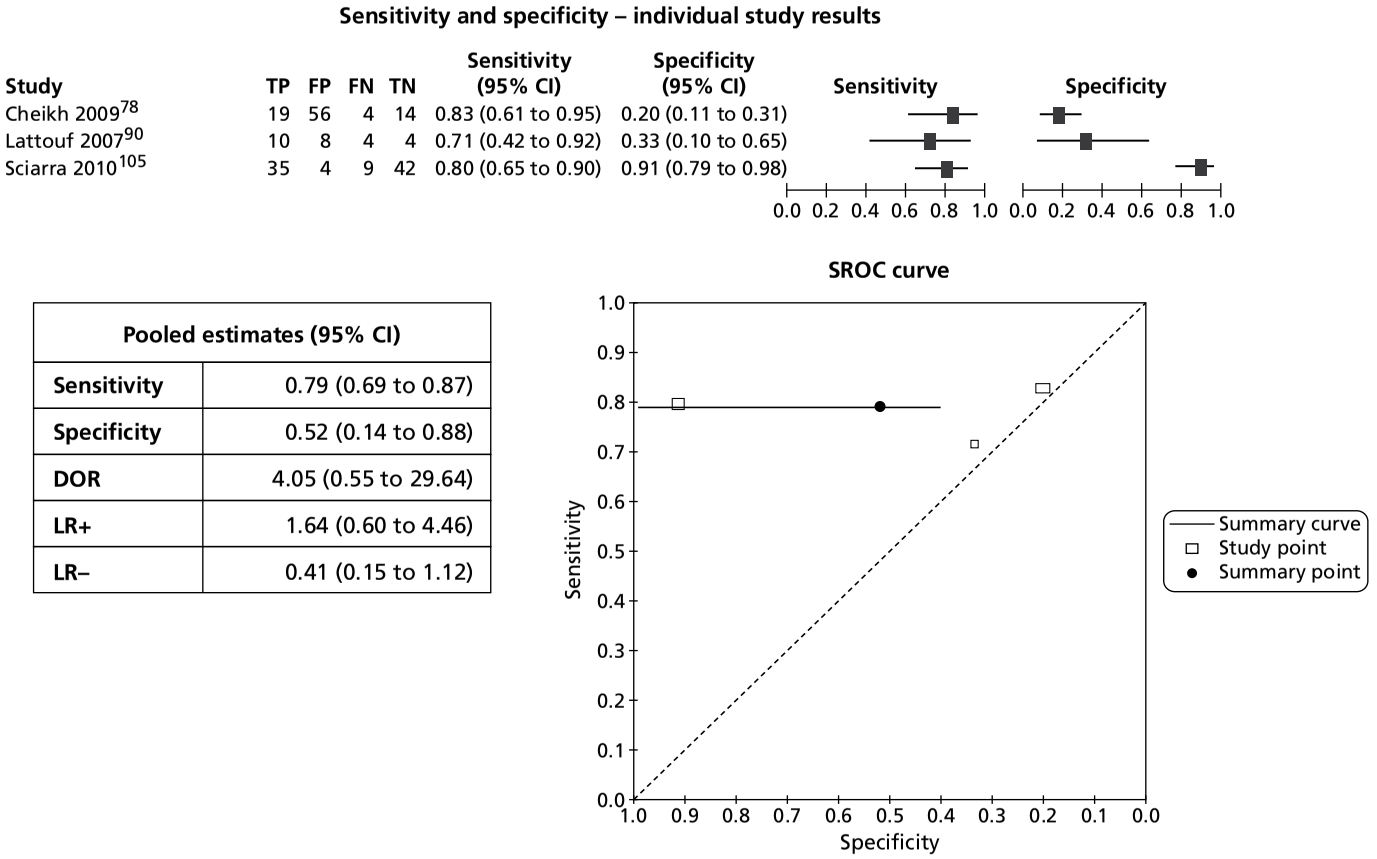
Three studies reported DW-MRI at biopsy or other non-patient-level analysis.[96,100,133] The study by Portalez *et al.*[100] used a 12- to 34-core TRUS-guided approach plus two biopsies of suspicious MRI areas. In a segment level analysis ($n = 408$) they reported a sensitivity of 39.0% and specificity of 96.0%. Valentini *et al.*[133] used a 24-core TRUS/Bx (transperineal) approach plus additional biopsies of suspicious MRI areas. In a biopsy-level analysis (number of biopsies not stated) they reported a sensitivity of 60% (specificity not reported). In the study by Park *et al.*[96] reporting a core level analysis (number of cores not stated), from the information provided it was possible to calculate PPV (78.9%) but not sensitivity or specificity.

T2-weighted magnetic resonance imaging

Patient-level analysis

Fifteen studies[57,74,76,78,79,84,90,101,106,108,112,128,134,136,137] involving 620 patients reported the diagnostic accuracy of T2-MRI and provided sufficient information for inclusion in a meta-analysis. All used a (mostly 10- or 12-core) TRUS-guided approach plus additional targeted cores on T2-MRI equivocal or suspicious areas, apart from the studies by Franiel *et al.*[84] and Wetter *et al.*,[108] which used a MRI-guided approach.

Across the studies the median (range) prevalence of PC was 35.7% (9.5% to 53.8%). The number of previous biopsy sessions the participants had undergone ranged from 1[108] to 1–12.[90] Most studies reported



Pooled estimates (95% CI)	
Sensitivity	0.79 (0.69 to 0.87)
Specificity	0.52 (0.14 to 0.88)
DOR	4.05 (0.55 to 29.64)
LR+	1.64 (0.60 to 4.46)
LR–	0.41 (0.15 to 1.12)

FIGURE 7 Dynamic contrast-enhanced MRI – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

TABLE 5 Dynamic contrast-enhanced MRI: individual study results (biopsy-level analysis)

Study ID	Level of analysis	No. analysed	Sensitivity (%)	Specificity (%)
Cheikh 2009[78]	Sector	670	52.3	83.5
Portalez 2010[100]	Segment	408	29.3	93.5
Sciarra 2010[105]	Core	NR	75.6	76.7
Valentini 2010[133]	Biopsy	NR	80.0	NR

NR, not reported.

that participants had undergone somewhere in the region of between one to six previous biopsy sessions. The number of cores extracted in the previous biopsy session ranged from 4 or 6[57] to (a mean of) 12–14.[112]

The studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains, apart from, for the flow and timing domain, Beyersdorff *et al.*[57] (not all patients were included in the analysis).[57] All studies were judged to have a high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for the patient selection, index test and reference standard domains, apart from, for the index test domain, Bhatia *et al.*[76] (both normal and equivocal results were classed as negative), Cirillo *et al.*[79] (only PZ assessed) and Prando *et al.*[101] (central gland not assessed).

Figure 8 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 86% (74% to 93%) and 55% (44% to 66%), respectively.

Four studies[74,78,108,112] reported sensitivity of 60% or lower. There was no obvious explanation for this in the studies by Amsellem-Ouazana *et al.*[74] or Cheikh *et al.*[78] In the study by Wetter *et al.*[108] only six patients had undergone a previously negative biopsy and this study also extracted biopsies transgluteally.[108] Yuen *et al.*[112] suggested that contributory factors to the low sensitivity reported might have been (1) difficulties in ensuring the correspondence of TRUS biopsy spatial accuracies to suspicious areas on MRS and (2) that MRS did not cover the entire PZ of the gland. Four studies[57,84,90,101] reported specificity of 35% or lower. There was no obvious explanation for this in the studies by Franiel *et al.*[84] and Prando *et al.*[101] Beyersdorff *et al.*[57] reported results either when suspicious and inconclusive, or just suspicious, were used as a cut-off for a positive test. The results using the cut-off of suspicious and inconclusive were included in the pooled estimates. However, if the results using a cut-off of just suspicious had been used this would have increased the specificity to 61.5% but reduced the sensitivity from 100% to 83.3%. The study by Lattouf *et al.*[90] reported sensitivity of 40% and specificity of 69.5%; however, using the actual 2×2 data presented in the paper led to a calculation of 92.9% for sensitivity and 16.7% for specificity, and these were the data used in the pooled estimates.[90]

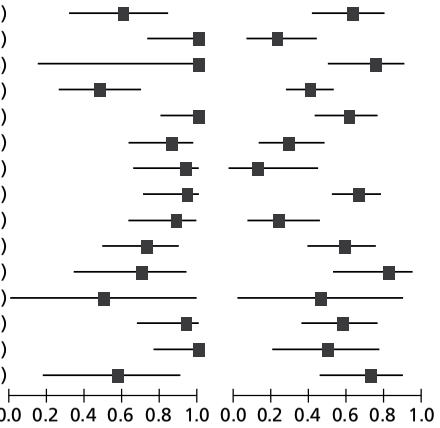
A sensitivity analysis comparing pooled estimates of the results of earlier studies (pre 2007) with those of studies published more recently (2007 onwards) found no significant differences between the two subgroups. The pooled (95% CI) estimates for sensitivity and specificity were pre 2007, 83% (63% to 94%) and 56% (39% to 71%) and 2007 onwards, 88% (72 to 95%) and 55% (41 to 69%) (see *Appendix 10*).

Biopsy-level analysis

Eight studies[57,76,78,79,84,100,106,112] reported the diagnostic accuracy of T2-MRI at biopsy or other non-patient-level analysis and provided sufficient information to be included in a meta-analysis. *Figure 9* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The units of analyses reported by the studies included biopsy,[57,76] sector,[78] site,[79] region,[84,106] segment[100] and core.[112] The

Sensitivity and specificity – individual study results

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Amsellem-Ouazana 2005[74]	9	9	6	18	0.60 (0.32 to 0.84)	0.67 (0.46 to 0.83)
Beyersdorff 2002[57]	12	19	0	7	1.00 (0.74 to 1.00)	0.27 (0.12 to 0.48)
Bhatia 2007[76]	2	4	0	15	1.00 (0.16 to 1.00)	0.79 (0.54 to 0.94)
Cheikh 2009[78]	11	39	12	31	0.48 (0.27 to 0.69)	0.44 (0.32 to 0.57)
Cirillo 2008[79]	17	13	0	24	1.00 (0.80 to 1.00)	0.65 (0.47 to 0.80)
Franiel 2011[84]	18	22	3	11	0.86 (0.64 to 0.97)	0.33 (0.18 to 0.52)
Lattouf 2007[90]	13	10	1	2	0.93 (0.66 to 1.00)	0.17 (0.02 to 0.48)
Perrotti 2002[127]	16	17	1	40	0.94 (0.71 to 1.00)	0.70 (0.57 to 0.82)
Prando 2005[101]	15	18	2	7	0.88 (0.64 to 0.99)	0.28 (0.12 to 0.49)
Testa 2010[106]	16	12	6	20	0.73 (0.50 to 0.89)	0.63 (0.44 to 0.79)
Wefer 2000[134]	7	2	3	12	0.70 (0.35 to 0.93)	0.86 (0.57 to 0.98)
Wetter 2005[108]	1	2	1	2	0.50 (0.01 to 0.99)	0.50 (0.07 to 0.93)
Yao 2009[136]	14	10	1	16	0.93 (0.68 to 1.00)	0.62 (0.41 to 0.80)
Younes 2001[137]	14	6	0	7	1.00 (0.77 to 1.00)	0.54 (0.25 to 0.81)
Yuen 2004[112]	4	4	3	13	0.57 (0.18 to 0.90)	0.76 (0.50 to 0.93)



Pooled estimates (95% CI)	
Sensitivity	0.86 (0.74 to 0.93)
Specificity	0.55 (0.44 to 0.66)
DOR	7.64 (3.37 to 17.30)
LR+	1.93 (1.50 to 2.47)
LR–	0.25 (0.13 to 0.49)

SROC curve

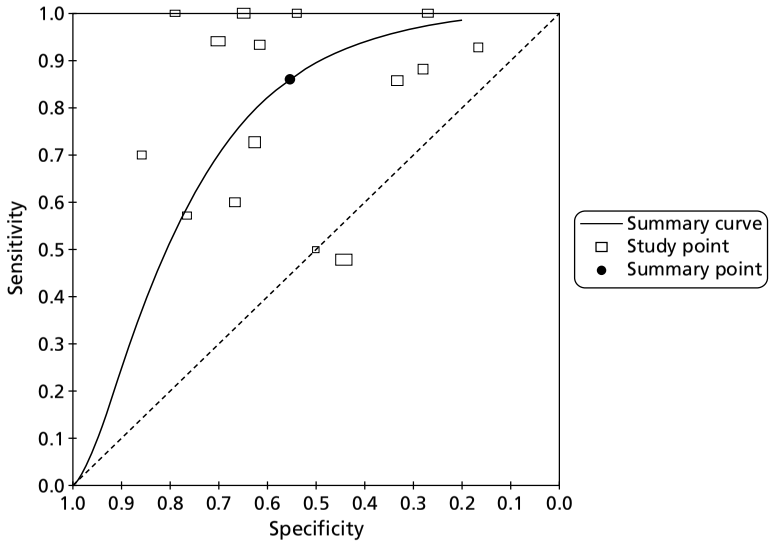
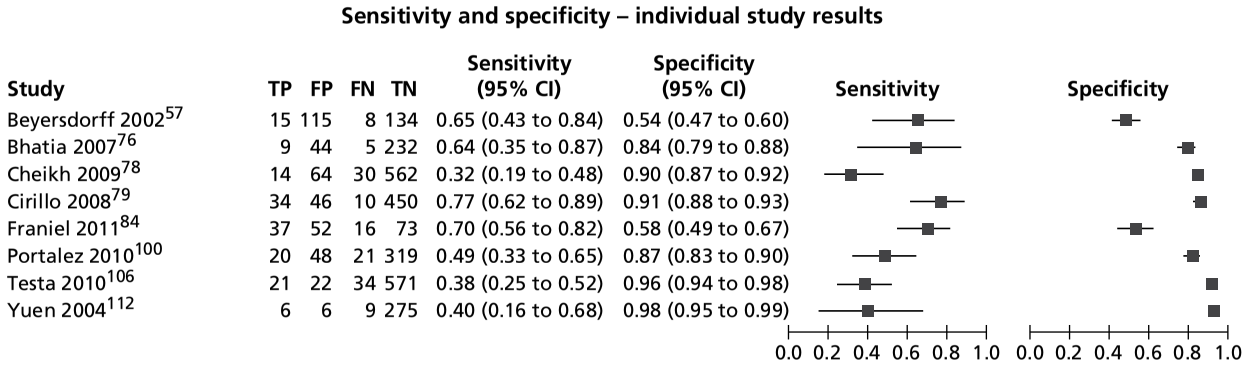


FIGURE 8 T2-weighted magnetic resonance imaging – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.



Pooled estimates (95% CI)	
Sensitivity	0.54 (0.42 to 0.66)
Specificity	0.87 (0.75 to 0.94)
DOR	8.31 (4.25 to 16.25)
LR+	4.33 (2.34 to 8.0)
LR–	0.52 (0.41 to 0.66)

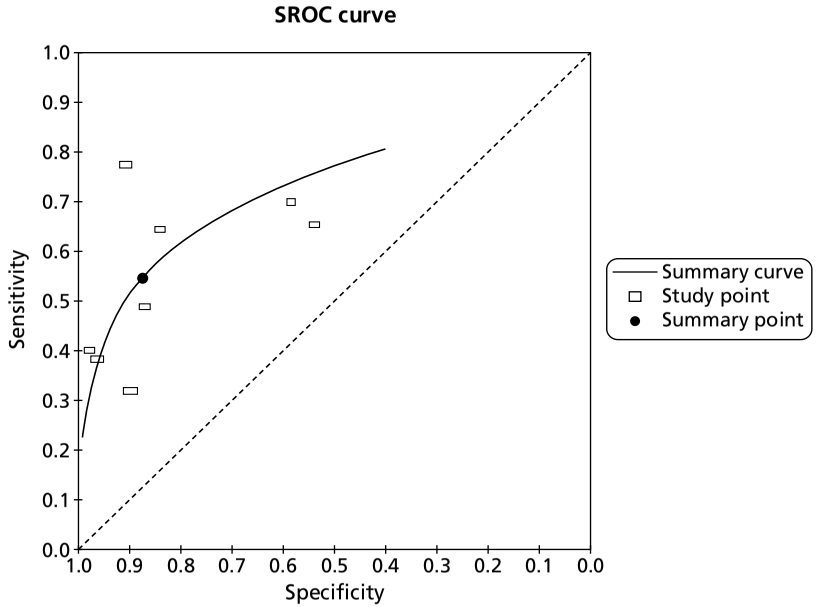


FIGURE 9 T2-weighted magnetic resonance imaging – biopsy-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

pooled (95% CI) estimates for sensitivity and specificity were 54% (42% to 66%) and 87% (75% to 94%), respectively.

Testa *et al.*[106] also reported region-based analysis separately for the PZ (sensitivity 27.0%, specificity 95.8%) and the TZ (sensitivity 61.1%, specificity 98.9%).

Transrectal ultrasonography

Patient-level analysis

Twenty-one studies[57,75,77,80,81,83,88,91–93,96–99,102,103,107,110,111,113,120] involving 8393 patients reported the sensitivity and/or specificity of systematic TRUS-guided biopsies. See *Appendix 11* for the individual study results.

Eleven of these studies[57,75,80,81,83,92,93,96,103,107,111] included the use of TRUS as an imaging test, of which six,[57,75,80,83,93,111] involving 782 patients, provided sufficient information for inclusion in a meta-analysis. The number of cores extracted ranged from 8 or 12[80] to 15.[93]

Across the six studies[57,75,80,83,93,111] the median (range) prevalence of PC was 26.5% (14.4% to 31.6%). The number of previous biopsy sessions the participants had undergone ranged from 1[80,93] to 1–6.[57] The number of cores extracted in the previous biopsy session ranged from 4 or 6[57] to 12.[93]

Most studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains. The study by Babaian *et al.*[75] was judged to be of unclear risk of bias for patient selection (did not report whether or not participant sample was consecutive or provide exclusion criteria) and for the index test (did not report whether or not the test was interpreted by an experienced person). The study by Eskicorapci *et al.*[83] was also judged to be of unclear risk of bias for patient selection (did not report whether or not participant sample was consecutive or provide exclusion criteria). The study by Beyersdorff *et al.*[57] was judged to be at high risk of bias for the flow and timing domain (not all participants received a reference standard and not all were included in the analysis). All studies were judged to have a high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for the patient selection, index test and reference standard domains, apart from, for the index test domain, Yuen *et al.*,[111] which was judged to have high applicability concerns (only PZ assessed).

Figure 10 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 27% (16% to 42%) and 81% (77% to 85%), respectively.

Six large-scale population screening studies enrolling 86,749 participants provided information on the performance of systematic biopsies using a TRUS-guided approach on a subset of their populations who had a previously negative biopsy ($n = 5771$).[81,88,97,99,103,113] The number of cores taken ranged from 4–6[88,103] to 16–21.[97] It was not possible to calculate specificity because the procedure merely extracted cores for histopathological assessment and therefore there were no positive or negative test results as such. It was possible to calculate sensitivity on the basis that, for participants with a first negative biopsy, cores taken during the second biopsy session and assessed histopathologically as positive were considered true-positive. For those patients negative on the second biopsy, cores taken during subsequent biopsy sessions and assessed histopathologically as positive were considered to be false-negative on the second biopsy session, thereby allowing sensitivity to be calculated. Across these studies the median (range) sensitivity was 72.5% (60.6% to 96.3%). In effect these studies provided an indication of the sensitivity of the reference standard, which is influenced by the method by which tissue samples are obtained. Across all of the 10 non-imaging TRUS/Bx studies,[77,88,91,97–99,102,110,113,120] the median (range) sensitivity was 72.5% (59.3% to 96.3%). The number of cores taken ranged from 4–6[88] to 16–21.[97]

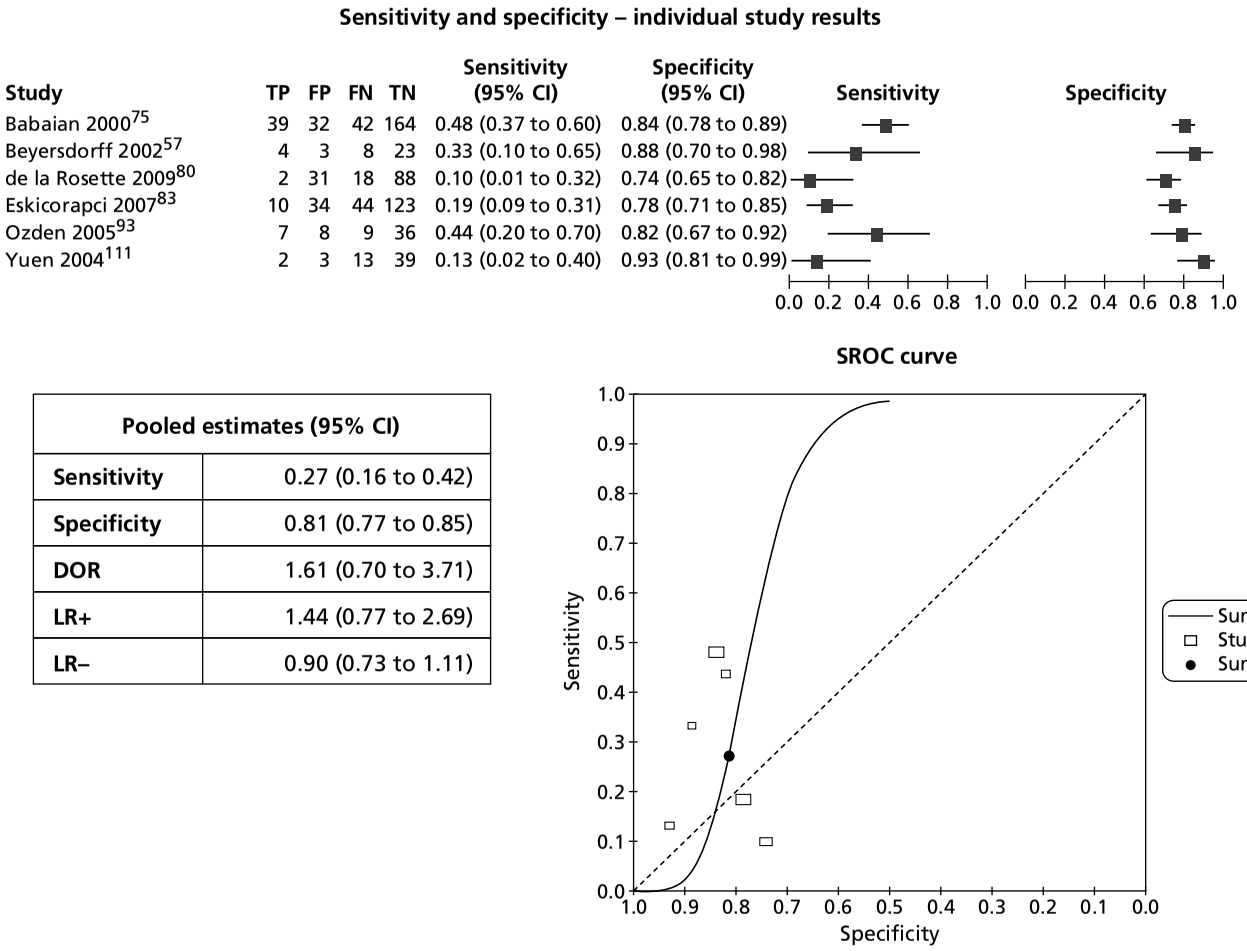


FIGURE 10 Transrectal ultrasonography – patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

Biopsy-level analysis

No studies reported sensitivity or specificity at a biopsy or other non-patient-level analysis. In the study by Lee *et al.*,[126] from the information provided it was possible to calculate PPV (3.5%) but not sensitivity or specificity. This study did not report the number of cores taken per patient but did report the overall number of cores sampled ($n = 903$ from 87 patients, average of 10 cores per patient).

Studies directly comparing tests

Seventeen studies[57,74,76,78,79,84,90,96,100,105,106,108,112,120,133,134,136] directly compared two or more tests (see *Appendix 12* for details of which studies reported which tests).

Magnetic resonance spectroscopy compared with T2-weighted magnetic resonance imaging

Six studies[74,76,79,106,108,112] involving 201 patients reported MRS compared with T2-MRI and provided sufficient information for inclusion in a meta-analysis. All used a (10- or 12-core) TRUS-guided approach plus additional targeted cores on MRS/T2-MRI equivocal or suspicious areas, apart from the study by Wetter *et al.*,[108] which used a MRI-guided approach.[108] Three studies reported the CC/C ratio used as a cut-off for a positive test result for MRS, which ranged from >0.6[108] to >0.86.[79]

Across the studies the median (range) prevalence of PC was 32.4% (9.5% to 40.7%). The number of previous biopsy sessions the participants had undergone ranged from 1[108] to 1–4.[74,106] The number of cores extracted in the previous biopsy session ranged from 6[76,108] to (a mean of) 12–14.[112] The studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains. All studies were judged to be at high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for patient selection, index test and reference standard domains, apart from, for the index test domain, Bhatia *et al.*[76] (unclear concern for applicability: both normal and equivocal test results categorised as negative) and Cirillo *et al.*[79] (high concern for applicability: only PZ assessed).

For the HSROC analysis, we made the assumption that the underlying shape parameter varies with the threshold and accuracy parameters. This is because using the original assumption of a common underlying shape made our models unstable. We provide the results of a sensitivity analysis with the original assumption in *Appendix 13*.

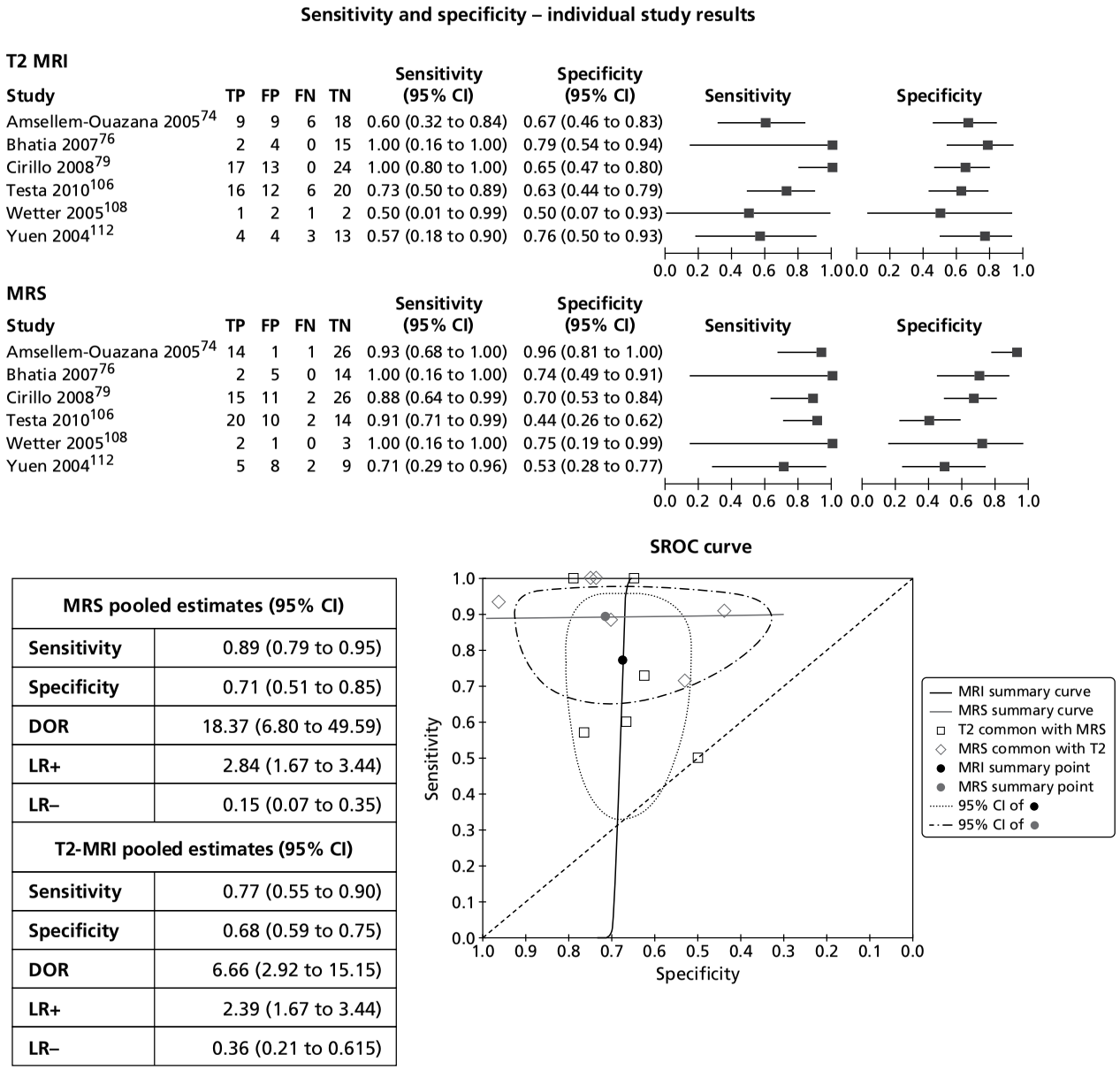
Figure 11 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC plot with 95% confidence region. The pooled (95% CI) estimates for sensitivity and specificity were 89% (79% to 95%) and 71% (51% to 85%) for MRS, and 77% (55% to 90%) and 68% (59% to 75%) for T2-MRI.

Magnetic resonance spectroscopy compared with dynamic contrast-enhanced magnetic resonance imaging

Two studies[100,105] involving 158 patients reported MRS compared with DCE-MRI (*Table 6*). Portalez *et al.*[100] reported segment-level but not patient-level analysis, whereas Sciarra *et al.*[105] reported both patient- and core-level analysis.[105] In the study by Portalez *et al.*[100] the sensitivity of the tests was similar but low, whereas specificity was also similar but high. In the study by Sciarra *et al.*[105] MRS had higher sensitivity

TABLE 6 Studies comparing MRS with DCE-MRI

			MRS		DCE	
Study ID	Unit of analysis	No. analysed	Sensitivity	Specificity	Sensitivity	Specificity
Portalez 2010[100]	Segment	408	29.3	90.2	29.3	93.5
Sciarra 2010[105]	Patient	90	88.6	93.5	79.5	91.3
	Core	NR	83.3	72.7	75.6	76.7



MRS pooled estimates (95% CI)	
Sensitivity	0.89 (0.79 to 0.95)
Specificity	0.71 (0.51 to 0.85)
DOR	18.37 (6.80 to 49.59)
LR+	2.84 (1.67 to 3.44)
LR–	0.15 (0.07 to 0.35)
T2-MRI pooled estimates (95% CI)	
Sensitivity	0.77 (0.55 to 0.90)
Specificity	0.68 (0.59 to 0.75)
DOR	6.66 (2.92 to 15.15)
LR+	2.39 (1.67 to 3.44)
LR–	0.36 (0.21 to 0.615)

FIGURE 11 Magnetic resonance spectroscopy compared with T2-MRI patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

than DCE-MRI at both patient- and core-level analysis, with broadly similar specificity, which was higher for patient-level analysis compared with core-level analysis. With regard to the low sensitivity reported by Portalez *et al.*,[100] the authors stated that in order to visualise the early phase of cancer enhancement and retain spatial resolution, they resorted to the shortest possible time with their MRI unit, which proved to yield adequate specificity but suboptimal sensitivity.[100]

Dynamic contrast-enhanced magnetic resonance imaging compared with T2-weighted magnetic resonance imaging

Three studies[78,90,100] involving 187 patients compared DCE-MRI with T2-MRI (*Table 7*). In the two studies reporting patient-level analysis,[78,90] DCE-MRI had higher sensitivity and lower specificity than T2-MRI in one, with lower sensitivity and higher specificity in the other. Cheikh *et al.*[78] reported low specificity for DCE-MRI, whereas Lattouf *et al.*[90] reported low specificity for both DCE-MRI and T2-MRI. The test combination 'DCE-MRI or T2-MRI' resulted in similar or increased sensitivity compared with the individual tests but reduced specificity, whereas the combination 'DCE-MRI and T2-MRI' reduced sensitivity with a moderate increase in specificity. In the two studies reporting non-patient-level analysis, DCE-MRI had higher sensitivity and slightly lower specificity than T2-MRI in one and lower sensitivity and slightly higher specificity in the other.

Dynamic contrast-enhanced magnetic resonance imaging compared with diffusion-weighted magnetic resonance imaging

Two studies[100,133] involving 79 patients compared DCE-MRI with DW-MRI (*Table 8*). Both reported non-patient-level analysis. DCE-MRI had higher sensitivity than DW-MRI in one study[133] and lower sensitivity[100] in the other, whereas the sensitivity reported for both DCE-MRI and DW-MRI was much higher in the study by Valentini *et al.*[133] than it was in the study by Portalez *et al.*[100] Portalez *et al.*[100] reported similarly high specificity for both tests.

Studies reporting combinations of tests

The following combinations of tests were reported:

- MRS or T2-MRI (eight studies)
- MRS and T2-MRI (five studies)
- MRS or DCE-MRI (two studies)
- MRS and DCE-MRI (one study)
- MRS or DCE-MRI or T2-MRI (one study)
- MRS or DW-MRI or T2-MRI (one study)
- MRS or DCE-MRI or DW-MRI or T2-MRI (one study)
- DCE-MRI or T2-MRI (three studies)
- DCE-MRI and T2-MRI (two studies)
- DCE-MRI or DW-MRI (one study)
- DCE-MRI or DW-MRI or T2-MRI (four studies)
- DCE-MRI and DW-MRI and T2-MRI (one study)
- DW-MRI or T2-MRI (three studies).

No studies reported MRS combined with DW-MRI.

In combinations linked by 'or' only one of the tests has to be positive for the result of the combination to be considered positive, while in combinations linked by 'and' all tests in the combination have to be positive before the result for the combination is considered positive. Combinations linked by 'or' generally result in higher sensitivity and lower specificity compared with the individual tests while the reverse is the case for combinations linked by 'and'.

TABLE 7 Studies comparing DCE-MRI with T2-MRI

			DCE-MRI		T2-MRI		DCE or T2		DCE and T2	
Study ID	Unit of analysis	No. analysed	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Cheikh 2009[78]	Patient	93	82.6	20.0	47.8	44.3	82.6	15.7	47.8	51.4
	Sector	670	52.3	83.5	31.8	89.8	52.3	83.1	31.8	92.3
Lattouf 2007[90]	Patient	26	71.4	33.3	92.9	16.7	100.0	16.7	64.3	33.3
Portalez 2010[100]	Segment	408	29.3	93.5	48.8	87.0	NR	NR	NR	NR

NR, not reported.

TABLE 8 Studies comparing DCE-MRI with DW-MRI

			DCE-MRI		DW-MRI	
Study ID	Unit of analysis	No. analysed	Sensitivity	Specificity	Sensitivity	Specificity
Portalez 2010[100]	Segment	408	29.3	93.5	39.0	96.0
Valentini 2010[133]	Biopsy	NR	80.0	NR	60.0	NR

NR, not reported.

Magnetic resonance spectroscopy or T2-weighted magnetic resonance imaging

Patient-level analysis

Eight studies[74,79,84,106,108,112,118,130] involving 316 patients reported the diagnostic accuracy of MRS or T2-MRI and provided sufficient information for inclusion in a meta-analysis. All used a (mostly 10- or 12-core) TRUS-guided approach plus additional targeted cores on MRS/T2-MRI equivocal or suspicious areas, apart from Franiel *et al.*[84] and Wetter *et al.*,[108] who used a MRI-guided approach. In the study by Destefanis *et al.*[118] all participants ($n = 26$) had ASAP. Four studies reported the CC/C ratio used as the cut-off for a positive test result, which ranged from >0.6[108] to >0.86.[79,118]

Across the studies the median (range) prevalence was 35.2% (29.2% to 40.7%). The number of previous biopsy sessions the participants had undergone ranged from 1[108,118] to 1–6.[84] The number of cores extracted in the previous biopsy session ranged from 6[108] to (a mean of) 16.[106]

The studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains. All studies were judged to be at high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for the patient selection, index test and reference standard domains, apart from, for the index test domain, Cirillo *et al.*[79] (only PZ assessed).

Figure 12 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 96% (90% to 98%) and 31% (21% to 42%), respectively.

Biopsy-level analysis

Three studies[79,84,106] reported MRS or T2-MRI and provided sufficient information for inclusion in a meta-analysis. The units of analyses reported by the studies included site[79] and region.[84,106] *Figure 13* shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 79% (71% to 86%) and 74% (45% to 90%), respectively. Testa *et al.*[106] also reported region-based analysis separately for the peripheral and TZs. For the PZ (540 regions analysed), sensitivity was 70.3% and specificity 83.3%, whereas for the TZ (108 regions analysed) sensitivity was 72.2% and specificity 92.2%.

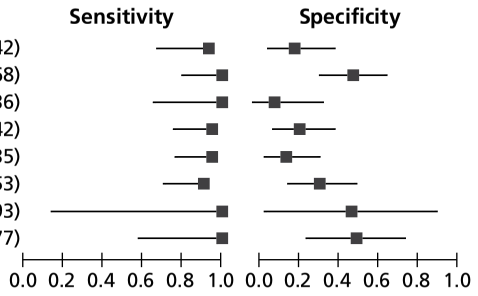
Magnetic resonance spectroscopy and T2-weighted magnetic resonance imaging

Patient-level analysis

Five studies[76,106,108,112,134] involving 129 patients reported the diagnostic accuracy of MRS and T2-MRI and provided sufficient information for inclusion in a meta-analysis. All used a (mostly 10- or 12-core) TRUS-guided approach plus additional targeted cores on MRS/T2-MRI equivocal or suspicious areas, apart from Wetter *et al.*,[108] which used a MRI-guided approach and extracted cores transgluteally. None of the studies reported the CC/C ratio value used as the cut-off for a positive test result.

Sensitivity and specificity – individual study results

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Amsellem-Ouazana 2005[74]	14	21	1	6	0.93 (0.68 to 1.00)	0.22 (0.09 to 0.42)
Cirillo 2008[79]	17	18	0	19	1.00 (0.80 to 1.00)	0.51 (0.34 to 0.68)
Destefanis 2009[118]	9	15	0	2	1.00 (0.66 to 1.00)	0.12 (0.01 to 0.36)
Franiel 2011[84]	20	25	1	8	0.95 (0.76 to 1.00)	0.24 (0.11 to 0.42)
Rahman 2003[130]	21	28	1	6	0.95 (0.77 to 1.00)	0.18 (0.07 to 0.35)
Testa 2010[106]	20	21	2	11	0.91 (0.71 to 0.99)	0.34 (0.19 to 0.53)
Wetter 2005[108]	2	2	0	2	1.00 (0.16 to 1.00)	0.50 (0.07 to 0.93)
Yuen 2004[112]	7	8	0	9	1.00 (0.59 to 1.00)	0.53 (0.28 to 0.77)



Pooled estimates (95% CI)	
Sensitivity	0.96 (0.90 to 0.98)
Specificity	0.31 (0.21 to 0.42)
DOR	10.19 (3.17 to 32.81)
LR+	1.38 (1.18 to 1.63)
LR–	0.14 (0.04 to 0.39)

SROC curve

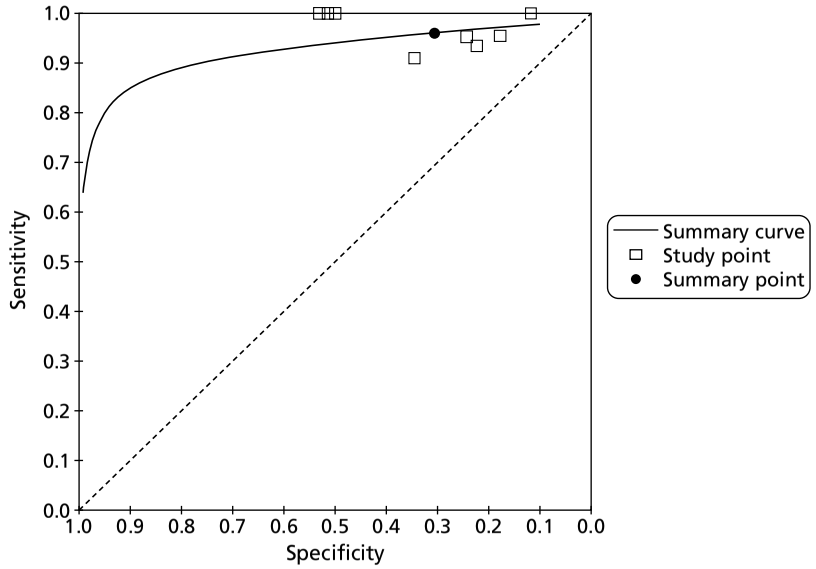
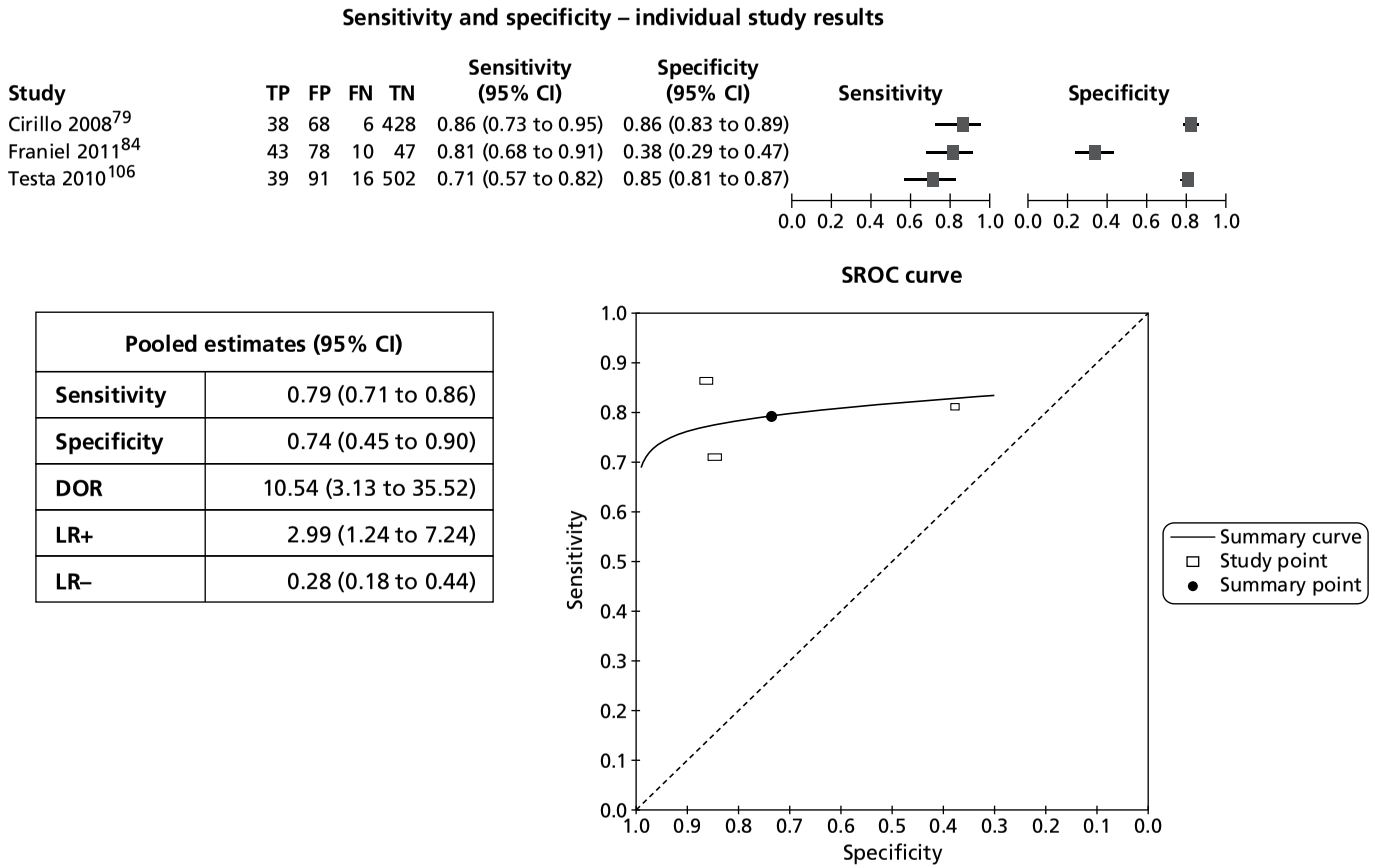


FIGURE 12 Magnetic resonance spectroscopy or T2-MRI patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.



Pooled estimates (95% CI)	
Sensitivity	0.79 (0.71 to 0.86)
Specificity	0.74 (0.45 to 0.90)
DOR	10.54 (3.13 to 35.52)
LR+	2.99 (1.24 to 7.24)
LR–	0.28 (0.18 to 0.44)

FIGURE 13 Magnetic resonance spectroscopy or T2-MRI biopsy-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

Across the studies the median (range) prevalence was 33.3% (9.5% to 41.7%). The number of previous biopsy sessions the participants had undergone ranged from 1[108] to 1–4.[106] The number of cores extracted in the previous biopsy session ranged from 6[76,108] to (a mean of) 16.[106]

The studies were judged to have low risk of bias for the patient selection, index test and flow of timing domains. All studies were judged to be at high risk of bias for the reference standard domain owing to a lack of follow-up. All studies were judged to have low applicability concerns for the patient selection, index test and reference standard domains, apart from, for the index test domain, Bhatia *et al.*[76] (normal and equivocal tests were categorised as negative for malignancy).

Figure 14 shows the sensitivity and specificity of the individual studies and pooled estimates (this analysis required to be undertaken without random effect parameters as otherwise the model would not converge and consequently it was not possible to produce a ROC curve). The pooled (95% CI) estimates for sensitivity and specificity were 60% (46% to 75%) and 74% (65% to 84%), respectively.

Biopsy-level analysis

Two studies reported the diagnostic accuracy of MRS and T2-MRI at biopsy or other non-patient-level analysis.[76,106] In a biopsy-level analysis ($n = 290$), Bhatia *et al.*[76] reported sensitivity of 64.3% and specificity of 91.7%, whereas in a region-based analysis ($n = 648$) Testa *et al.*[106] reported sensitivity of 34.5% and specificity of 98.8%, as well as region-based analysis separately for the PZ and TZ.[106] For the PZ (540 regions analysed), sensitivity was 21.6% and specificity 98.6%, whereas for the TZ (108 regions analysed) sensitivity was 61.1% and specificity 100%.

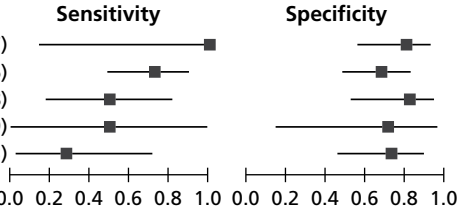
Magnetic resonance spectroscopy or dynamic contrast-enhanced magnetic resonance imaging

Patient-level analysis

Two studies involving 131 patients reported MRS or DCE-MRI.[95,105] Panebianco *et al.*[95] reported sensitivity of 92.9% and specificity of 86.6%, whereas Sciarra *et al.*[105] reported sensitivity of 93.2% and specificity of 91.3%. No studies reported biopsy-level analysis.

Sensitivity and specificity – individual study results

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bhatia 2007[76]	2	3	0	16	1.00 (0.16 to 1.00)	0.84 (0.60 to 0.97)
Testa 2010[106]	16	9	6	23	0.73 (0.50 to 0.89)	0.72 (0.53 to 0.86)
Wefer 2000[134]	5	2	5	12	0.50 (0.19 to 0.81)	0.86 (0.57 to 0.98)
Wetter 2005[108]	1	1	1	3	0.50 (0.01 to 0.99)	0.75 (0.19 to 0.99)
Yuen 2004[112]	2	4	5	13	0.29 (0.04 to 0.71)	0.76 (0.50 to 0.93)



Pooled estimates (95% CI)	
Sensitivity	0.60 (0.46 to 0.75)
Specificity	0.74 (0.65 to 0.84)
DOR	4.45 (0.97 to 7.92)
LR+	2.36 (1.34 to 3.39)
LR–	0.53 (0.32 to 0.74)

FIGURE 14 Magnetic resonance spectroscopy and T2-MRI patient-level analysis: sensitivity, specificity and pooled estimates.

Magnetic resonance spectroscopy and dynamic contrast-enhanced magnetic resonance imaging

Patient-level analysis

One study, by Sciarra *et al.*[105] involving 90 patients reported sensitivity of 75% and specificity of 93.5% for MRS and DCE-MRI.

Biopsy-level analysis

Sciarra *et al.*[105] reported sensitivity of 89.7% and specificity of 80.4% for core-level analysis.

Other combinations involving magnetic resonance spectroscopy

Franiel *et al.*[84] reported other combinations of tests involving MRS, both at patient-level ($n = 54$) and region-level ($n = 178$) analysis (*Table 9*).

In the study by Roethke *et al.*[104] reporting MRS or T2-MRI or DCE-MRI or DW-MRI ($n = 100$), from the information provided it was possible to calculate PPV (52%), but not sensitivity or specificity.

Dynamic contrast-enhanced magnetic resonance imaging or T2-weighted magnetic resonance imaging

Patient-level analysis

Three studies[78,84,90] involving 173 patients reported the diagnostic accuracy of DCE-MRI or T2-MRI and provided sufficient information for inclusion in a meta-analysis. The studies by Cheikh *et al.*[78] and Lattouf *et al.*[90] used a 12-core TRUS-guided approach plus additional targeted cores from suspicious areas on the imaging tests.[78,90] The study by Franiel *et al.* used a MRI-guided approach.[84]

Across the studies the median (range) prevalence of PC was 38.9% (24.7% to 53.8%). The number of previous biopsy sessions the participants had undergone ranged from 1–5[78] to 1–12.[90] Only Cheikh *et al.*[78] reported the number of cores extracted in the previous biopsy session (mean of 12.6). The studies were judged to have low risk of bias and applicability concerns for all domains apart from the reference standard domain, for which all three were judged to be at high risk of bias owing to a lack of follow-up.

Figure 15 shows the sensitivity and specificity of the individual studies, pooled estimates and SROC curve. The pooled (95% CI) estimates for sensitivity and specificity were 88% (80% to 96%) and 14% (8% to 20%), respectively.

Biopsy-level analysis

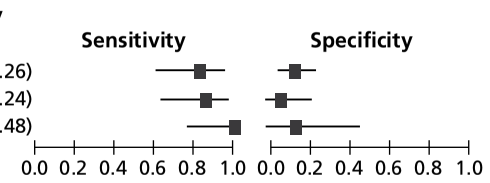
Two studies[78,84] reported DCE-MRI or T2-MRI. Cheikh *et al.*,[78] in a sector-based analysis ($n = 670$), reported sensitivity of 52.3% and specificity of 83.1%, whereas Franiel *et al.*,[84] in a region-based analysis ($n = 178$), reported sensitivity of 83.0% and specificity of 33.6%.

TABLE 9 Other combinations of tests involving MRS

		Patient-level analysis		Region-level analysis	
Study ID	Test combination	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Franiel 2011[84]	MRS or DCE or T2-MRI	95.2	9.1	90.6	14.4
	MRS or DW or T2-MRI	100.0	3.0	94.3	19.2
	MRS or DCE or DW or T2-MRI	100.0	0.0	100.0	0.0

Sensitivity and specificity – individual study results

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cheikh 2009[78]	19	59	4	11	0.83 (0.61 to 0.95)	0.16 (0.08 to 0.26)
Franiel 2011[84]	18	30	3	3	0.86 (0.64 to 0.97)	0.09 (0.02 to 0.24)
Lattouf 2007[90]	14	10	0	2	1.00 (0.77 to 1.00)	0.17 (0.02 to 0.48)



Pooled estimates (95% CI)	
Sensitivity	0.88 (0.80 to 0.96)
Specificity	0.14 (0.08 to 0.20)
DOR	1.18 (0.06 to 2.30)
LR+	1.02 (0.90 to 1.14)
LR–	0.87 (0.15 to 1.59)

SROC curve

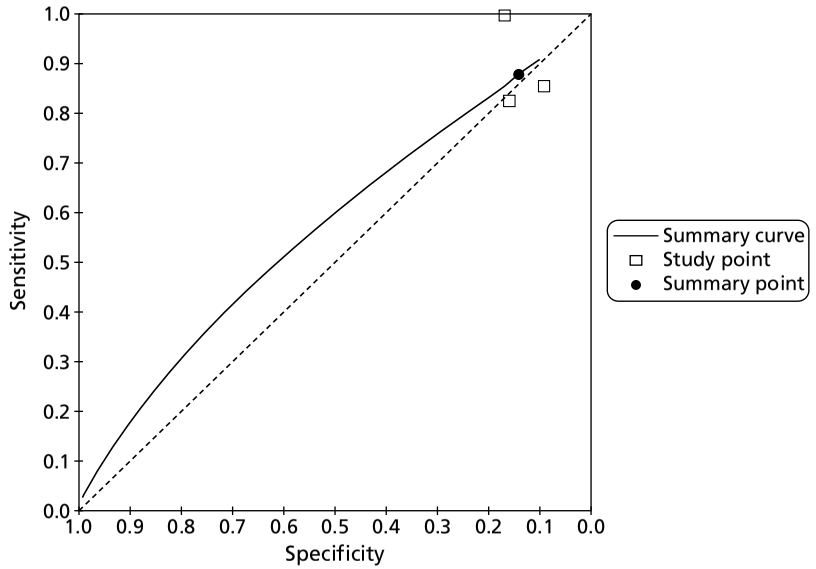


FIGURE 15 Dynamic contrast-enhanced MRI or T2-MRI patient-level analysis: sensitivity, specificity, pooled estimates and SROC curve.

Dynamic contrast-enhanced magnetic resonance imaging and T2-weighted magnetic resonance imaging

Patient-level analysis

Two studies[78,90] involving 119 patients reported the diagnostic accuracy of DCE-MRI and T2-MRI; Cheikh *et al.*[78] reported sensitivity of 47.8% and specificity of 51.4%, whereas Lattouf *et al.*[90] reported sensitivity of 64.3% and specificity of 33.3%.

Biopsy-level analysis

One study, by Cheikh *et al.*,[78] in a sector-based analysis ($n = 670$), reported sensitivity of 31.8% and specificity of 92.3%.[78]

Dynamic contrast-enhanced magnetic resonance imaging or diffusion-weighted magnetic resonance imaging

Biopsy-level analysis

No study reported a patient-level analysis of DCE-MRI combined with DW-MRI. Valentini *et al.*,[133] in a study involving 11 patients, reported a biopsy-level analysis (number of biopsies not reported) for DCE-MRI or DW-MRI. This study used a TRUS-guided approach (24 cores plus additional biopsies of suspicious MRI areas). From the information provided in the study it was possible to calculate PPV (17.2%) but not sensitivity or specificity.

Dynamic contrast-enhanced magnetic resonance imaging or diffusion-weighted magnetic resonance imaging or T2-weighted magnetic resonance imaging

Patient-level analysis

Four studies[84,86,87,109] involving 395 patients reported DCE-MRI or DW-MRI or T2-MRI. Franiel *et al.*[84] reported sensitivity of 100% and specificity of 0%. However, from the information provided in the other three studies[86,87,109] it was possible to calculate PPV (100%,[86] 40.9%,[87] 55.6%[109]) but not sensitivity or specificity.

Biopsy-level analysis

Three studies[84,87,109] reported DCE-MRI or DW-MRI or T2-MRI at a region-level analysis. However, only the study by Franiel *et al.*[84] reported sensitivity (94.3%) and specificity (16.0%). From the information provided in the other two studies[87,109] it was possible to calculate PPV (33.4%,[87] 46.2%[109]) but not sensitivity or specificity.

Dynamic contrast-enhanced magnetic resonance imaging and diffusion-weighted magnetic resonance imaging and T2-weighted magnetic resonance imaging

Patient-level analysis

One study, by Labanaris *et al.*[89] involving 260 patients reported sensitivity of 88.1% and specificity of 62.4% for DCE-MRI and DW-MRI and T2-MRI. No studies reported biopsy-level analysis.

Diffusion-weighted magnetic resonance imaging or T2-weighted magnetic resonance imaging

Patient-level analysis

Two studies[84,126] involving 141 patients reported DW-MRI or T2-MRI at a patient-level analysis. The study by Franiel *et al.*[84] used a MRI-guided approach. Franiel *et al.*[84] reported sensitivity of 100% and specificity of 3.0%, whereas Lee *et al.*[126] reported sensitivity of 95.7% and specificity of 7.3%.

Biopsy-level analysis

Three studies[84,116,126] reported DW-MRI or T2-MRI at a biopsy or other non-patient-level analysis. Chung *et al.*[116] reported sensitivity of 82.8% and specificity of 68.9%, whereas Franiel *et al.*[84] reported sensitivity of 84.9% and specificity of 36.8%. From the information provided in the study by Lee *et al.*[54] it was possible to calculate PPV (12.7%) but not sensitivity or specificity.[126]

Indirect comparison

Table 10 shows the results of the indirect comparison (see also *Appendix 13*).

Patient-level analysis

For the patient-level estimates of tests with three or more studies, comparing T2-MRI against all the other tests showed statistically significant differences ($p < 0.001$). Compared with DCE-MRI, T2-MRI was observed to have lower sensitivity and significantly higher specificity. Sensitivity (95% CI) for DCE-MRI was 87% (74% to 94%) compared with 83% (75% to 89%) for T2-MRI ($p = 0.499$). Specificity (95% CI) for DCE was 40% (25% to 56%) compared with 57% (47% to 67%) for T2-MRI ($p = 0.041$).

Magnetic resonance spectroscopy was observed to have higher sensitivity and specificity than T2-MRI. Sensitivity for MRS was 93% (87% to 97%) compared with 83% (75% to 89%) for T2-MRI ($p = 0.008$). Specificity for MRS was 64% (52% to 75%) compared with 57% (47% to 67%) for T2-MRI ($p = 0.194$).

When T2-MRI was used in combination with MRS ('T2-MRI and MRS', both tests had to be suspicious for the combination to be considered positive) T2-MRI used alone was observed to have higher sensitivity but significantly lower specificity. Sensitivity for 'T2-MRI and MRS' was 71% (50% to 85%) compared with 83% (75% to 89%) for T2-MRI ($p = 0.172$). Specificity for 'T2-MRI and MRS' was 73% (58% to 85%) compared with 57% (47% to 67%) for T2-MRI ($p = 0.011$).

TABLE 10 Results of the indirect comparison (patient-level analysis)

		95% CI			
Parameter	Estimate	Lower	Upper	Ratio (95% CI)	*p*-value
Sensitivity for T2-MRI	83	75	89	1	
Sensitivity for DCE	87	74	94	1.04 (0.93 to 1.17)	0.499
Sensitivity for MRS	93	87	97	1.12 (1.03 to 1.22)	0.008
Sensitivity for T2-MRI and MRS	71	50	85	0.85 (0.67 to 1.07)	0.172
Sensitivity for T2-MRI or DCE	92	81	97	1.10 (1.00 to 1.21)	0.046
Sensitivity for T2-MRI or MRS	97	91	99	1.16 (1.07 to 1.26)	0.001
Sensitivity for TRUS	24	13	39	0.28 (0.16 to 0.50)	<0.001
Specificity for T2-MRI	57	47	67	1	
Specificity for DCE	40	25	56	0.70 (0.49 to 0.98)	0.041
Specificity for MRS	64	52	75	1.12 (0.95 to 1.32)	0.194
Specificity for T2-MRI and MRS	73	58	85	1.28 (1.06 to 1.55)	0.011
Specificity for T2-MRI or DCE	24	13	39	0.42 (0.26 to 0.68)	<0.001
Specificity for T2-MRI or MRS	34	23	46	0.59 (0.44 to 0.78)	<0.001
Specificity for TRUS	88	79	94	1.54 (1.27 to 1.86)	<0.001

DCE, dynamic contrast enhanced.

When T2-MRI was used in combination with DCE-MRI ('T2-MRI or DCE-MRI', if either test is suspicious the combination is considered positive), T2-MRI used alone was observed to have lower sensitivity but significantly higher specificity. Sensitivity for 'T2-MRI or DCE-MRI' was 92% (81% to 97%) compared with 83% (75% to 89%) for T2-MRI ($p = 0.046$). Specificity for 'T2-MRI or DCE-MRI' was 24% (13% to 39%) compared with 57% (47% to 67%) for T2-MRI ($p < 0.001$).

When T2-MRI was used in combination with MRS ('T2-MRI or MRS', if either test is suspicious the combination is considered positive), this combination had significantly higher sensitivity than T2-MRI alone but significantly lower specificity. Sensitivity for 'T2-MRI or MRS' was 97% (91% to 99%) compared with 83% (75% to 89%) for T2-MRI ($p = 0.001$). Specificity for 'T2-MRI or MRS' was 34% (23% to 46%) compared with 57% (47% to 67%) for T2-MRI ($p < 0.001$).

Compared with TRUS used as an imaging test, T2-MRI was observed to have significantly higher sensitivity but significantly lower specificity. Sensitivity for TRUS was 24% (13% to 39%) compared with 83% (75% to 89%) for T2-MRI ($p < 0.001$). Specificity for TRUS was 88% (79% to 94%) compared with 57% (47% to 67%) for T2-MRI ($p < 0.001$).

These differences are based on between-study comparisons, so may have been due to differences between the studies rather than true differences between the tests.

For the estimates comparing T2-MRI with other tests, in terms of relative sensitivity, the direction of effect favoured (1) MRS; (2) 'T2-MRI or DCE'; and (3) 'T2-MRI or MRS' over T2-MRI, while favouring T2-MRI over (1) DCE-MRI; (2) 'T2-MRI and MRS'; and (3) TRUS, although the only results that were statistically significant were for 'T2-MRI or MRS' compared with T2-MRI ('T2-MRI or MRS' better) and T2-MRI compared with TRUS (T2-MRI better). See *Appendix 13.1* for further details.

In terms of relative specificity the direction of effect favoured (1) MRS; (2) 'T2-MRI and MRS'; and (3) TRUS over T2-MRI, while favouring T2-MRI over (1) DCE-MRI; (2) 'T2-MRI or DCE-MRI'; and (3) 'T2-MRI or MRS', although the only results that were statistically significant were for 'T2-MRI and MRS' compared with T2-MRI ('T2-MRI and MRS' better), T2-MRI compared with TRUS (TRUS better), 'T2-MRI or DCE-MRI' compared with T2-MRI (T2-MRI better) and 'T2-MRI or MRS' compared with T2-MRI (T2-MRI better). See *Appendix 13.1* for further details.

Biopsy-level analysis

The highest sensitivity (95% CI) was for the combination 'T2-MRI or MRS' at 75% (61% to 86%), whereas the highest specificity was for T2-MRI at 87% (78% to 93%), with MRS also reporting a similarly high specificity at 84% (72% to 91%). See *Appendix 13.2* for further details.

For the estimates comparing T2-MRI with other tests, in terms of relative sensitivity both (1) MRS and (2) 'T2-MRI or MRS' had statistically significantly higher sensitivity than T2-MRI, whereas for specificity the direction of effect favoured T2-MRI over both (1) MRS and (2) 'T2-MRI or MRS', although only the comparison with 'T2-MRI or MRS' was statistically significant. See *Appendix 13.2* for further details.

False-positive results

Eleven studies[57,74,76,78,79,101,106,108,109,133,137] provided further information on the MR-imaging false-positive results in their studies (see *Appendix 14* for individual study details). The false-positive rate for patient-level analysis (six studies[74,76,79,101,108,137]) ranged from 2.4%[74] to 100%[108] and for biopsy or other non-patient-level analysis (five studies[57,78,106,109,133]) ranged from 13.0%[106] to 46.2%.[57] High-grade PIN and prostatitis accounted for a substantial proportion of the false-positive results.[109] Cirillo *et al.*[79] presented this information separately for MRS and T2-MRI. For MRS (11 false-positives), there was PIN in six (54.5%), fibrosis in four (36.4%) and normal prostatic tissue in one (9.1%); for T2-MRI (13 false-positives), there was PIN in three (23.0%), fibrosis in five (38.5%) and normal prostatic tissue in five (38.5%).[79] Beyersdorff

et al.[57] concluded that the T2-MRI technique used in their study did not enable reliable differentiation of PC from prostatitis, fibrosis or PIN.

Detection of clinically significant disease

Twenty-nine studies[74,76,78–80,82,84,86,87,90,91,95,96,104–106,108,109,111,112,136] reported the Gleason score based on the biopsy results of patients diagnosed with PC (see *Appendix 15* for individual study details). Most studies reported a median Gleason score of ≥6. The percentage of patients diagnosed with PC who had a Gleason score of ≥7 ranged from 20.3%[86] to 66.7%.[109] In 13 studies[74,80,81,83,87,91,96–98,102,111,113,136] it was not possible to calculate this information.

Six MRI studies reported a median Gleason score of >6 (*Table 11*). In these studies the percentage of patients diagnosed with PC who had a Gleason score of ≥7 ranged from 50.0%[90,108] to 66.7%.[109]

Results: assessment of non-diagnostic outcomes

Altered treatment as a result of the tests

No studies reported information on altered treatment as a result of the tests.

Acceptability of the tests

No studies provided information on the acceptability of the tests used.

Interpretability of the tests

Three studies[78,101,106] reported the interpretability of the tests used. Cheikh *et al.*,[78] in a study using T2-MRI and DCE-MRI, reported that in 1 (1.1%) of 93 patients analysed, DCE images could not be interpreted because of inadequate quality due to artefacts induced by a hip prosthesis. This patient was 1 of 23 diagnosed with cancer.

In a study that employed T2-MRI and MRS, Prando *et al.*[101] stated that suitable spectroscopic voxels were rated as optimal, fair or poor on the basis of spectral quality (*Table 12*).[101] They reported that, out of 42 patients analysed, the quality of spectral data was rated as optimal in 23 (55%), fair in 10 (24%) and poor in 9 (21%).

Testa *et al.*,[106] in a study using T2-MRI and MRS, reported that 4 (7%) of 58 patients were excluded because more than one-third of the prostate was not included in the MRI volume of interest, or more than

TABLE 11 Studies reporting a median Gleason score of > 6

Study ID	Test(s)	No. analysed	No. with PC	Prevalence (%)	Median (range) Gleason score	Percentage with Gleason score ≥ 7
Amsellem-Ouazana 2005[74]	T2-MRI/MRS	42	15	35.7	6.6 (5 to 9)	NR
Lattouf 2007[90]	T2-MRI/DCE	26	14	53.8	6.5 (5 to 9)	50.0
Park 2008[96]	DW-MRI	43	17	39.5	7 (6 to 9)	NR
Roethke 2012[104]	T2-MRI/MRS/DCE-MRI/DW-MRI	100	52	52.0	7 (5 to 9)	59.7
Wetter 2005[108]	T2-MRI/MRS	6	2	33.3	(6, 7)	50.0
Yakar 2011[109]	T2-MRI/DCE-MRI/DW-MRI	9	5	55.6	7 (6 to 8)	66.7

NR, not reported.

TABLE 12 Voxel rating system used by Prando *et al.*[101]

Spectral quality	Definition
Optimal	Signal–noise ratio of all metabolites >10, all metabolic resonances well resolved, no baseline distortions due to residual water or lipids
Fair	Signal–noise ratio of all metabolites 8–10, all metabolic resonances reasonably well resolved, or minimal baseline distortions owing to residual water or lipids
Poor	Lower signal–noise ratios and substantial lipid contamination

one-third of spectroscopic voxels were not interpretable owing to lipid contamination or presented low spectral resolution. Out of the remaining 54 patients included in the analysis, in 18 (3%) of 648 regions MRS imaging was not interpretable (corresponding to six patients) and these regions were excluded from the analysis. None of these 18 regions was in the TZ.[106]

Effect of testing on quality of life

No studies reported the effects of the tests on QoL.

Adverse effects of testing

Ten studies[57,76,81,82,86,87,89,109,111,112] reported adverse events, all of which appeared to be related to TRUS-guided biopsies, with one of the most frequently reported adverse events being transient haematuria (see *Appendix 16* for individual study details). Of the other more serious adverse events reported, Beyersdorff *et al.*[57] reported that two patients (5%) experienced haemorrhage in the prostate; Djavan *et al.*[81] reported that 1.4% experienced moderate to severe vasovagal episodes, 0.5% experienced severe haematuria and 0.1% major rectal bleeding (numbers of patients not reported); Hoeks *et al.*[87] reported that one patient (0.4%) experienced sepsis with hospitalisation and four (1.5%) experienced a vasovagal reaction; Labanaris *et al.*[89] reported that 190 patients (73%) experienced macroscopic haematuria; Yuen *et al.*[111] reported that three patients (1.4%) experienced macroscopic haematuria, five (2.3%) experienced fever and five (2.3%) experienced acute retention of urine (all 13 treated conservatively as inpatient), while one patient (0.5%) experienced rectal bleeding, requiring admission to hospital. None of the studies provided information on injuries resulting from multiple biopsies over time. Neither did any study report the extremely rare adverse event of biopsy leading to disease seeding along needle tracks.

Summary

Sixty-five reports of 51 studies met the inclusion criteria (39 full text, 12 abstracts). The majority of studies were considered to have a low risk of bias for the patient selection (74%, 29/39), index test (100%, 39/39) and flow and timing (92%, 36/39) domains. In the reference standard domain, the majority of studies (64%, 25/39) were considered at high risk of bias due to a lack of follow-up. All 39 studies had low concern for applicability for the reference standard domain and the majority also had low concerns for applicability for the patient selection (95%, 37/39) and index test (87%, 34/39) domains.

The sensitivity and specificity of the tests (patient-level analysis) are summarised in *Table 13* (results of the meta-analyses for the individual tests, combinations of tests and for those studies directly comparing MRS with T2-MRI), *Table 14* (results for the tests and combinations of tests for which it was not considered appropriate or feasible to include in a meta-analysis) and *Table 15* (pooled estimates for the individual tests and combinations of tests included in the indirect comparison).

In the meta-analyses for the individual tests, sensitivity was highest for MRS (92%), followed by T2-MRI (86%) and DCE-MRI (79%), whereas specificity was highest for TRUS (used as an imaging test) (81%), followed by MRS (76%). TRUS used as an imaging test had poor sensitivity (27%). In the pooled estimates for combinations of tests, sensitivity was highest for 'MRS or T2-MRI' (96%) followed by 'DCE-MRI or

TABLE 13 Summary of meta-analysis results (patient-level analysis)

Test(s)	No. of studies	No. of participants	Sensitivity: pooled estimate, % (95% CI)	Specificity: pooled estimate, % (95% CI)
Individual tests				
MRS	10	438	92 (86 to 95)	76 (61 to 87)
DCE-MRI	3	209	79 (69 to 87)	52 (14 to 88)
T2-MRI	15	620	86 (74 to 93)	55 (44 to 66)
TRUS (imaging test)	6	782	27 (16 to 42)	81 (77 to 85)
Combinations of tests				
MRS or T2-MRI	8	316	96 (90 to 98)	31 (21 to 42)
MRS and T2-MRI	5	129	60 (46 to 75)	74 (65 to 84)
DCE-MRI or T2-MRI	3	173	88 (80 to 96)	14 (8 to 20)
Studies directly comparing MRS with T2-MRI				
MRS	6	201	89 (79 to 95)	71 (51 to 85)
T2-MRI			77 (55 to 90)	68 (59 to 75)

TABLE 14 Descriptive summary of results for tests/combinations not included in meta-analysis (patient-level analysis)

Test(s)	No. of studies	No. of participants	Sensitivity (%)	Specificity (%)
DW-MRI	1	43	100	NR
MRS or DCE	2	131	93, 93	87, 91
MRS and DCE	1	90	75	94
MRS or DCE-MRI or T2-MRI	1	54	95	9
MRS or DW-MRI or T2-MRI	1	54	100	3
MRS or DCE-MRI or DW-MRI or T2-MRI	1	54	100	0
DCE-MRI and T2-MRI	2	119	48, 64	51, 33
DCE-MRI or DW-MRI or T2-MRI	1	54	100	0
DCE-MRI and DW-MRI and T2-MRI	1	260	88	62
DW-MRI or T2-MRI	2	141	96, 100	7, 3

TABLE 15 Indirect comparison (patient-level analysis)

Test(s)	Sensitivity: pooled estimate, % (95% CI)	Specificity: pooled estimate, % (95% CI)
MRS	93 (87 to 97)	64 (52 to 75)
DCE-MRI	87 (74 to 94)	40 (25 to 56)
T2-MRI	83 (75 to 89)	57 (47 to 67)
MRS or T2-MRI	97 (91 to 99)	34 (23 to 46)
MRS and T2-MRI	71 (50 to 85)	73 (58 to 85)
DCE-MRI or T2-MRI	92 (81 to 97)	24 (13 to 39)
TRUS (imaging test)	24 (13 to 39)	88 (79 to 94)

T2-MRI' (88%), whereas specificity was highest for 'MRS and T2-MRI' (74%). The gain in sensitivity from MRS as a single test (92%) to the combination 'MRS or T2-MRI' (96%) was offset by a large decrease in specificity from 76% to 31%.

In the meta-analysis of the six studies[74,76,79,106,108,112] directly comparing MRS with T2-MRI, sensitivity and specificity for MRS was 89% and 71%, respectively, compared with 77% and 68% for T2-MRI.

Only one small study[96] involving 43 patients reported DW-MRI, with sensitivity of 100% (specificity not reported). A number of other combinations of tests were reported, mostly by single studies.

The results of the indirect comparison broadly reflected those of the meta-analyses of the individual tests and combinations of tests. In the indirect comparison, the highest sensitivity reported was for the combination of 'MRS or T2-MRI' (97%), followed by MRS (93%) and 'DCE-MRI or T2-MRI' (92%). TRUS as an imaging test had poor sensitivity (24%). However, TRUS had the highest specificity (88%), followed by the combination of 'MRS and T2-MRI' (73%) and MRS (64%).

Six large-scale population screening studies[81,88,97,99,103,113] provided information on the performance of systematic biopsies using a (non-imaging) TRUS-guided approach on a subset of their patient populations with a previous negative biopsy ($n = 5771$). Across these studies the median (range) sensitivity was 72.5% (60.6% to 96.3%). Across all of the 10 non-imaging TRUS/Bx studies,[77,88,91,97–99,102,110,113,120] the median (range) sensitivity was 72.5% (59.3% to 96.3%).

Eleven studies[57,74,76,78,79,101,106,108,109,133,137] provided information on the MR-imaging false-positive results, with the false-positive rate for patient-level analysis (six studies[74,76,79,101,108,137]) ranging from 2.4% to 100%. High-grade PIN and prostatitis accounted for a substantial proportion of the false-positive results. Twenty-nine studies[74,76,78–84,86,87,90,91,95–98,102–106,108–113,136] reported the Gleason score based on the biopsy results of patients diagnosed with PC, with most reporting a median Gleason score of ≥6. The percentage of patients diagnosed with PC that had a Gleason score of ≥7 ranged from 20.3% to 66.7%. Ten studies[57,76,81,82,86,87,89,109,111,112] reported adverse events related to TRUS-guided biopsies, with one of the most frequently reported adverse events being transient haematuria.

Chapter 5 Assessment of cost-effectiveness

The purpose of this chapter is to assess the cost-effectiveness of utilising different MRI sequences to direct prostate biopsy following a previous negative biopsy.

The specific economic objectives are to estimate:

- the costs of standard practice (i.e. repeated TRUS/Bx) and the alternative, directed biopsies in the form of T2-MRI, MRS, DCE-MRI and DW-MRI techniques in the diagnosis of prostate abnormalities
- the cost-effectiveness of T2-MRI, MRS, DCE-MRI and DW-MRI in comparison with standard practice in men with suspected PC.

Structured review of cost-effectiveness studies

Although a systematic literature review of cost-effectiveness studies was not included as part of the protocol for this study, a systematic search was undertaken to locate studies considering the cost-effectiveness of MRS and enhanced MRI techniques for aiding the localisation of prostate abnormalities for biopsy. A broader search for health-state utility data and existing economic modelling studies in the area of PC, to inform subsequent cost-effectiveness modelling, was conducted simultaneously. Databases searched included the NHS Economic Evaluation Database (NHS EED) (November 2011), the IDEAS Economics and Finance Research database (November 2011), MEDLINE, the NHS Economic Evaluation Database (NHS EED), and the Cost-effectiveness Analysis Registry (CEA Registry) (specifically for health utilities). Details of the full search strategies used are given in *Appendix 2*.

Efforts were made to identify papers reporting full economic evaluations on the use of MRS/MRI techniques to direct/guide prostate biopsies. A total of 1315 titles and abstracts were screened for possible relevance but only one non-English-language paper was found comparing both the costs and consequences of alternatives of interest. From review of the available English-language abstract of the latter paper, this study used modelling techniques to assess the cost-effectiveness of using MRI (type not specified) to determine and direct prostate biopsies compared with the standard practice of systematic TRUS/Bx for all patients.[138] The authors reported their results in terms of a hypothetical cohort of 100,000 patients, and concluded that although the use of MRI could prevent the need for 64,000 unnecessary biopsies, it would result in increased costs to the health insurer for only a small increase in quality-adjusted life-years (QALYs). They concluded that their estimates did not permit a clear recommendation for or against the use of MRI in the diagnosis of PC. The abstract also stated that the use of MRI was being evaluated in the context of patients undergoing their first biopsy, so the results are not directly applicable to the decision problem being addressed in this report.

Independent economic assessment

Based on consideration of existing economic modelling studies and trial-based evidence, a de novo economic model was developed to assess the cost-effectiveness of using alternative MRS/MRI sequences to direct TRUS-guided biopsies, compared with the standard practice of relying on systematic TRUS-guided biopsies (in patients with a previous negative biopsy). The alternative diagnostic pathways were embedded in a Markov model simulating the progression of undiagnosed cancer and the downstream impact of diagnosis and treatment on survival and health-related QoL.

After considering a number of existing economic models of treatment and screening strategies for PC,[9,139–145] we chose to adopt a Markov cohort approach similar to that used in a model developed to

inform NICE clinical guidance on prostatectomy for localised cancer.[9] However, we included a greater number of states so as to capture the risk stratified natural history of localised PC, associated treatment effects, and treatment complications. Costs incorporated in the model included the costs associated with obtaining the final diagnosis (cancer/no cancer), management of biopsy complications, cancer staging, cancer treatment, and the management of complications resulting from cancer treatment.

Survival benefits of diagnosis were captured through the application of relative risk parameters reflecting the effects of appropriately targeted radical treatment by stage of underlying cancer. It was assumed that via a risk targeted approach, the observed benefits of radical treatment over observation could be achieved for diagnosed cohorts without the need to treat all patients immediately. Limited, high-quality randomised evidence was identified for the effect of radical treatment compared with observation in men with localised PC. A recently updated Cochrane review on prostatectomy compared with watchful waiting[146] identified only two randomised trials for inclusion: the VACURG trial,[147] which was judged to be of poor quality, and the SPCG-4 trial,[148] which was judged to be of good quality. The SPCG-4 trial,[148] carried out in Sweden, provides up to 15 years' follow-up on 695 men with localised PC randomised to either radical prostatectomy ($n = 347$) or watchful waiting ($n = 348$). It recruited patients prior to the widespread introduction of PSA screening, and, as such, uncertainty exists regarding its applicability to men with localised disease identified through PSA screening. However, as systematic PSA screening is not policy in the UK, and as no more contemporary randomised data on the effect of radical prostatectomy compared with watchful waiting were available at time of model development, we based our modelled progression risks and relative treatment effects (post diagnosis) on this trial. Late in our study period, the PIVOT trial[149] published preliminary results on the effect of radical prostatectomy compared with watchful waiting in men with localised disease identified through PSA screening.[149] As such, we also performed a sensitivity analysis with the model recalibrated to the progression rates and treatment effects observed in this more recent study.

Health-state utilities associated with cancer stage and the occurrence of treatment complications were incorporated in the model to estimate QALYs. Experimental strategies were compared incrementally with standard practice in terms of their incremental cost per life-year (LY) and QALY gained. For each cost per QALY analysis, the strategy with the highest net monetary benefit (NMB) was identified using the formula: $NMB = (E \times r^c) - C$, where NMB is the net monetary benefit of a strategy, E is the mean effect (in terms of QALYs), r^c represents decision-makers' maximum willingness to pay for a QALY, and C is the mean cost of the strategy. A value of £30,000 was applied for r^c.

Methods

Relevant patient population

The modelled cohorts consisted of men with suspected PC with a prior negative/inconclusive biopsy, with indications for repeat biopsy (i.e. sustained suspicion of PC as a result of clinical and/or pathological findings).[40] We carried out several analyses applying cancer prevalence rates consistent with those observed in the literature for different subgroups defined by factors that influence disease prevalence at repeat biopsy. The base-case analysis was carried out using a prevalence of 24%, which is consistent with cancer detection rate (with 24-core saturation biopsy) reported for a cohort of patients with a previous benign biopsy result but persistently elevated PSA (>4 ng/ml) and/or abnormal DRE.[38] Further analyses were carried out, with the prevalence of underlying cancer set at a higher level consistent with that reported for patients with ASAP or percentage free to total PSA level of <10% (i.e. 50%). Further, we also set the cancer prevalence at the lower level of 10% to represent a lower risk cohort selected for repeat biopsy.

Analyses were conducted separately for men aged 60 years and men aged 70 years at time of repeat biopsy, as age influences the cost-effectiveness of diagnosing and treating PC. It was assumed that a PC diagnosis would not be aggressively pursued in men aged 75 years and over. Men with cancer were initially spread across the undiagnosed cancer states in the model (*Table 16*), based on the reported Gleason scores of tumours detected during the studies included in the systematic review, and other

available data on the clinical and/or pathological stages/grades of cancers detected at second biopsy.[2,37,38] Although the frequency of higher grade cancer may increase with age and underlying prevalence, data limitations precluded adjustment of the proportions by selection criteria for repeat biopsy. As such, results of subgroup analyses (by age and prevalence) should be treated with caution. If a higher proportion of older men have more advanced or higher risk tumours, this would serve to improve the cost-effectiveness of more sensitive strategies in comparison with the base-case estimates we provide for 70-year-old men.

Diagnostic strategies to be evaluated

The experimental strategies chosen for evaluation were selected based on the availability of data from the systematic review of diagnostic accuracy (*Table 17*). It was not possible to obtain comparable pooled sensitivity/specificity estimates for all sequences of clinical interest. Further, the majority of studies included in the diagnostic accuracy review assessed the accuracy of MRI sequences for directing TRUS-guided biopsies, rather than for directly guiding the biopsy. Thus, the economic analysis focused on evaluating the use of MRS/MRI in this context, i.e. using it to identify areas of the prostate for targeting in a subsequent TRUS/Bx. As the patient-level sensitivities obtained from the diagnostic accuracy meta-analysis reflect detection rates achieved when both targeted cores and a number of systematic cores (8 to 12) are taken from patients with positive findings on MRS/MRI, we modelled targeted biopsies to proceed in this same manner in the economic model. Insufficient data were available to ascertain how patient-level sensitivity would be affected if only targeted cores were obtained from patients positive on imaging. As a consequence, we assumed that MRI/imaging prior to biopsy would not alter the cost of the biopsy procedure in the base-case analysis. We also assumed that patients with no visible pathology on MRS/MRI would not proceed to biopsy. The model was specified to simulate the use of MRS/MRI in the index repeat

TABLE 16 Cohort information

Parameter	Proportion (ranges across studies)	Sources (references)
Cancer prevalence	0.24 (0.10 to 0.50)	Stewart 2001,[2] Campos-Fernandez 2009,[37] Scattoni 2011[38] (assumptions)
Localised disease	0.878 (0.767 to 0.938)	Stewart 2001,[2] Campos-Fernandez 2009,[37] Scattoni 2011[38] (assumptions)
Risk status of localised disease		
Low	0.540 (0.330 to 1.000)	Bhatia 2007,[76] Cheikh 2009,[78] Cirrillo 2008,[79] Engelhard 2006,[82] Franiel 2011,[84] Hambrock 2008,[85] Lattouf 2007,[90] Testa 2010,[106] Wetter 2005,[108] Yakar 2011,[109] Yuen 2004,[112] Panebianco 2011,[95] Roethke 2012,[104] Sciarra 2010[105]
Intermediate	0.301 (0.000 to 0.500)	
High	0.159 (0.000 to 0.330)	
Locally advanced	0.122 (0.052 to 0.233)	Stewart 2001,[2] Campos-Fernandez 2009,[37] Scattoni 2011[38] (assumptions)

TABLE 17 Diagnostic accuracy of strategies evaluated in the economic model

Strategy	Sensitivity	Specificity	Source
Systematic extended-core TRUS/Bx	0.832 (0.78 to 0.88)	1.00	Scattoni 2011[38]
T2-MRI	0.86 (0.74 to 0.93)	0.55 (0.44 to 0.66)	Systematic review
MRS	0.92 (0.86 to 0.95)	0.76 (0.61 to 0.87)	Systematic review
DCE-MRI	0.79 (0.69 to 0.87)	0.52 (0.14 to 0.88)	Systematic review
T2-MRI or MRS	0.96 (0.90 to 0.98)	0.31 (0.21 to 0.42)	Systematic review
T2-MRI or DCE-MRI	0.88 (0.80 to 0.96)	0.14 (0.08 to 0.20)	Systematic review

Note: reference standard differs for extended-cores TRUS/Bx and MRI methods. A 24-core TRUS-guided saturation biopsy serves as the gold standard for the extended-cores estimate, whereas MRI methods are validated on histopathology of any targeted cores and a varying number of additional cores taken under TRUS guidance.

biopsy only. It was assumed that any patients missed by the index repeat biopsy (false-negatives), would have persistently elevated PSA level, which would trigger the offer of a saturation biopsy (>24 cores) 12 months later, and that acceptance would be high (assumption based on attitudes to repeat biopsy reported by Rosario *et al.*[150]). These conservative assumptions, which favour less-sensitive cancer detection strategies, were subjected to sensitivity analysis.

A systematic TRUS-guided extended-cores (14–16 cores) biopsy for all, carried out in an outpatient setting, was selected as the base comparator against which to assess the cost-effectiveness of using MRS/MRI (see *Table 17*). A limitation of the available literature is that no existing studies have directly assessed the relative sensitivity/specificity of MRI-directed biopsies in comparison with systematic biopsy sampling schemes with different numbers of cores. Thus, in modelling the comparison we were forced to rely on diagnostic accuracy data for the comparator and index tests derived from different sources using different reference standards. The sensitivity of the systematic extended-cores biopsy was derived from a study assessing the proportion of cancers detected by systematic biopsy schemes with variable numbers of cores,[38] using the results of a TRUS-guided saturation biopsy as the reference standard. The MRS/MRI sensitivities/specificities were derived from the systematic review (see *Chapter 4*), where the reference standard was histopathological assessment of biopsied tissue but the number of cores taken varied from study to study. Sensitivity analysis was performed to assess the sensitivity of findings to variation in these parameters.

How care pathways were determined and modelled, including an illustration of the model

The diagnostic and care pathways were determined based on a review of guidelines, expert opinion, and the availability of data. A schematic review of the diagnostic pathways was provided in *Chapter 1* (see *Figure 2*). *Figure 16* shows the tree structure used to model the index repeat biopsy within the economic model.

The diagnostic pathways were embedded in a Markov model developed to simulate the progression of diagnosed (treated) and undiagnosed PC (*Figure 17*). Seven basic states were used to model the natural history of PC: (1) no or undetectable cancer; (2) localised (T1–T2) PC (low risk); (3) localised PC (intermediate risk); (4) localised PC (high risk); (5) locally advanced cancer (T3); (6) metastatic cancer; and (7) PC death. Patients with localised and locally advanced disease were modelled to progress towards metastatic disease based on age, tumour risk status, and whether or not their cancer was diagnosed and appropriately treated. To begin with, patients with suspected PC following a first negative biopsy were spread across the undiagnosed states (using the proportions in *Table 16*). In the first cycle of the model, all patients were modelled to undergo their repeat biopsy, either by standard means or directed by one of the MRS/MRI sequences. Patients with underlying cancer (undetected) identified by the second biopsy as having disease, as determined by the sensitivity of the biopsy procedure, were modelled to transit to the appropriate diagnosed cancer state for the subsequent model cycle. Those with undetected cancer missed by the second negative biopsy remained in the appropriate undiagnosed state. Those remaining undiagnosed faced a higher risk of progression to metastases (based on progression rates observed for patients under watchful waiting), whereas those detected were modelled to progress at rates observed for patients receiving radical treatments. The model was cycled on a 3-monthly basis, such that probabilities of progression and costs of treatment and monitoring were expressed in terms of this constant cycle length.

Patients remaining in an undiagnosed cancer state after the index repeat biopsy were modelled to have their PSA levels monitored on a 6-monthly basis. An assumption was made that these patients would have persistently elevated PSA level and would therefore be selected for a further biopsy 12 months later. It was assumed that a saturation biopsy (≥24 cores) would be offered at this stage, that there would be 90% uptake,[150] and that the biopsy would have 98% sensitivity for detecting the remaining undiagnosed cancers (based on clinical opinion within the team). For patients without underlying PC, it was assumed that no further biopsies would be indicated unless incident PCs developed. These assumptions were subjected to sensitivity analysis.

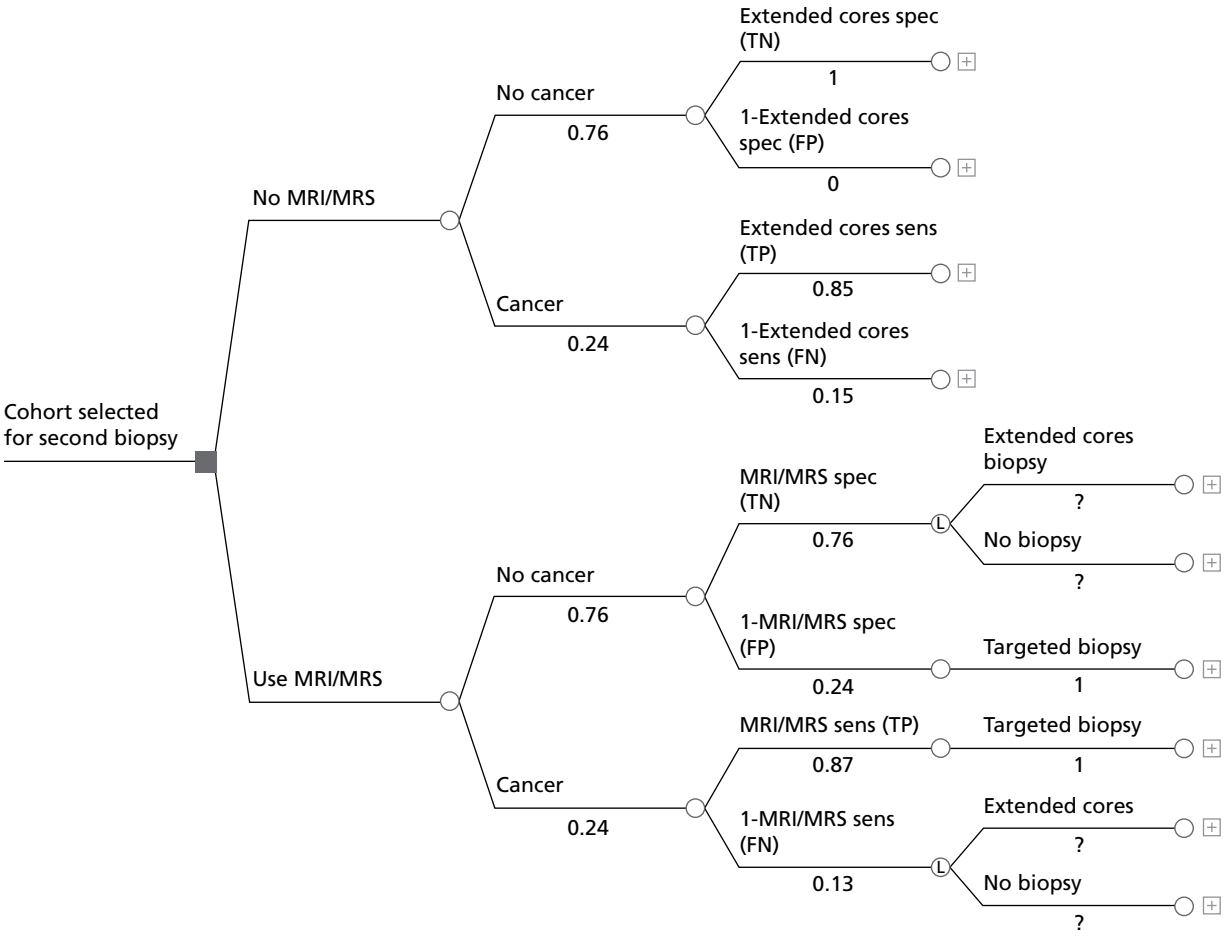


FIGURE 16 Diagnostic pathways for index re-biopsy. The base-case analysis assumed that all patients negative on MRS/MRI would not proceed to biopsy, but we also assessed the impact of assuming these patients would proceed to an extended-cores TRUS/Bx. FN, false-negative; FP, false-positive; sens, sensitivity; spec, specificity; TN, true-negative; TP, true-positive.

For every biopsy undertaken, modelled patients also faced an associated risk of complications (bleeding, infection, urinary retention). Patients crossing to the diagnosed states were modelled to receive appropriate staging, treatment and monitoring. In addition, patients receiving treatment faced a risk of experiencing complications, which incurred further health service costs and quality-of-life decrements. Following treatment for localised disease, a proportion of the cohort was modelled to experience tumour recurrence, triggering further treatment and costs.

Costs associated with biopsy procedures, PSA monitoring, staging, treatment and disease monitoring were incorporated into the model based on the application of unit costs to procedures and treatment protocols (derived from expert opinion and current guidelines). Utilities associated with the different cancer states were used to quality adjust the time spent by patients in each state, and utility decrements associated with complications arising from treatment were also applied. Thus the model enabled cumulative costs, LYs and QALYs to be tracked over the lifetime of modelled cohorts under alternative diagnostic strategies. The model captures the potential trade-offs between increased short-term costs associated with incorporating MRI sequencing into the care pathways and any cost savings and potential survival gains resulting from fewer repeat biopsies and earlier cancer treatment. The model also accounts for the fact that treatment may have a detrimental impact on patients' health-related QoL.

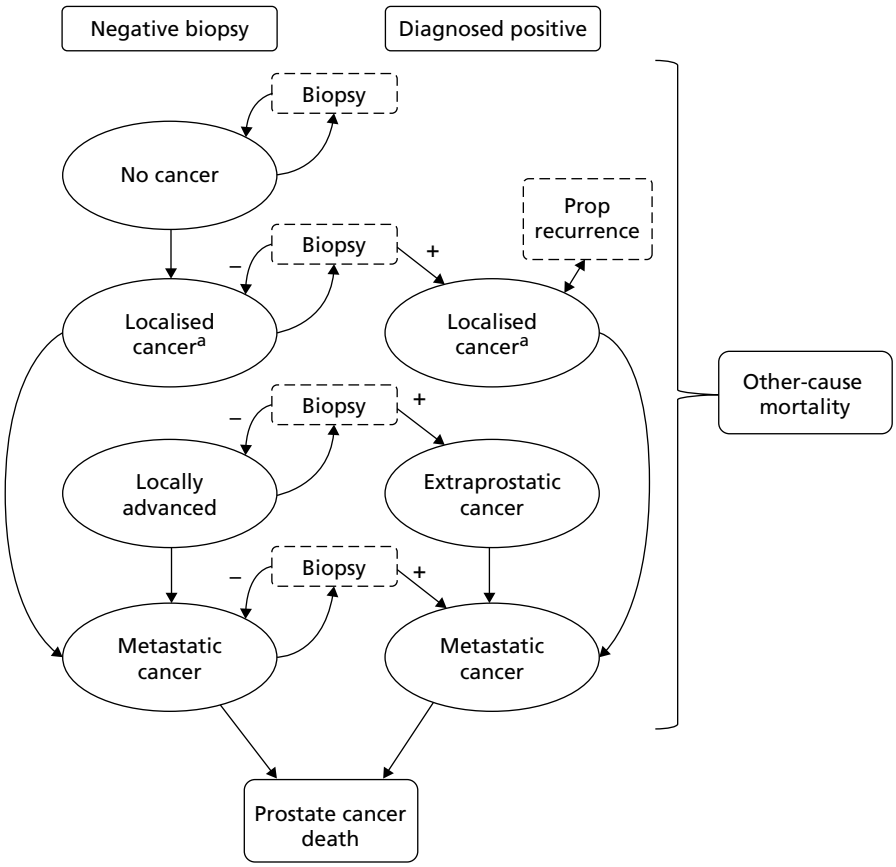


FIGURE 17 Model structure. a, Patients with localised cancer were risk stratified by cancer grade (low, intermediate and high) and modelled to progress to metastatic disease at different rates. Prop recurrence, proportion with local recurrence following treatment.

Complications of biopsy

The occurrence of biopsy complications was modelled on the basis of two data sources: the ProtecT trial[150] and a cohort study reported by Nam *et al.*[151] The resultant probabilities are provided in *Table 18*. Costs associated with these complication events were estimated and incorporated into the model.

Risk of cancer progression (undiagnosed and diagnosed patients)

A simplifying assumption of the model was that all men in a cancer state are at risk of disease progression, and that men progress towards metastatic disease. It was also assumed that all cancer-related deaths occur following transition to metastatic disease. Given a lack of comparable data on the rate of transition from localised to locally advanced disease, and from locally advanced to metastatic disease (and the relative effect of diagnosis and treatment on these transitions), the model structure was simplified such that progression from localised disease to metastases was modelled in a single step (using a Weibull function fitted to observed published data for this transition).

Men were initially spread across the 'no cancer', 'localised cancer' and 'locally advanced cancer' states (see *Table 16*). They were then modelled to progress according to their cancer and diagnostic status using observed follow-up data on the cumulative incidence of metastatic disease combined with estimates of relative treatment effects (i.e. baseline transition risks were adjusted downwards to reflect the impact of appropriate treatment in those receiving a diagnosis). The progression risk for localised cancer was modelled based on data reported by Bill-Axelson *et al.*[148] whereas the progression risk for men starting in the locally advanced state was modelled based on data from a European Organisation for Research and Treatment of Cancer (EORTC) study reported by Bolla *et al.*[152]

TABLE 18 Risks of complications following prostate biopsy

Event	Probability (95% CI)	Distribution for PSA	Source
Biopsy complication			
	0.117 (0.100 to 0.137)	*Beta*	Rosario 2012[150]
		Alpha: 134	
		Beta: 1013	
Probability of hospital admission given biopsy complication			
	0.112 (0.069 to 0.176)	*Beta*	Rosario 2012[150]
		Alpha: 15	
		Beta: 119	
Reasons for hospital admission			
		Dirichlet	Nam 2010[151]
Urinary infection related	0.716 (0.675 to 0.738)	Alpha: 556	
Urinary bleeding related	0.194 (0.166 to 0.221)	Alpha: 151	
Urinary obstruction related	0.090 (0.081 to 0.124)	Alpha: 79	
Biopsy-related consultation given complication			
	0.888 (0.824 to 0.931)	*Beta*	Rosario 2012[150]
		Alpha: 119	
		Beta: 15	
Location of consultation			
		Dirichlet	Rosario 2012[150]
GP	0.773 (0.690 to 0.839)	Alpha: 92	
Urology department nurse	0.118 (0.071 to 0.188)	Alpha: 14	
Other – NHS Direct	0.109 (0.065 to 0.178)	Alpha: 13	

GP, general practitioner.

Regression methods[153] were used to fit Weibull functions to the observed metastases-free survival probabilities reported for men receiving watchful waiting over a 15-year follow-up period;[148] separate functions were fitted for men of <65 years of age and men aged ≥65 years. The estimated parameters of the Weibull functions were then used to derive 3-monthly transition probabilities for the risk of developing metastatic disease from undiagnosed localised cancer. In order to risk-stratify the probabilities of progression, separate functions were determined for patients with low-, moderate- and high-risk localised cancer. This was achieved by adjusting the rate parameters of the Weibull functions to yield the cumulative incidence of metastases or PC mortality observed for cohorts with low-[148] and high-risk[154] localised cancer. The cumulative incidence rates of metastatic disease reported for the two age-specific cohorts (<65/≥65) as a whole by Bill-Axelson *et al.* were taken to represent the risk of progression for moderate risk patients in each respective modelled age group. Transition probabilities for developing metastatic disease following diagnosis and treatment were estimated by multiplying the rate parameters of the Weibull functions by published relative risk estimates associated with radical prostatectomy.[148] The resultant modelled cumulative incidence of metastases in treated and untreated patients is shown in *Figure 18* compared with the observed values derived from published sources. As a sensitivity analysis, we calibrated the model transition rates to yield the PC-specific survival probabilities (by risk status) observed for patients (>12 years of follow-up) in the control group of a recently published randomised controlled

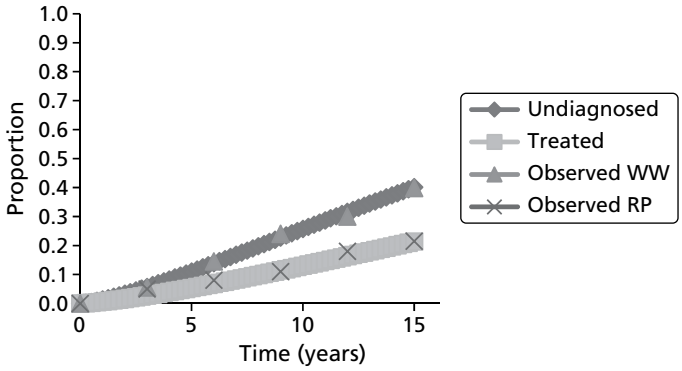


FIGURE 18 Modelled and observed cumulative incidence of metastases. WW, watchful waiting; RP, radical prostatectomy.

trial of radical prostatectomy compared with observation for localised disease.[149] In addition, we applied the corresponding relative risk estimates obtained from this trial.

For those starting the model in the locally advanced cancer stage, a similar approach as above was used to model the risk of progression to metastatic disease. However, given the lack of contemporary data on the risk of developing metastases from untreated locally advanced disease, we applied the metastases-free survival data reported for a cohort of patients treated with EBRT alone. These rates were then adjusted downwards for diagnosed patients using the relative risk reduction associated with EBRT combined with adjuvant hormone therapy.[152] All of the relative risk parameters applied in the model are presented in *Table 19*.

TABLE 19 Relative risk parameters applied to diagnosed patients in the model

Parameter	Value (95% CI)	Distribution for PSA	Source
Localised disease			
Relative risk of metastases (<65 years, low risk)	0.41 (0.18 to 0.95)	Log-normal; Ln mean: –0.8916 Ln SE: 0.424364	Bill-Axelson *et al*. 2011[148]
Relative risk of metastases (<65 years, intermediate/high risk)	0.47 (0.32 to 0.70)	Log-normal: Ln mean: –0.75502 Ln SE: 0.199684	Bill-Axelson *et al*. 2011[148]
Relative risk of metastases (≥65 years, low risk)	0.46 (0.19 to 1.11)	Log-normal: Ln mean: –0.77653 Ln SE: 0.450278	Bill-Axelson *et al*. 2011[148]
Relative risk of metastases (≥65 years, intermediate/high risk)	0.77 (0.51 to 1.15)	Log-normal: Ln mean: –0.026136 Ln SE: 0.207425	Bill-Axelson *et al*. 2011[148]
Locally advanced disease			
Relative risk of metastases	0.28 (0.18 to 0.46)	Log-normal: Ln mean: –1.27297 Ln SE: 0.239354	Bolla *et al*. 2002[152]

SE, standard error.

For those with metastatic disease, a constant 3-monthly risk of death from PC was estimated from English observational data[155] and applied in the model. The age-specific risk of death from other causes was also incorporated based on age- and sex-specific interim UK life tables.[156]

Resource use and unit cost estimation

All costs were estimated based on resource-use inputs and unit costs for the 2009–10 financial year.

Standard transrectal ultrasound-guided biopsy

The cost of a TRUS-guided needle biopsy was taken from the NHS reference costs[41] using the appropriate HRG (LB27Z). There is some uncertainty as to how hospitals in England and Wales are, or would be, reimbursed for repeat biopsies using the systematic extended-cores or MRI-/MRS-directed approach. Although both approaches can be carried out as outpatient procedures without general anaesthetic, it is likely that at least some organisations commission these as day-case procedures. As a result of outpatient procedure coding being non-mandatory, it is not possible to accurately ascertain the proportion of procedures carried out in each care setting, and this is likely to vary from trust to trust. Thus, adopting a conservative approach in favour of less sensitive less costly diagnostic strategies, we initially assumed that all index repeat biopsies would be carried as outpatient procedures, incurring an average cost of £212.

Note, however, that although this tariff-based cost should reflect the budget impact on NHS primary care trusts of commissioning such procedures, it might not fully capture the opportunity cost that hospitals face in delivering the procedure, particularly for extended-cores biopsies that can substantially increase pathology time over standard TRUS/Bx (10–12 cores). We therefore assessed the impact of increasing this cost through sensitivity analysis.

In the base case we also made the conservative assumption that the use of MRS/MRI would not influence the cost of the biopsy procedure itself. This was due to a lack of certainty as to how the patient-level pooled sensitivity estimates obtained for MRS/MRI imaging (from the systematic review) would be affected if only targeted cores were taken in the subsequent biopsy. However, we explored the impact of increasing the cost of extended-cores biopsies, but not the cost of MRI-/MRS-targeted biopsies.

For patients with underlying cancer missed by the index re-biopsy, we assumed that a saturation biopsy (≥24 cores) would be indicated at 12 months, and applied the day-case NHS reference cost for all these procedures (£447). We also explored the impact of increasing this cost to reflect potential underestimation of histopathology costs associated with obtaining larger numbers of cores (for further deterministic scenario analyses, see *Results*, below).

Magnetic resonance imaging sequences for guiding biopsy

The costs of performing alternative MRI sequences to guide prostate biopsy were estimated using a bottom-up approach. Radiographer and radiologist time associated with the performance of different sequences was estimated by asking all of the radiologists involved in the project to provide estimates of time inputs they deemed to be representative of standard practice. Within these estimates, allowance was made for preparation (getting the patient into the machine) and scanning time (two radiographers) and reading/reporting time (one consultant radiologist). The average reported time inputs for sequences included in the economic model are outlined in *Table 20*. Unit costs obtained from the Unit Costs of Health and Social Care[157] were applied to these resource-use inputs. These unit costs included salaries, on-costs (employer superannuation and national insurance contributions) and an apportionment of capital space and overhead costs to capture the opportunity cost of space and overheads attributable to the alternative procedures. Capital equipment required for the alternative MRI sequences was costed by applying current market prices obtained from NHS Grampian. These initial outlay costs were annuitised over the useful working lifespan of the piece of equipment in question, applying an annual discount rate of 3.5% to account for the opportunity cost of the investment over time. The equivalent annual cost of each piece of equipment was divided through by its estimated running time to give a cost per minute estimate. The scanning time estimates associated with alternative MRI sequences were then multiplied

TABLE 20 Summary of MRS/MRI procedure cost estimates

Sequence	Grade/ band	Patient preparation time (minutes)	Time per patient (minutes)	Cost per hour (£)	Staff cost per patient (£)	Equipment cost per patient (£)	Total cost per patient[a] (£)
T2-MRI							
Radiographer 1	6 + 7 + 7	10.00	14.33	48.33	19.60		
Radiographer 2	7	10.00	14.33	50.00	20.28		
Radiologist	Consultant		5.00	162.00	13.50		
Totals					**53.38**	**46.90**	**106.29**
DW-MRI (+ T2-MRI)							
Radiographer 1	6 + 7 + 7	10.00	21.33	48.33	25.24		
Radiographer 2	7	10.00	21.33	50.00	26.11		
Radiologist	Consultant		8.67	162.00	23.40		
Totals					**74.75**	**60.65**	**141.30**
DCE-MRI (+ T2-MRI)							
Radiographer 1	6 + 7 + 7	12.00	22.67	48.33	27.93		
Radiographer 2	7	12.00	22.67	50.00	28.89		
Radiologist	Consultant		10.00	162.00	27.00		
Totals					**83.81**	**71.21**	**189.71**
MRS (+ T2-MRI)							
Radiographer 1	6 + 7 + 7	10.00	27.33	48.33	30.07		
Radiographer 2	7	10.00	27.33	50.00	31.11		
Radiologist	Consultant		16.67	162.00	45.00		
Totals					**106.19**	**73.93**	**185.68**
T2-MRI + DW-MRI + DCE-MRI							
Radiographer 1	6 + 7 + 7	12.00	31.33	48.33	34.91		
Radiographer 2	7	12.00	31.33	50.00	36.11		
Radiologist	Consultant		16.67	162.00	45.00		
Totals					**116.02**	**88.42**	**239.06**
T2-MRI + DW-MRI + MRS							
Radiographer 1	6 + 7 + 7	10.00	37.67	48.33	38.40		
Radiographer 2	7	10.00	37.67	50.00	39.72		
Radiologist	Consultant		20.33	162.00	54.90		
Totals					**133.02**	**94.61**	**233.18**
T2-MRI + DCE-MRI + MRS							
Radiographer 1	6 + 7 + 7	12.00	37.33	48.33	39.74		
Radiographer 2	7	12.00	37.33	50.00	41.11		
Radiologist	Consultant		21.67	162.00	58.50		
Totals					**139.35**	**101.71**	**275.34**

TABLE 20 Summary of MRS/MRI procedure cost estimates (*continued*)

Sequence	Grade/ band	Patient preparation time (minutes)	Time per patient (minutes)	Cost per hour (£)	Staff cost per patient (£)	Equipment cost per patient (£)	Total cost per patient[a] (£)
T2-MRI + DW-MRI + DCE-MRI + MRS							
Radiographer 1	6 + 7 + 7	12.00	46.00	48.33	46.72		
Radiographer 2	7	12.00	46.00	50.00	48.33		
Radiologist	Consultant		25.33	162.00	68.40		
Totals					**163.46**	**118.92**	**316.60**

a Total costs also include estimates of administration and consumable costs per scan.

by the appropriate equipment cost per minute estimates to give estimates of the capital equipment costs attributable to each different MRI sequence. Costs of equipment used only for DCE-MRI (pump) or MRS (MRS software) were only allocated to sequences involving these procedures. The annual equivalent costs of these items were divided through by the number of uses per year (Dr Lutfi Kurban, Aberdeen Royal Infirmary, March 2012, personal communication; Dr Anwar Padhani, Mount Vernon Cancer Centre, April 2012, personal communication) to give cost per use estimates, which were then applied to sequences incorporating these procedures. Finally, consumables associated with DCE-MRI (contrast, pump pack, others) were costed using unit prices provide by NHS Grampian.

As the MRI costs represent the opportunity costs to hospitals of providing alternative scan sequences, they are well suited to assessing the relative cost-effectiveness of using alternative sequences. However, the estimated costs for some of the simpler scans may underestimate the costs of commissioning such activity. This makes them somewhat less comparable with the tariff-based cost estimate for TRUS/Bx. However, we did not adjust these costs further in the base-case analysis given the concurrent conservative approach to costing TRUS/Bx. As a sensitivity analysis we adjusted the costs of sequences by setting the cost of T2 + DCE-MRI equal to the NHS reference cost for HRG RA03Z (Magnetic Resonance Imaging Scan, one area, pre and post contrast) (£229)[41] and maintained the incremental differences in cost between sequences as estimated from the bottom-up calculations.

Biopsy complication costs

Standard practice for repeat biopsy in the UK is systematic TRUS-guided extended-cores or saturation biopsy. The incidence of adverse events post biopsy was determined from the literature[150,151] and categorised into hospital admissions or biopsy-related consultations (see *Table 18*). A risk of death from biopsy complications was experienced only by patients who developed an infection ($p = 0.0009$) and all other patients were assumed to recover after initial treatment.

Hospital admissions resulting from biopsy complications were reported by Nam[151] and Rosario[150] as being due to one of three urological diagnoses: urinary infection; urinary bleeding (haematuria); or urinary obstruction (*Table 21*). For inpatient admissions due to urinary tract infection (UTI) we applied the NHS reference cost for HRG LA04G (Kidney or Urinary Tract Infections with length of stay 1 day or less) (£401). Admission for haematuria was assumed to require insertion of a haematuria catheter for bladder irrigation HRG LB18Z (Attention to Suprapubic Bladder Catheter) at a cost of £567 per patient.[41] Urinary retention was assumed to be temporary and was modelled to incur the cost of inserting and subsequently removing a urethral catheter: day-case HRGs LB09Z (Ureter Intermediate Endoscopic Procedures) and LB15E (Bladder Minor Procedure 19 years and over) at £652 and £368, respectively.[41] It was further assumed that the NHS would incur the daily cost of an overnight catheter bag and the weekly cost of a leg bag (apart from in the first week when two leg bags would be required) over the course of 1 month (£6.47 and £12.61, respectively).

TABLE 21 Unit costs associated with biopsy complications

Procedure	Unit cost (£)	Assumptions	Lower/higher estimates (distribution)	Source
Hospital admissions				
			Gamma	
UTI	401	HRG LA04G (Kidney or Urinary Tract Infections with length of stay 1 day or less)	£286/£466 (Alpha: 8.91; beta: 45.00)	Department of Health 2011[41]
Urinary bleeding (haematuria)	567	HRG LB18Z (Attention to Suprapubic Bladder Catheter)	£293/£635 (Alpha: 4.94; beta: 114.88)	Department of Health 2011[41]
Urinary obstruction	1039.08	HRG LB09Z (Ureter Intermediate Endoscopic Procedures) and LB15E (Bladder Minor Procedure 19 years and over) + cost of catheter bags	£595/£1225 (Alpha: 4.88; beta: 212.73)	Department of Health 2011;[41] Ramsay *et al*. 2012[144]
Biopsy-related consultations				
GP visit	36.27	11.7 minutes for surgery consultation		Curtis 2011[157]
Urology department nurse visit	70		£46/£85 (Alpha: 5.78; beta: 12.10)	Department of Health 2011[41]
Call to NHS Direct	20.98		Applied deterministically	

GP, general practitioner.

Rosario *et al.*[150] also reported the 35-day incidence of consultations with general practitioners, urology department nurses, and 'other sources of medical advice' (e.g. NHS Direct). The cost associated with a general practitioner (GP) consultation was derived from the *Unit Costs of Health and Social Care*.[157] The average duration of a GP consultation is 11.7 minutes[157] at a cost of £3.10 per surgery minute,[157] giving a unit cost of £36.27 per consultation. The cost of a consultation with a urology department nurse was derived from the relevant NHS tariff – non-consultant-led follow-up attendance, non-admitted, face to face – at cost of £70.[41] The cost per NHS direct contact was derived from the NHS Direct National Health Service Trust Annual Report and Accounts 2009–10, and was based on the total reported staff wages divided by the number of calls logged, giving a cost of £20.98 per call.

Prostate cancer treatment costs for localised disease

Potential treatment pathways by cancer stage were derived from the current NICE guidance.[9] The costs associated with implementing alternative treatment pathways, on an ongoing 3-monthly basis, were estimated using data from a variety of sources including the Department of Health NHS reference costs,[41] the *Unit Costs of Health and Social Care*,[157] and a recently completed technology assessment report (TAR) evaluating the cost-effectiveness of robotic radical prostatectomy compared with laparoscopic prostatectomy[144] for localised PC. Clinical opinion was relied upon to enable an appropriate estimation of timelines for treatment pathways.

It is typical practice in the UK to monitor PSA level for the duration of the patient's life post treatment; every 3 months for the first 2 years and then every 6 months thereafter (based on clinical opinion within the research team). The cost of PSA level monitoring was thus estimated, based on a consultation with a practice nurse (£12)[157] plus £5.91 for laboratory services,[144] and included in the model (*Table 22*).

Patients with localised PC were modelled to follow one of three alternative treatment pathways: (1) active surveillance; (2) radical prostatectomy followed by PSA level monitoring; or (3) EBRT followed by PSA level

TABLE 22 Cost of PSA testing

Procedure	Unit cost (£)	Source
PSA test	5.91	Ramsay *et al.*[144]
Practice nurse	12 per consultation	*Unit Costs of Health and Social Care*[157]
PSA unit cost	**17.91**	

monitoring. The proportion of patients receiving each management strategy, by D'Amico Risk category,[31] was derived from routine Scottish health episode data (Dr Karina Laing, MSc in Surgical Sciences thesis, University of Edinburgh, May 2012, personal communication). It was assumed that the alternative treatment modalities would be applied appropriately based on the risk of progression and that, as such, the observed risk reduction associated with radical prostatectomy [148] could be achieved at the level of the cohort as a whole.

The cost of active surveillance was estimated based on the cost of PSA testing (see *Table 22*) on a 3-monthly basis, followed by a repeat TRUS/Bx[41] at 12 months, and every 3 years thereafter (based on clinical opinion within the research team).

The cost of radical prostatectomy was taken as the NHS reference cost for HRG LB21Z (Bladder Neck Open Procedures – Male). Of the two most common approaches to radical surgery (open and laparoscopic radical prostatectomy) the overall activity reported for open procedures was higher,[41] and, as such, the cost for this procedure was applied in the model.

The cost associated with a programme of EBRT was calculated on the basis of 37 sessions within a 7.5-week time frame (expert opinion) at a cost per session of £129.[41] EBRT treatment is generally accompanied by a course of androgen deprivation therapy. Although all patients with localised PC were modelled to receive 3 months of hormone therapy from commencement of EBRT, hormone therapy prior to EBRT treatment was assumed to occur only for those with intermediate- or high-risk disease. Before commencing EBRT, these patients were initially modelled to receive a 21-day course of bicalutamide (Casodex®, AstraZeneca: £96.00), followed by a 3-month course of the LHRH agonist triptorelin (Decapeptyl® SR, Ipsen: 11.25-mg 3-month injection) at a cost of £207.[158] As localised low-risk patients do not generally receive hormone therapy prior to EBRT treatment, it was assumed that the costs of hormone treatment for these patients would be incurred in the first 3-month cycle following diagnosis, concurrently with the EBRT sessions. It was assumed in all cases that triptorelin would be administered by a practice nurse in a primary care setting, at a cost of £12 per visit.

Treatment costs associated with locally advanced disease

External beam radiotherapy with adjuvant hormone therapy was identified as the most appropriate treatment option for patients with locally advanced PC upon diagnosis.[9] A small proportion of men were also modelled to receive radical prostatectomy. The cost streams and timelines for these treatments were assumed to be consistent with those outlined above for patients with moderate- to high-risk localised disease, with the exception that hormone therapy was continued to 2 years post EBRT.

Costs associated with local progression following treatment for localised disease

A proportion of the cohort was modelled to experience biochemical recurrence following radical treatment for localised cancer. These patients were modelled to receive either salvage EBRT or hormone therapy alone.

Salvage EBRT is delivered at lower gray, with fewer sessions (33 sessions within a 6.5-week time frame). As such, we applied the NHS reference cost (£107) for the appropriate HRG (SC22Z) to each treatment

session.[41] In addition, hormone treatment for patients receiving salvage EBRT for biochemical recurrence was extended for a period of 2 years post EBRT treatment.

The 3-monthly cost of hormone therapy was assumed to correspond to the cost of hormone therapy administered pre and post EBRT (21-day course of bicalutamide, followed by 3-monthly injections of triptorelin). However, treatment was assumed to extend for the duration of the patient's lifetime when initiated for biochemical relapse.

Costs associated with metastatic disease

Upon transiting to the metastatic disease state, it was initially assumed that all patients would be treated with hormone therapy, incurring a continuous 3-monthly cost of £219 (*Table 23*). Without explicitly modelling the initiation and impact of chemotherapy, we also assumed that 50% of patients developing metastatic disease would undergo a first-line docetaxel-based chemotherapy regimen (£10,450) and that 70% of these patients would go on to receive a second-line abiraterone-based regimen (£24,670) prior to death, as per the assumptions used in the costing template for the NICE abiraterone technical appraisal.[39]

Costs of complications arising from treatment

Radical prostatectomy

Three common adverse events following radical prostatectomy were modelled: (1) bladder neck contracture; (2) urinary incontinence (UI); and (3) ED (*Table 24*). The probability of experiencing bladder neck contracture following surgery was taken from the systematic review of a recently completed

TABLE 23 Unit cost estimates for treatment pathways

Procedure	Unit cost (£)	Assumption	Lower/higher quartile (distributions)	Source
Active surveillance				
TRUS/Bx	212	HRG = LB27Z (outpatient)	£137/£295 (*Gamma*; alpha: 3.23, beta: 65.58)	Department of Health 2011[41]
Radical treatment				
Open radical prostatectomy	4614	HRG = LB21Z	£3650/£5408 (*Gamma*; alpha: 12.37; beta: 373.04)	Department of Health 2011[41]
EBRT: 37 sessions	4773	HRG = SC23Z £129 × 37	£3848/£5439 (*Gamma*; alpha: 16.16; beta: 295.35)	Department of Health 2011[41]
Salvage treatment				
EBRT: 33 sessions	3531	HRG = SC22Z £107 × 33	£2211/£4983 (*Gamma*; alpha: 2.91; beta: 1211.93)	Department of Health 2011[41]
Hormone therapy				
A 21-day course of bicalutamide	96	50 mg per day	Applied deterministically	BNF 63[158]
Three months' decapeptyl	219	Drugs + administration: £207 + £12	Applied deterministically	BNF 63;[158] Curtis 2011[157]
Two years' hormones	1752	£219 × 8	Applied deterministically	BNF 63;[158] Curtis 2011[157]

BNF, *British National Formulary*.

TABLE 24 Long-term complications associated with radical prostatectomy and EBRT

Long-term complications	Probability (95% CI)		Distribution		Unit cost of treatment (£)	Source
	<65 years	≥65 years	<65 years	≥65 years		
Radical prostatectomy						
Urinary stricture	0.022	0.022			1112 (one-off)	Ramsay[144]
Urinary incontinence						
3 months	0.318 (0.289 to 0.348)	0.318 (0.289 to 0.348)	Alpha: 305 Beta: 653		65.90 (every 3 months)	Sacco[159]
6 months	0.220 (0.195 to 0.247)	0.220 (0.195 to 0.247)	Alpha: 211 Beta: 747			
12 months	0.131 (0.110 to 0.154)	0.131 (0.110 to 0.154)	Alpha: 125 Beta: 833			
ED						
Baseline	0.115 (0.094 to 0.140)	0.262 (0.228 to 0.300)	Alpha: 83 Beta: 640	Alpha: 149 Beta: 419	232.08 (every 3 months)	Stanford[160]
12 months	0.763 (0.728 to 0.794)	0.840 (0.802 to 0.872)	Alpha: 488 Beta: 152	Alpha: 352 Beta: 67		
24 months	0.656 (0.619 to 0.692)	0.790 (0.748 to 0.826)	Alpha: 420 Beta: 220	Alpha: 331 Beta: 88		
EBRT (late toxicity)						
			Beta			
Urinary stricture	0.072 (0.050 to 0.102)	0.072 (0.050 to 0.102)	Alpha: 27 Beta: 350		1112 (one-off)	Ataman[161]
Urinary incontinence	0.053 (0.035 to 0.081)	0.053 (0.035 to 0.081)	Alpha: 20 Beta: 357		65.90 (every 3 months)	Ataman[161]
Bowel problems	0.119 (0.090 to 0.156)	0.119 (0.090 to 0.156)	Alpha: 45 Beta: 332		18 (every 3 months)	Ataman[161]
ED	0.45	0.45	Applied deterministically		232.08 (every 3 months)	Heidenreich[162]

technology assessment review.[144] All patients were assumed to recover from bladder neck contracture and incur the one-off inpatient admission cost for a bladder neck minor endoscopic procedure (HRG LB27Z). Increases in the proportions of patients suffering from ED and/or UI at different time points following radical prostatectomy were derived from cohort studies (Sacco *et al.*;[159] Stanford *et al.*[160]). Patients experiencing UI were assumed to enter a continuous period of self-management using containment pads at a 3-monthly cost of £65.90.[144] Additionally, 10% of patients experiencing UI were modelled to incur the cost of oxybutynin hydrochloride (Ditropan, Sanofi Aventis) (clinical opinion) at a 3-monthly cost of £36.66.[158] Patients recovering urinary continence were modelled to receive no further management costs for this complication, whereas those remaining incontinent continued to incur the costs of containment pads.

Patients suffering from ED were modelled to receive sildenafil (Viagra®, Pfizer) (84%) or alprostadil (MUSE®, Astra) (16%). Proportions of patients using both were identified in the literature and the weighted average cost was applied to estimate the 3-monthly treatment cost. All of the unit costs for treatment complications are provided in *Table 24*.

External beam radiotherapy

Four common complications (see *Table 24*) following EBRT treatment were identified from the EUA Guidelines on Prostate Cancer:[161,162] urinary stricture, UI, ED, and bowel problems. An identical assumption was made for patients diagnosed with urinary stricture as for those diagnosed with bladder neck contracture following radical prostatectomy; i.e. all patients were assumed to recover following a minor bladder neck endoscopic procedure carried out in an inpatient setting (£1112). The cost of managing UI following EBRT was assumed to correspond to that reported for radical prostatectomy, as were the costs of treating ED.

Health measurement and valuation

Cancer states

The model was used to estimate cumulative costs and LYs over the lifetime of the simulated cohorts. Attempts were then made to identify appropriate utility weights (*Table 25*) for the different cancer states, so as to enable the estimation of QALYs. A similar approach to the one taken in the Robotic report[144] was used to adjust time spent in PC health states. For localised cancer, we used the European Quality of Life-5 Dimensions (EQ-5D) utility weights reported for a cohort of patients undergoing prostatectomy at baseline, 6 months, 1 year and 4 years. We assumed that patients with no cancer or undiagnosed localised cancer would have the same health-state utility as prostatectomy patients at baseline. For PC found to be locally advanced upon diagnosis, and for local recurrence following initial treatment, we applied further utility weights reported by Korfage *et al.*[163] for a cohort of patients undergoing EBRT. This cohort of patients was slightly older on average, with more advanced disease. For patients with metastatic disease, we applied the average of the time trade-off weights for metastatic and castration resistant metastatic disease – elicited from a sample of 45- to 70-year-old married males (with no history of PC) presenting at a primary care medical facility in the USA.[144]

Biopsy and treatment complications

The EQ-5D weights reported by Korfage *et al*.[163] were the mean values reported for cohorts where a substantial proportion of patients experienced the main complications of prostatectomy or EBRT but nevertheless reported high levels of health-related QoL on the EQ-5D.[163] As such in the base-case analysis we made no further adjustment to health-related QoL for those modelled to experience treatment complications. However, we did explore the impact of applying further disutilities for complications through sensitivity analyses.

In order to do this we applied utilities reflecting the presence of mild/moderate bowel problems,[164] UI,[9,165] and ED[9,165] in a multiplicative fashion, such that if a modelled patient had localised cancer and UI, then their overall utility pay-off was equal to the product of the utilities for localised cancer and UI.

Discount rate (costs and benefits)

Costs and benefits (LYs and QALYs) were discounted at the treasury recommended rate of 3.5% per annum.[167] We also assessed the impact of discounting benefits at the rate of 1.5% per annum, while maintaining a discount rate of 3.5% for costs, as suggested by NICE in instances where treatment effects '… are both substantial in restoring health and sustained over a very long period (normally at least 30 years)'.[167]

List of assumptions

- All patients were initially spread across the states: no cancer, localised cancer (low, intermediate, high risk) or locally advanced cancer.
- Imaging test sensitivities were not adjusted by grade and stage of underlying cancer in the base-case analysis, but the observed correlation between MRS and DW-MRI test performance and tumour grade was explored through sensitivity analysis.

TABLE 25 Health-state utilities applied in the economic model

Health-state utility	Utility value	Distribution for PSA	Source
Cancer states			
		Beta: mean (SEM)	
Localised (undiagnosed)	0.89	0.89 (0.0133)	Korfage 2005[163]
Localised (diagnosed)			Korfage 2005[163]
<6 months	0.89	0.89 (0.0133)	
6–12 months	0.91	0.91 (0.014427)	
12–51 months	0.90	0.90 (0.015328)	
≥52 months	0.88	0.88 (0.018276)	
Locally advanced (undiagnosed)	0.81	0.81 (0.014625)	Korfage 2005[163]
Locally advanced (diagnosed)			Korfage 2005[163]
<6 months	0.81	0.81 (0.0146)	
6–12 months	0.83	0.83 (0.0156)	
12–51 months	0.82	0.82 (0.0149)	
≥52 months	0.76	0.76 (0.0205)	
Metastases	0.635	0.635 (0.04)	Volk *et al*. 2004[166]
Treatment complications			
Urinary incontinence	0.84	Applied deterministically	Shimizu *et al*. 2008[165]
Bowel problems	0.83	Applied deterministically	Krahn *et al*. 2003[164]
ED	0.88	Applied deterministically	Shimizu *et al*. 2008[165]

SEM, standard error of mean.

- All patients with cancer were modelled to be at risk of progression to metastatic disease based on their D'Amico risk status (low, intermediate, high).
- All cancer deaths occurred through distant metastases.
- Diagnosed patients experienced a reduction in the risk of progression to metastases in line with that observed for patients receiving radical prostatectomy (favours more sensitive strategies). Although not all patients with localised disease were modelled to receive radical treatment upon diagnosis, it was assumed that appropriate risk-based targeting of treatment could maintain the relative treatment effects observed for radical prostatectomy, without the need to implement radical treatment immediately for all patients.
- Given the lack of contemporary data on the risk of progressing to metastatic disease from locally advanced disease without treatment, progression was modelled to occur at the rate observed for patients receiving EBRT alone. Progression in those diagnosed was modelled to occur at the rate observed for patients receiving EBRT with adjuvant hormone therapy.
- The starting point for the model was the first repeat biopsy, and it was assumed that patients with cancer missed by this biopsy would have persistently elevated PSA level, which would trigger a further definitive saturation biopsy 12 months later (base case).
- For patients without underlying cancer, the assumption was made that management beyond the first repeat biopsy would remain the same, regardless of which strategy was used for the first repeat biopsy. No further biopsies were modelled for this group in the base-case analysis, unless incident PC developed.

- A TRUS-guided systematic extended 14- to 16-core biopsy scheme was used as the comparator against which the cost-effectiveness of MRI-/MRS-directed TRUS/Bx was assessed in the base case.
- It was assumed in the base case that MRI-/MRS-directed biopsy would not reduce the cost of the biopsy procedure or the risk of biopsy-related complications relative to the TRUS-guided extended-cores biopsy.

Time horizon

Once it was established that the model made internally consistent predictions of cancer-related mortality over the period to which the observed input data related (15 years), the analysis proceeded over a 30-year time horizon. By this stage the majority of the modelled cohorts were dead and the additional QALYs per cycle had fallen to <0.001.

Internal validation

To assess the internal validity of the model, *Figures 19* and *20* show the Markov traces for treated and untreated patients with localised cancer (men aged 60 years) over a 15-year follow-up period. The modelled cumulative incidence of PC death does not match the data reported by Bill-Axelson *et al*.[148] exactly (23% vs 26% for untreated; 12% vs 16% for treated) owing to the application of UK age-specific rates of death from other causes and the application of a constant UK-specific risk of death from metastatic PC. However, the cumulative PC mortality rate is generally consistent with the data reported by

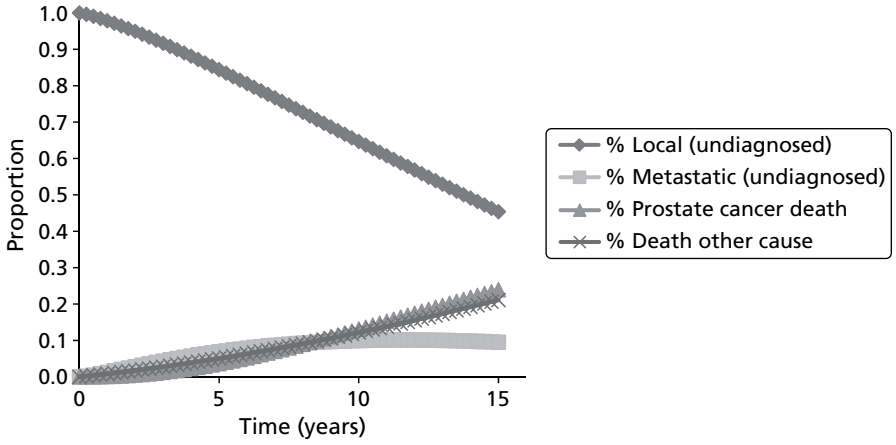


FIGURE 19 Markov trace for undiagnosed/untreated local cancer in patients aged 60 years.

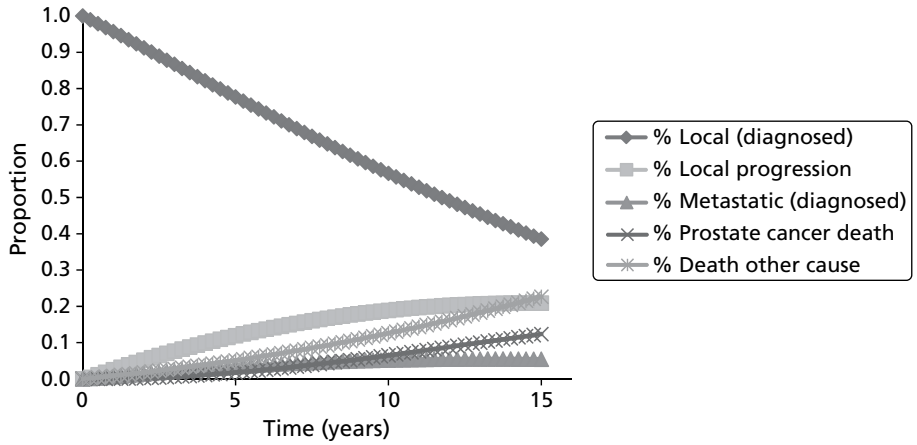


FIGURE 20 Markov trace for diagnosed/treated local cancer for patients aged 60 years.

Bill-Axelson and other similar cohorts; for example, Albertson *et al.*[168] estimated prostate-specific mortality of ~20% at 15 years in men aged 60–64 years with a Gleason score of 6.[168] However, our modelled rates are significantly higher than those reported in the recently published PIVOT trial,[149] which identified men through PSA screening. As such, sensitivity analysis was undertaken to assess the impact of recalibrating the model to yield the PC mortality rates observed by Wilt *et al.*[149]

Analysis

The model was first of all analysed deterministically, and the impact of altering key parameters and structural assumptions was demonstrated using deterministic sensitivity analysis. A probabilistic analysis was also undertaken, whereby Monte Carlo simulation was used to randomly draw a value for each model parameter from its assigned probability distribution for each of 1000 runs. The NMB approach was used to generate cost-effectiveness acceptability curves (CEACs) using the output from this probabilistic sensitivity analysis. One thousand probabilistic iterations were found to produce stable CEACs. Although the mean values obtained from probabilistic sensitivity analysis provide a more appropriate estimate of expected costs and effects for non-linear models, the analysis was found to be too computationally intensive to demonstrate the impact of all deterministic uncertainties on the mean probabilistic results. For this reason, the mean results from probabilistic sensitivity analysis are presented for only the main base-case analyses in 60- and 70-year-old men.

For the PSA, beta or Dirichlet distributions were used to represent uncertainty surrounding probabilities and proportions; beta distributions were assigned for health-state utilities, gamma distributions were used for costs, and log-normal distributions were assigned for relative risk parameters (see parameter tables, above – *Tables 19, 21, 23, 24* and *25*). To reflect the joint uncertainty surrounding the estimated sensitivity/specificity of each MRI sequence, the logit of the sensitivity/specificity of each sequence was modelled to follow a bivariate normal distribution (derived from the meta-analysis), with negative correlation specified between sensitivity and specificity on the logit scale. As insufficient data were available to estimate the correlation between sensitivity and specificity for each sequence, correlation (–0.3), obtained from the bivariate meta-analysis model for T2-MRI (the sequence with most information available for estimating correlation), was applied to all sequences. Underlying cancer prevalence and the initial proportional spread of the cohorts across cancer stages and risk strata were omitted from the PSA. This was due to uncertainty as to how the estimated variability of these parameters (see *Table 16*) reflected heterogeneity rather statistical impression. Instead, the impact of uncertainty surrounding these parameters was addressed using subgroup analysis and deterministic sensitivity analysis.

Results

Mean costs and mean effects, and incremental analysis

Tables 26 and *27* present the mean costs, mean LYs, and incremental cost per LY gained for each strategy in men aged 60 years at the time of repeat biopsy (based on deterministic and the probabilistic analyses, respectively), assuming a prevalence of underlying cancer of 24%. *Tables 28* and *29* present the same analyses using QALYs as the measure of effect. A breakdown of strategy costs into diagnosis and pre-diagnosis monitoring costs, biopsy complication costs, and cancer treatment and treatment complication costs is provided in *Appendix 17*. *Appendix 17* also provides a summary of the expected numbers of unnecessary and appropriate biopsies undertaken with each strategy. *Figures 21* and *22* present the findings of the cost per LY and cost per QALY analyses graphically on the cost-effectiveness plane. Strategies falling above and behind the lines plotted through the cost-effectiveness planes represent options that are more costly and less effective than other strategies or combinations of strategies. Strategies falling on the lines (the cost-effectiveness frontier) represent potentially cost-effective options, dependent on decision-makers' willingness to pay per LY or QALY gained.

TABLE 26 Incremental cost per LY gained from deterministic analysis (men aged 60 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average LYs	Incremental LYs[a]	Incremental cost per LY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3895	–	14.16796	–	–	–
T2-MRI	3902	7	14.16890	0.00094	7447	7447
MRS	3952	49	14.17081	0.00191	25,849	19,796
DCE-MRI	3984	32	14.16669	–0.00412	Dominated	Dominated
T2-MRI or MRS	4031	80	14.17203	0.00122	65,208	33,425
T2-MRI or DCE-MRI	4056	25	14.16949	–0.00254	Dominated	105,351

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and LYs are estimated in comparison with the next less costly non-dominated strategy.

TABLE 27 Incremental cost per LY gained from the probabilistic analysis (men aged 60 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average LYs	Incremental LYs[a]	Incremental cost per LY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3910	–	14.15935	–	–	–
T2-MRI	3916	7	14.16013	0.00078	8512	8512
MRS	3967	51	14.16189	0.00176	28,715	22,535
DCE	3999	32	14.15802	–0.00387	Dominated	Dominated
MRI or MRS	4045	78	14.16313	0.00124	63,393	35,903
MRI or DCE	4069	23	14.16065	–0.00248	Dominated	122,575

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and LYs are estimated in comparison with the next less costly non-dominated strategy.

TABLE 28 Incremental cost per QALY gained from deterministic analysis (men aged 60 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	Incremental cost per QALY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	**3902**	**7**	**12.48498**	**0.00066**	**10,626**	**10,626**
MRS	3952	49	12.48630	0.00132	37,382	28,502
DCE-MRI	3984	32	12.48346	–0.00285	Dominated	Dominated
T2-MRI or MRS	4031	80	12.48714	0.00083	95,481	48,367
T2-MRI or DCE-MRI	4056	25	12.48538	–0.00175	Dominated	152,323

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

TABLE 29 Incremental cost per QALY gained from probabilistic analysis (men aged 60 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	Incremental cost per QALY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3910	–	12.47303	–	–	–
T2-MRI	**3916**	**7**	**12.47357**	**0.00054**	**12,315**	**12,315**
MRS	3967	51	12.47478	0.00121	41,927	32,811
DCE-MRI	3999	32	12.47213	–0.00264	Dominated	Dominated
T2-MRI or MRS	4045	78	12.47562	0.00084	92,865	52,378
T2-MRI or DCE-MRI	4069	23	12.47392	–0.00170	Dominated	178,746

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

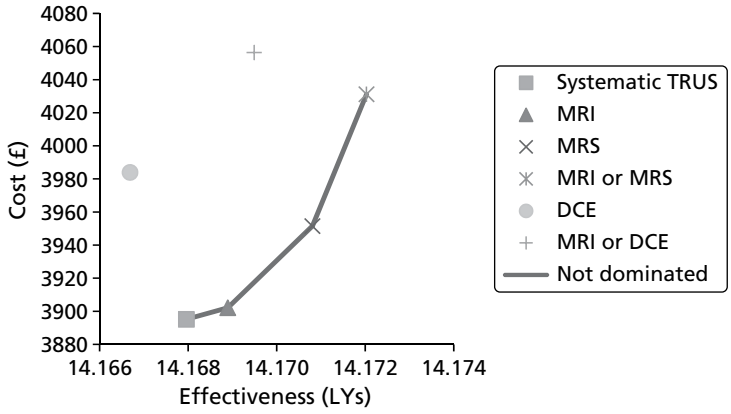


FIGURE 21 Cost-effectiveness frontier based on the cost per LY analysis (men aged 60 years, underlying cancer prevalence 24%).

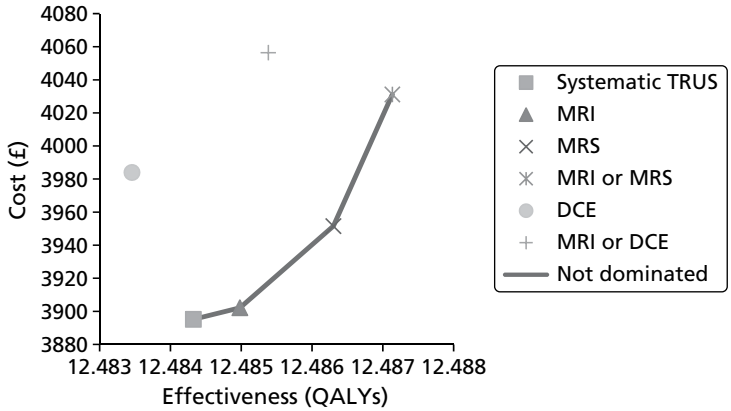


FIGURE 22 Cost-effectiveness frontier based on the cost per QALY analysis (men aged 60 years, underlying cancer prevalence 24%).

The base-case results show systematic extended-core TRUS/Bx to be the least costly option. However, using T2-MRI to determine which patients to biopsy (and to subsequently direct the biopsy) increases the costs by only a very small margin, with corresponding very small survival and QALY gains. Although these differences are very small and insignificant, T2-MRI-directed biopsy does have a favourable incremental cost per LY and QALY gained in comparison with systematic TRUS/Bx.

Using MRS to determine and direct biopsies results in a further cost increase and survival gain over T2-MRI but its incremental cost-effectiveness ratios (ICERs) are somewhat less favourable; although the incremental cost per QALY gained with MRS compared with systematic TRUS/Bx is just < £30,000 (deterministic analysis), it is > £30,000 in comparison with T2-MRI. Using positive findings on T2-MRI or MRS to determine and direct biopsies again increases costs, LYs and QALYs further. However, the ICERs (for LYs and QALYs) for using any visible abnormalities detected on T2-MRI or MRS, compared with only using abnormalities detected on MRS alone, are well above £30,000. This is due to a substantial loss of specificity associated with combined strategy, compared with using the findings on MRS alone to guide biopsy (31% for T2-MRI or MRS vs 76% for MRS alone), for only a small gain in sensitivity (96% vs 92%).

Tables 30 and *31* presents the incremental cost per LY analysis for men aged 70 years at the time of repeat biopsy, assuming a prevalence of underlying cancer of 24%. *Tables 32* and *33* present the same analysis but use QALYs as the unit of outcome (*see Appendix 17* for a breakdown of strategy costs by component categories). *Figures 23* and *24* present the findings of the respective analyses graphically on the cost-effectiveness plane.

A similar pattern of results is observed as for the cohort of men aged 60 years, but the survival benefit associated with the more sensitive strategies is smaller in the older cohort, owing to there being a higher risk of death from other causes (a competing risk for death from PC) and a smaller relative risk reduction associated with radical treatment in older men. As a consequence, the additional costs per LY and QALY gained with T2-MRI, MRS, and 'T2-MRI or MRS', are higher. However, the ICERs for T2-MRI compared with systematic TRUS/Bx remain < £30,000 despite the very small survival/QALY benefits.

Differential results for subgroups according to disease prevalence

Although few data were available to ascertain how diagnostic accuracy parameters vary by risk status of the cohort and underlying prevalence of cancer, *Tables 34* and *35* present the incremental cost per LY and

TABLE 30 Incremental cost per LY gained from deterministic analysis (men aged 70 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs	Incremental LYs[a]	Incremental cost per LY (£)	ICER vs common baseline (£)
Syst. TRUS	3199	–	10.55176	–	–	–
T2-MRI	3206	7	10.55233	0.00057	12,569	12,569
MRS	3256	50	10.55347	0.00115	43,305	33,121
DCE-MRI	3287	31	10.55100	–0.00247	Dominated	Dominated
T2-MRI or MRS	3336	80	10.55420	0.00073	109,800	55,916
T2-MRI or DCE-MRI	3360	25	10.55268	–0.00152	Dominated	175,340

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and LYs are estimated in comparison with the next less costly non-dominated strategy.

TABLE 31 Incremental cost per LY gained from probabilistic analysis (men aged 70 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs	Incremental LYs[a]	Incremental cost per LY (£)	ICER vs common baseline (£)
Syst. TRUS	3187	–	10.54702	–	–	–
T2-MRI	3194	7	10.54748	0.00046	14,696	14,696
MRS	3245	51	10.54854	0.00105	48,305	38,088
DCE-MRI	3275	31	10.54624	–0.00229	Dominated	Dominated
T2-MRI or MRS	3323	78	10.54926	0.00073	107,834	60,716
T2-MRI or DCE-MRI	3346	23	10.54780	–0.00147	Dominated	205,281

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.
a Incremental costs and LYs are estimated in comparison with the next less costly non-dominated strategy.
Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

TABLE 32 Incremental cost per QALY gained from deterministic analysis (men aged 70 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	Incremental cost per QALY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3199	–	9.30639	–	–	–
T2-MRI	**3206**	**7**	**9.30677**	**0.00038**	**18,727**	**18,727**
MRS	3256	50	9.30752	0.00075	65,825	50,010
DCE-MRI	3287	31	9.30590	–0.00162	Dominated	Dominated
T2-MRI or MRS	3336	80	9.30799	0.00047	170,109	85,071
T2-MRI or DCE-MRI	3360	25	9.30699	–0.00100	Dominated	266,423

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.
a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.
Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

TABLE 33 Incremental cost per QALY gained from probabilistic analysis (men aged 70 years; underlying cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	Incremental cost per QALY[a] (£)	ICER vs common baseline (£)
Syst. TRUS	3187	–	9.29963	–	–	–
T2-MRI	**3194**	**7**	**9.29993**	**0.00030**	**22,677**	**22,677**
MRS	3245	51	9.30061	0.00068	74,586	58,798
DCE-MRI	3275	31	9.29914	–0.00147	Dominated	Dominated
T2-MRI or MRS	3323	78	9.30108	0.00047	167,637	93,943
T2-MRI or DCE-MRI	3346	23	9.30013	–0.00095	Dominated	316,854

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.
a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.
Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

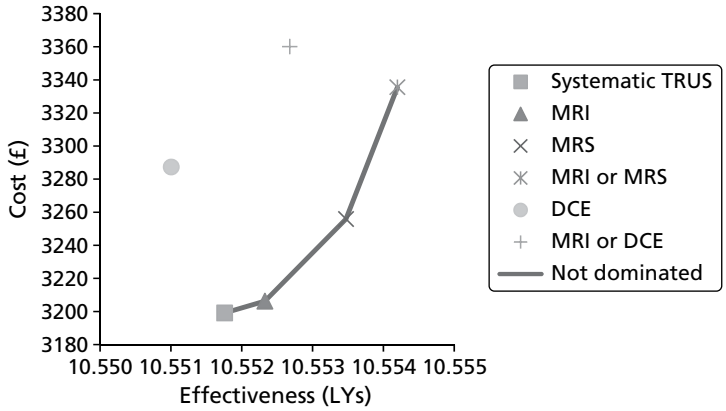


FIGURE 23 Cost-effectiveness frontier based on the cost per LY analysis (men aged 70 years, underlying cancer prevalence 24%).

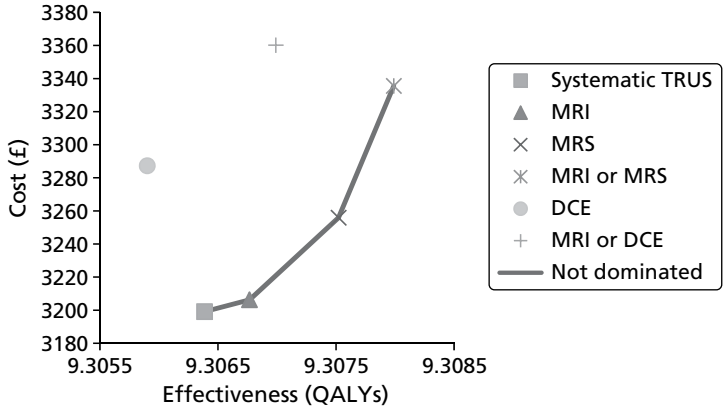


FIGURE 24 Cost-effectiveness frontier based on the cost per QALY analysis (men aged 70 years, underlying cancer prevalence 24%).

QALY findings for a high-prevalence cohort (50%) and low-prevalence cohort (10%) of men aged 60 and 70 years, respectively (assumes patient-level sensitivities not influenced by cancer prevalence). The findings seem to indicate that, for the 60-year-old cohorts (see *Table 34*), the more sensitive, more costly strategies have a higher chance of being considered cost-effective if used to direct biopsies in groups at higher risk of harbouring PC (e.g. men with ASAP on first biopsy). In the lower prevalence cohort, the T2-MRI strategy dominates systematic TRUS/Bx as a result of its specificity taking on greater significance with the underlying cancer prevalence set at only 10%.

A similar pattern of results is observed for the older cohort (see *Table 35*), with the cost-effectiveness of MRS improving relative to systematic TRUS/Bx and T2-MRI in the high-prevalence cohort. However, the ICER for MRS does not drop below £30,000 per QALY in this cohort. Moreover, the cost-effectiveness of T2-MRI rises above £30,000 in this cohort owing to the lower influence of specificity with high cancer prevalence combined with only very small gain in sensitivity with T2-MRI compared with systematic TRUS/Bx. Thus, none of the MRS/MRI sequences appears cost-effective in this older cohort.

For the 70-year-old low-prevalence cohort, the same finding is observed as for the low-prevalence 60-year-old cohort, i.e. T2-MRI dominates systematic TRUS-guided extended-cores biopsy for all.

TABLE 34 Incremental costs per LY and QALY by prevalence subgroup based on deterministic analysis (men aged 60 years)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs/ QALYs	Incremental LYs/QALYs[a]	ICER (£)	ICER vs common baseline (£)
Prevalence 50%; unit of effect LYs						
Syst. TRUS	6372	–	13.82903	–	–	–
T2-MRI	6404	32	13.83091	0.00188	16,929	16,929
MRS	6472	68	13.83486	0.00395	17,086	17,035
DCE-MRI	6477	5	13.82631	–0.00855	Dominated	Dominated
T2-MRI or MRS	6529	58	13.83746	0.00260	22,176	18,620
T2-MRI or DCE-MRI	6537	7	13.83220	–0.00527	Dominated	51,871
Prevalence 50%; unit of effect QALYs						
Syst. TRUS	6372	–	12.06553	–	–	–
T2-MRI	6404	32	12.06683	0.00131	24,402	24,402
MRS	**6472**	**68**	**12.06956**	**0.00273**	**24,757**	**24,642**
DCE-MRI	6477	5	12.06366	–0.00590	Dominated	Dominated
T2-MRI or MRS	6529	58	12.07135	0.00179	32,256	26,981
T2-MRI or DCE-MRI	6537	7	12.06772	–0.00363	Dominated	75,120
Prevalence 10%; unit of effect LYs						
T2-MRI	2555	–	14.35089	–	–	–
Syst. TRUS	2561	6	14.35046	–0.00043	Dominated	Dominated
MRS	2595	40	14.35170	0.00081	48,866	48,866
DCE-MRI	2641	47	14.34997	–0.00173	Dominated	Dominated
T2-MRI or MRS	2686	91	14.35218	0.00048	191,367	101,707
T2-MRI or	2721	35	14.35111	–0.00107	Dominated	756,814
Prevalence 10%; unit of effect QALYs						
T2-MRI	**2555**	**–**	**12.71014**	**–**	**–**	**–**
Syst. TRUS	2561	6	12.70983	–0.00031	Dominated	Dominated
MRS	2595	40	12.71070	0.00056	70,309	70,309
DCE-MRI	2641	47	12.70950	–0.00120	Dominated	Dominated
T2-MRI or MRS	2686	91	12.71102	0.00032	285,797	148,351
T2-MRI or DCE-MRI	2721	35	12.71028	–0.00074	Dominated	1,164,444

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

TABLE 35 Incremental costs per LY and QALY by prevalence subgroup based on deterministic analysis (men aged 70 years)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs/QALYs	Incremental LYs/QALYs[a]	ICER (£)	ICER vs common baseline (£)
Prevalence 50%; unit of effect LYs						
Syst. TRUS	5287	–	10.36606	–	–	–
T2-MRI	5319	32	10.36719	0.00113	28,394	28,394
MRS	5388	68	10.36956	0.00237	28,791	28,662
DCE-MRI	5391	4	10.36444	–0.00512	Dominated	Dominated
T2-MRI or MRS	5446	58	10.37111	0.00155	37,381	31,342
T2-MRI or DCE-MRI	5452	6	10.36796	–0.00315	Dominated	86,624
Prevalence 50%; unit of effect QALYs						
Syst. TRUS	**5287**	**–**	**9.06143**	**–**	**–**	**–**
T2-MRI	5319	32	9.06218	0.00075	42,942	42,942
MRS	5388	68	9.06373	0.00155	43,891	43,583
DCE-MRI	5391	4	9.06037	–0.00336	Dominated	Dominated
T2-MRI or MRS	5446	58	9.06474	0.00101	57,324	47,782
T2-MRI or DCE-MRI	5452	6	9.06268	–0.00207	Dominated	131,943
Prevalence 10%; unit of effect LYs						
T2-MRI	2068	–	10.65202	–	–	–
Syst. TRUS	2075	6	10.65175	–0.00026	Dominated	Dominated
MRS	2108	40	10.65250	0.00049	81,213	81,213
DCE-MRI	2154	46	10.65146	–0.00104	Dominated	Dominated
T2-MRI or MRS	2199	91	10.65278	0.00028	326,605	170,521
T2-MRI or DCE-MRI	2234	35	10.65214	–0.00064	Dominated	1,321,142
Prevalence 10%; unit of effect QALYs						
T2-MRI	**2068**	**–**	**9.43847**	**–**	**–**	**–**
Syst. TRUS	2075	6	9.43829	–0.00018	Dominated	Dominated
MRS	2108	40	9.43879	0.00032	122,508	122,508
DCE-MRI	2154	46	9.43811	–0.00069	Dominated	Dominated
T2-MRI or MRS	2199	91	9.43897	0.00018	522,072	262,608
T2-MRI or DCE-MRI	2234	35	9.43854	–0.00042	Dominated	2,219,778

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

Illustrative analysis incorporating diffusion-weighted-magnetic resonance imaging-directed biopsy

Although the lack of sensitivity/specificity estimates for DW-MRI in repeat biopsy cohorts precluded its incorporation in the base-case analysis, it was still felt to be a relevant alternative based on evidence from other cohorts coupled with its lower cost compared with MRS. As such, an illustrative analysis was undertaken to assess how it would compare in terms of cost-effectiveness if it could be demonstrated to have sensitivity at least equal to that of MRS (92%) and specificity at least equal to that of T2-MRI (55%). *Table 36* presents the cost per QALY findings from this analysis for a 60-year-old cohort.

The findings indicate that if DW-MRI could be shown to achieve this level of diagnostic accuracy then it would be preferred on grounds of cost-effectiveness over MRS in this cohort of patients [see *Table 32* (scenario 1) and *Figure 25*]. Under this scenario, DW-MRI is also borderline cost-effective compared with T2-MRI (incremental cost per QALY gained: £30,298).

When the sensitivities of DW-MRI and MRS are adjusted by cancer grade so that all false-negatives arising with these strategies occur in patients with low-risk cancer – to reflect the observation from other cohorts that MRS and DW-MRI positivity is highly correlated with tumour Gleason score – the ICER for DW-MRI compared with MRI falls to £18,260 [see *Table 32* (scenario 2) and *Figure 26*], i.e. below the £20,000–£30,000 per QALY range often used to make judgements on cost-effectiveness. This analysis gives an

TABLE 36 Cost-effectiveness of scenarios incorporating DW-MRI based on deterministic analysis (unit of outcome QALYs)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	Incremental cost per QALY (£)[a]	ICER vs common baseline (£)
Scenario 1. DW-MRI incorporated assuming sensitivity 0.92/specificity 0.55						
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	**3902**	**7**	**12.48498**	**0.00066**	**10,626**	**10,626**
DW-MRI	3943	41	12.48629	0.00130	31,061	24,221
MRS	3952	9	12.48630	0.00002	529,885[b]	28,502
DCE-MRI	3984	32	12.48346	–0.00285	Dominated	Dominated
T2-MRI or MRS	4031	88	12.48714	0.00085	104,032	48,367
T2-MRI or DCE-MRI	4056	25	12.48538	–0.00175	Dominated	152,323
Scenario 2. DW-MRI incorporated assuming sensitivity 0.92/specificity 0.55 (and that all false-negatives with DW-MRI and MRS occur in individuals with low-risk cancer)						
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	3902	7	12.48498	0.00066	10,626	10,626
DW-MRI	**3947**	**45**	**12.48734**	**0.00236**	**19,008**	**17,186**
MRS	3956	9	12.48736	0.00002	529,885	20,013
DCE-MRI	3984	28	12.48346	–0.00390	Dominated	Dominated
T2-MRI or MRS	4031	75	12.48714	–0.00023	–334,729	48,367
T2-MRI or DCE-MRI	4056	100	12.48538	–0.00198	Dominated	152,323

–, common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

b Strategy dominated by combinations of other strategies.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

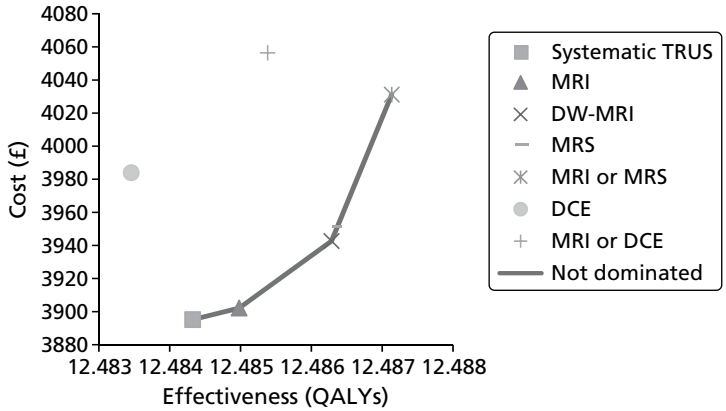


FIGURE 25 Comparison with DW-MRI included (assuming 92% sensitivity, 55% specificity).

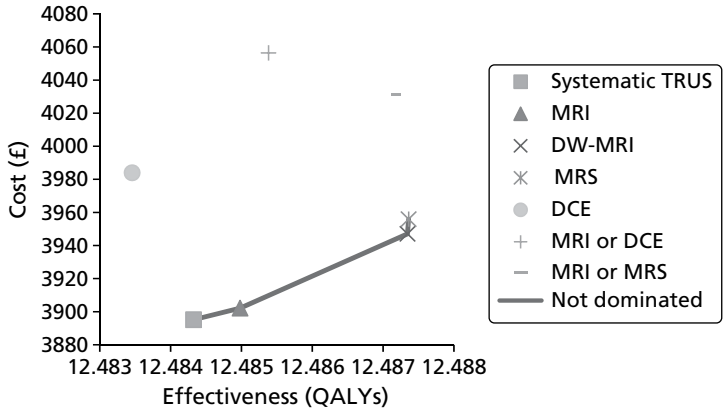


FIGURE 26 Comparison with DW-MRI included (assuming 92% sensitivity, 55% specificity, and that DW-MRI and MRS miss only low-risk cancers).

indication of sensitivity/specificity requirements for DW-MRI to be considered cost-effective for directing biopsies (holding all other model parameters constant at base-case values).

Deterministic sensitivity analysis scenarios (60-year-old cohort)

Several deterministic analyses were carried out to assess the sensitivity of the base-case cost per QALY findings to assumptions surrounding the incorporation of health-state utilities. We assessed the impact of applying a utility decrement of 0.035 (half of the disutility associated with having moderate anxiety rather than no anxiety on the EQ-5D) to patients with undiagnosed cancer, to reflect potential disutility resulting from raised anxiety associated with having a high PSA but no diagnosis. Further, we tested a multiplicative utility model whereby utility levels for diagnosed cancer states were set equal to the product of the cancer state utility and the utility of any treatment complications experienced. Finally, we assessed the impact of applying both of these modifications simultaneously. These deterministic sensitivity analyses were carried out only for the 60-year-old cohort, owing to there being a higher likelihood of changes to base-case assumptions affecting the cost-effectiveness of strategies in this group.

Table 37 shows the cost per QALY findings to be highly sensitive to these alterations. Under the first adjustment (utility decrement associated with undiagnosed cancer), the cost-effectiveness of MRS compared with T2-MRI improves substantially. However, applying the multiplicative model to further adjust utility for complications associated with radical treatment results in all of the MRS/MRI sequences having unfavourable incremental cost per QALY ratios in comparison with the less-sensitive systematic TRUS.

TABLE 37 Sensitivity of cost per QALY findings to health-state utility assumptions

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 1. Additional utility decrement for persistently elevated PSA without a diagnosis						
Syst. TRUS	3895	–	12.47968	–	–	–
T2-MRI	3902	7	12.48059	0.000914	7633	7633
MRS	**3952**	**49**	**12.48246**	**0.001873**	**26,373**	**20,229**
DCE-MRI	3984	32	12.47842	–0.00404	Dominated	Dominated
T2-MRI or MRS	4031	80	12.48366	0.001201	66,262	34,098
T2-MRI or DCE-MRI	4056	25	12.48118	–0.00249	Dominated	107,510
Scenario 2. Multiplicative model to further adjust for adverse treatment effects						
Syst. TRUS	**3895**	**–**	**12.32446**	**–**	**–**	**–**
T2-MRI	3902	7	12.32466	0.000202	34,521	34,521
MRS	3952	49	12.32501	0.000348	141,776	102,408
DCE-MRI	3984	32	12.32427	–0.00074	Dominated	Dominated
T2-MRI or MRS	4031	80	12.32519	0.000185	429,592	184,823
T2-MRI or DCE-MRI	4056	25	12.32474	–0.00046	Dominated	575,872
Scenario 3. Combination of scenarios 1 and 2						
Syst. TRUS	3895	–	12.31981	–	–	–
T2-MRI	**3902**	**7**	**12.32027**	**0.00046**	**15,182**	**15,182**
MRS	3952	49	12.32117	0.00090	54,886	41,468
DCE-MRI	3984	32	12.31923	–0.00193	Dominated	Dominated
T2-MRI or MRS	4031	80	12.32172	0.00055	143,966	71,109
T2-MRI or DCE-MRI	4056	25	12.32053	–0.00119	Dominated	223,564

Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy (common baseline).

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

Applying both changes simultaneously (see *Table 37*, scenario 3) results in a pattern of findings more in keeping with the base-case analysis.

Further deterministic scenario analyses

The process of populating the model required a number of parameter and structural assumptions. To further assess the influence of these assumptions on findings, the following deterministic sensitivity analyses were undertaken:

1. Costs adjusted such that pathology costs for TRUS/Bx are increased by £86 to reflect a 25-minute increase in pathologist time for biopsies involving more than 10 cores, and MRI costs are adjusted to the NHS reference costs.
2. Sensitivity of MRS adjusted so that it misses only low-risk localised disease.
3. Comparator for MRS/MRI assumed to be a standard TRUS/Bx (10–12 cores) with sensitivity 60% (the lowest estimated sensitivity value obtained for systematic TRUS/Bx from studies assessed for inclusion in the systematic review) (see *Appendix 11*).

4. Application of the sensitivity/specificity estimates obtained from the indirect comparison (see *Appendix 13.10*).
5. Assumed a 14-core TRUS/Bx is £86 more costly than a MRI-/MRS-directed biopsy, and £112 more costly than obtaining a MRS scan.
6. Assumed that MRI-/MRS-directed biopsy reduces the risk of biopsy complications by 50% because fewer cores are obtained per patient.
7. Subsequent repeat biopsies (i.e. following a first repeat biopsy) have 95% sensitivity with 80% uptake (repeat offered every 12 months for those remaining with undiagnosed cancer).
8. Application of lower discount rate for health benefits (1.5% for QALYs vs 3.5% for costs).
9. Application of lower baseline risks of progression and less significant diagnosis treatment effects, based on new trial evidence on the effect of radical prostatectomy compared with watchful waiting.[149]
10. Assumed all patients who are negative on MRI proceed with an extended 14-core TRUS biopsy.

Table 38 presents the results of these scenarios using QALYs as the unit of outcome. *Appendix 17, Table 43,* presents the results for these same scenarios using LYs as the unit of outcome.

These analyses demonstrate that T2-MRI-directed biopsy dominates systematic TRUS/Bx under several scenarios; specifically, when the sensitivity and specificity of T2-MRI are set equal to the values obtained from the indirect comparison (see *Table 38*, scenario 3), and when it is assumed that T2-MRI direction reduces the cost of the subsequent biopsy procedure relative to the cost of an extended-cores biopsy (scenario 4). The ICER for MRS compared with systematic TRUS also remains at < £30,000 for most scenarios. The cost-effectiveness of MRS compared with T2-MRI appears less sensitive to scenarios presented in *Table 38*. The ICER for MRS-directed biopsy (relative to T2-MRI) falls below £30,000 when (1) the cost of all biopsies is increased (scenario 1); (2) when it is assumed that MRS misses only low-risk cancer (scenario 2); and (3) when the discount rate applied to health benefits is reduced to 1.5% (scenario 7). Although increasing the costs of systematic extended-cores TRUS/Bx (but not MRI-/MRS-directed TRUS/Bx) results in both T2-MRI and MRS being more effective and less costly than systematic TRUS/Bx, this specific scenario has little impact on the comparison between MRS and T2-MRI. Application of the sensitivity/specificity estimates obtained from the indirect comparison also undermines the cost-effectiveness of MRS in relation to T2-MRI, owing to a substantial decline in the specificity of MRS.

The application of lower relative diagnosis/treatment effects and lower baseline cancer progression rates (scenario 8) undermine the cost-effectiveness of MRS compared with T2-MRI and systematic TRUS/Bx. The incremental cost per QALY gained with the most sensitive imaging strategy (positive on either T2-MRI or MRS) does not fall below £30,000 for any of the scenarios assessed. Further, none of the MRI strategies compares very favourably in terms of cost-effectiveness when it is assumed that all patients who are negative on MRI proceed to an extended-cores TRUS/Bx regardless (scenario 9).

In addition to the scenarios presented in *Table 38*, threshold analysis would suggests that MRS would dominate systematic extended-cores TRUS/Bx in contexts where the cost saving per biopsy averted is ≥ ~£115 more than the cost of obtaining the MRS sequences to determine whether or not a biopsy should proceed.

Probabilistic sensitivity analysis

To assess the impact of joint uncertainty surrounding all model parameters and inputs, appropriate distributions were assigned and randomly sampled for each of 1000 iterations of the base-case analysis. The results were used to estimate the probability of each diagnostic strategy being preferred on grounds of cost-effectiveness for different values of decision-makers' willingness to pay for a QALY. The resultant CEAC is displayed in *Figure 27*. The results indicate that under base-case parameter values and assumptions, none of the strategies demonstrates a high probability of being the preferred option at the threshold value of £30,000 per QALY gained. The cost-effectiveness acceptability frontier (*Figure 28*) displays the probability of the strategy with the highest NMB, at different values of decision-makers' willingness to pay per QALY gained, being cost-effective. At a threshold ratio of £30,000 per QALY, T2-MRI provides the

TABLE 38 Deterministic sensitivity analysis scenarios using QALYs as unit of outcome (men aged 60 years; cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 1. Biopsy costs inflated to account for additional pathology time associated with more than 10 cores; MRS/MRI costs also adjusted to the NHS reference costs						
Syst. TRUS	4018	–	12.48432	–	–	–
T2-MRI	4024	7	12.48498	0.00066	10,271	10,271
MRS	**4060**	**35**	**12.48630**	**0.00132**	**26,848**	**21,347**
DCE-MRI	4108	49	12.48346	–0.00285	Dominated	Dominated
T2-MRI or MRS	4169	109	12.48714	0.00083	130,497	53,719
T2-MRI or DCE-MRI	4205	37	12.48538	–0.00175	Dominated	177,295
Scenario 2. Sensitivity of MRS adjusted to miss only low-grade cancer						
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	3902	7	12.48498	0.000656	10,626	10,626
MRS	**3956**	**54**	**12.48736**	**0.00238**	**22,602**	**20,013**
DCE-MRI	3984	28	12.48346	–0.0039	Dominated	Dominated
T2-MRI or MRS	4031	75	12.48714	–0.00023	Dominated	48,367
T2-MRI or DCE-MRI	4056	100	12.48538	–0.00198	Dominated	152,323
Scenario 3. Sensitivity of comparator reduced to 60%						
Syst. TRUS	3882	–	12.47825	–	–	–
T2-MRI	**3899**	**16**	**12.48395**	**0.00571**	**2858**	**2858**
MRS	3948	49	12.48527	0.00132	37,399	9353
DCE-MRI	3981	32	12.48243	–0.00285	Dominated	23,455
T2-MRI or MRS	4028	80	12.48611	0.00083	95,498	18,490
T2-MRI or DCE-MRI	4053	25	12.48435	–0.00175	Dominated	27,926
Scenario 4. Application of sensitivity/specificity estimates obtained from the indirect comparison (T2-MRI sensitivity 0.84/specificity 0.58; MRS sensitivity 0.92/specificity 0.65)						
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	**3895**	**0**	**12.48455**	**0.00022**	**240**	**240**
MRS	3970	75	12.48629	0.00175	42,903	38,052
DCE-MRI	3986	16	12.48346	–0.00284	Dominated	Dominated
T2-MRI or MRS	4029	59	12.48735	0.00106	55,218	44,066
T2-MRI or DCE-MRI	4052	23	12.48669	–0.00066	Dominated	66,176

continued

TABLE 38 Deterministic sensitivity analysis scenarios using QALYs as unit of outcome (men aged 60 years; cancer prevalence 24%) (*continued*)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 5. Biopsy costs uplifted for systematic TRUS (assumes 14-core TRUS biopsy is £86 more costly than MRI-/MRS-directed biopsy, and £112 more costly than MRS)						
T2-MRI	**3907**	**–**	**12.48498**	**–**	**–**	**–**
MRS	3955	48	12.48630	0.00132	36,200	36,200
DCE-MRI	3991	36	12.48346	–0.00285	Dominated	Dominated
Syst. TRUS	3991	36	12.48432	–0.00198	Dominated	Dominated
T2-MRI or MRS	4034	79	12.48714	0.00083	94,233	58,653
T2-MRI or DCE-MRI	4061	27	12.48538	–0.00175	Dominated	£382,270
Scenario 6. MRI reduces the risk of biopsy complications by 50%						
Syst. TRUS	3895	–	12.48432	–	–	–
T2-MRI	**3899**	**4**	**12.48501**	**0.00068**	**6063**	**6063**
MRS	3949	50	12.48632	0.00131	38,173	27,182
DCE-MRI	3981	32	12.48348	–0.00284	Dominated	Dominated
T2-MRI or MRS	4027	78	12.48717	0.00085	91,288	46,354
T2-MRI or DCE-MRI	4052	25	12.48543	–0.00175	Dominated	142,198
Scenario 7. Subsequent repeat biopsy offers have 80% uptake (repeat offer every 12 months for those remaining with undiagnosed cancer)						
Syst. TRUS	3888	–	12.483	–	–	–
T2-MRI	**3895**	**8**	**12.48377**	**0.00077**	**9753**	**9753**
MRS	3946	51	12.48534	0.00157	32,261	24,839
DCE-MRI	3976	30	12.48196	–0.00338	Dominated	Dominated
T2-MRI or MRS	4026	80	12.48634	0.00100	80,567	41,506
T2-MRI or DCE-MRI	4050	24	12.48425	–0.00208	Dominated	129,183
Scenario 8. QALYs discounted at 1.5% per annum						
Syst. TRUS	3895	–	15.13056	–	–	–
T2-MRI	**3902**	**7**	**15.13138**	**0.000815**	**8553**	**8553**
MRS	3952	49	15.13302	0.001643	30,052	22,923
DCE-MRI	3984	32	15.12948	–0.00354	Dominated	Dominated
T2-MRI or MRS	4031	80	15.13406	0.001038	76,676	38,882
T2-MRI or DCE-MRI	4056	25	15.13188	–0.00218	Dominated	122,465
Scenario 9. Disease progression calibrated to PC mortality rates observed in the PIVOT trial[149]						
Syst. TRUS	3751	–	12.57939	–	–	–
T2-MRI	**3758**	**7**	**12.57969**	**0.000303**	**23,054**	**23,054**
MRS	3808	49	12.58026	0.000563	87,749	65,132
DCE-MRI	3840	32	12.57906	–0.0012	Dominated	Dominated
T2-MRI or MRS	3887	80	12.58059	0.000328	242,585	113,923
T2-MRI or DCE-MRI	3913	25	12.57984	–0.00074	Dominated	356,787

TABLE 38 Deterministic sensitivity analysis scenarios using QALYs as unit of outcome (men aged 60 years; cancer prevalence 24%) (*continued*)

Strategy	Average cost (£)	Incremental cost[a] (£)	Average QALYs	Incremental QALYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 10. Use extended-cores biopsy for all patients negative on MRS/MRI						
Syst. TRUS	**3895**	–	**12.48432**	–	–	–
T2-MRI	4007	112	12.48747	0.003144	35,561	35,561
MRS	4087	80	12.48769	0.000219	362,957[b]	56,913
DCE-MRI	4087	80	12.48783	0.000366	218,506	54,618
T2-MRI or MRS	4090	3	12.48721	–0.00062	Dominated	67,370
T2-MRI or DCE-MRI	4090	3	12.48754	–0.00029	Dominated	60,667

– common baseline; Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and QALYs are estimated in comparison with the next less costly non-dominated strategy.

b Strategy dominated by combinations of other strategies.

Note: bold text denotes the strategy with the highest NMB at a ceiling willingness-to-pay ratio of £30,000 per QALY.

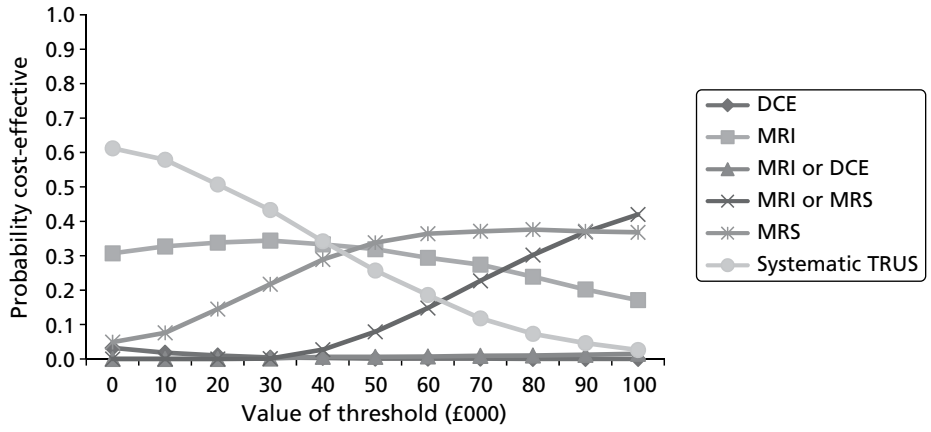


FIGURE 27 Cost-effectiveness acceptability curves under base-case assumptions.

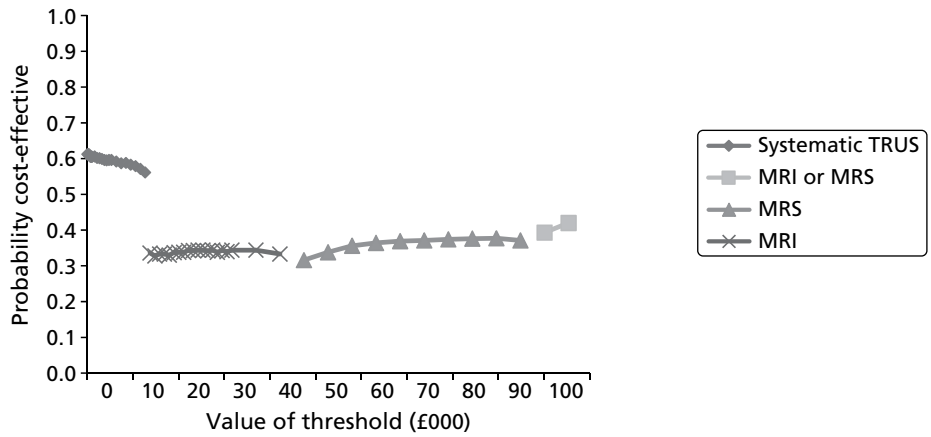


FIGURE 28 Cost-effectiveness acceptability frontier under base-case assumptions.

option with the highest NMB but with only a 34% probability. The expected value of perfect information at this threshold (i.e. of eliminating uncertainty) is £27.30 per patient.

In order to assess the sensitivity of the probabilistic analysis findings to several base-case assumptions, the analysis was repeated with the biopsy costs inflated to account for the possibility of higher pathology time requirements and the MRS/MRI costs were adjusted to the reference cost for direct access DCE-MRI (see *Table 38*, scenario 1). Further, DW-MRI was incorporated under the assumption that it could achieve sensitivity equal to that of MRS and specificity equal to that of T2-MRI. In addition, it was assumed that MRS and DW-MRI would miss only low-risk cancer (see *Table 38*, scenario 2). Under this specification, there is 74% probability of either DW-MRI or MRS being cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained (*Figure 29*). MRS in fact retains the higher probability of being cost-effective in this scenario because, with biopsy costs set at a higher level, the superior specificity of MRS (over the assumed specificity of DW-MRI, which was set at 55% purely for illustrative purposes) outweighs the additional cost of running the sequence.

Discussion

Summary of key results

The results of the deterministic economic modelling suggest that, when considering LYs as the unit of outcome, the use of T2-MRI, to determine and direct biopsies, may be cost-effective in comparison with systematic TRUS-guided extended-cores biopsy. This results from its modest implementation cost and slightly improved sensitivity over systematic extended-cores TRUS/Bx (14–16 cores). At the same time its specificity would suggest that it could avert the need for 55% of patients without cancer having to undergo a biopsy. The base-case incremental cost per QALY estimates for the more sensitive enhanced MRS/MRI techniques are somewhat less favourable (i.e. are > £30,000 per QALY gained in comparison with the next less costly option). However, the ICER for MRS compared with T2-MRI does fall below £30,000 in the high-prevalence (50%) 60-year-old cohort. In the lower-prevalence (10%) cohorts, T2-MRI was found to dominate systematic TRUS/Bx (i.e. be less costly and more effective) owing to its specificity, resulting in more biopsies being averted in this group.

Moreover, the deterministic sensitivity analysis shows the cost-effectiveness of MRS compared with T2-MRI (and systematic TRUS/Bx) to be particularly sensitive to two key parameters. The ICER for MRS falls below £30,000 when (1) the cost of biopsies is increased to £298 and (2) when MRS is modelled to detect all moderate- and high-risk cancer (only missing low-risk disease). The latter assumption is in keeping with data from case series, which suggest high levels of correlation between MRS positivity and tumour Gleason scores.[52,54] The cost-effectiveness of MRS also improves considerably when the accuracy of and compliance with subsequent repeat biopsies decreases. Thus, our findings would suggest that the use of MRS may well

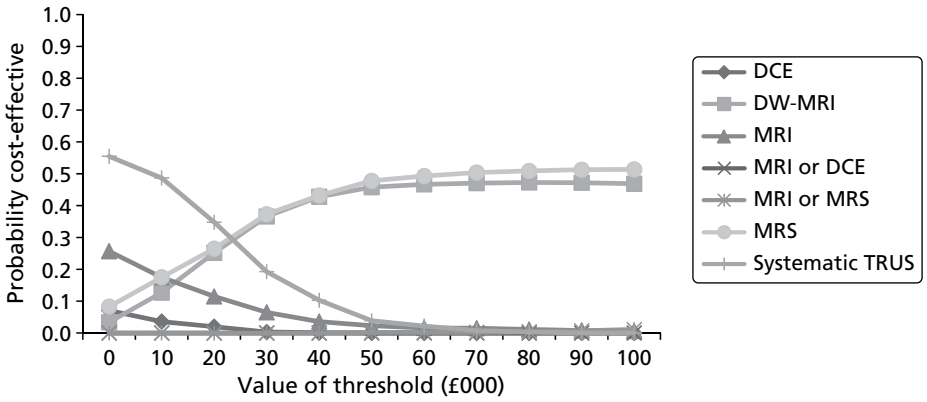


FIGURE 29 Cost-effectiveness acceptability curves, assuming DW-MRI has sensitivity equal to that of MRS and specificity equal to that of T2-MRI, and that MRS and DW-MRI miss only low-risk cancer.

be cost-effective in certain contexts, for example in settings where the cost of TRUS/Bx exceeds the cost of obtaining a MRS sequence by ~£115. It is likely that practice and costs will vary substantially locally.

Unfortunately, there were insufficient data on the diagnostic accuracy of DW-MRI in the population of interest, and as such we did not include it as a comparator in the base-case analysis. With its lower cost in comparison with MRS, our modelling suggests it could represent a cost-effective approach if it could be shown to have sensitivity similar to that of MRS and specificity similar to that of T2-MRI. At these levels of sensitivity/specificity, however, it might also need to be able to discriminate between low-risk and moderate/high-risk disease (so that false-negatives would be concentrated in the low-risk cases) to be cost-effective in comparison with T2-MRI alone. Evidence from other case series suggest it may be able to do this.[169,170]

By the same token, changes to some of the model assumptions also undermine the cost-effectiveness of strategies that improve cancer detection rates at increased costs over standard practice and T2-MRI. These include reductions in the baseline risk of disease progression and reductions in the relative risk reductions associated with diagnosis and treatment.

Considering the probabilistic sensitivity analysis, when parameter distributions are centred on the base-case point estimates and all of the strategies are compared simultaneously, none of the strategies achieves a high probability of being preferred on grounds of cost-effectiveness (see *Figure 27*) at the threshold ceiling ratio of £30,000 per QALY gained. Although the point estimate of the ICER of T2-MRI compared with systematic TRUS/Bx is favourable, its probability of being cost-effective at £30,000 per QALY is only ~60% in comparison with TRUS/Bx and only 34% considering all strategies simultaneously (see *Figure 28*).

However, *Figure 29* demonstrates how the uncertainty surrounding the relative cost-effectiveness of strategies reduces if the average cost of biopsies is increased to £300 (the upper quartile reference cost reported for biopsies carried out in an outpatient setting) and MRS and DW-MRI are modelled to miss low-risk cancer only. Under this alternative model specification, the choice between strategies becomes one between MRS and DW-MRI above a willingness-to-pay threshold of ~£20,000 per QALY gained. Note this still assumes disease progression rates and relative diagnosis/treatment effects in line with Bill-Axelson *et al*.[148]

Generalisability of results

In developing the model we have attempted to use data applicable to the UK setting as far as possible. However, many of the data on disease progression and relative treatment effects were derived from a European cohort identified in the pre-PSA era.[148] Although we have tried as far as possible to model the risk of progression by clinical grade (low, intermediate, high), it is possible that the progression rates observed for low-risk patients in this pre-PSA cohort are higher than would be observed for low-risk patients identified in clinical practice in the UK today. This is potentially important as reducing progression rates and treatment effects for low-risk patients reduces the cost-effectiveness of more sensitive and more costly diagnostic strategies, and further emphasises the potential importance of further research to assess the sensitivity of alternative imaging sequences by tumour grade in cohorts of patients undergoing biopsy. The ongoing PROMIS trial may help address this question.[171]

The modelling also relied on health-state utility data from a number of sources outwith the UK. Attempts were made to identify EQ-5D data from UK cohorts for the modelled states and treatment complications of interest, but limited data were identified. A decision was made to use the EQ-5D utilities observed for a European cohort post diagnosis and at varying time points post treatment with radical prostatectomy or EBRT. As these average utilities were obtained from cohorts with proportions experiencing complications, we chose not to further adjust utility for modelled treatment complications in the base-case analysis. Given a lack of EQ-5D-based utility estimates for metastatic and castration resistant metastatic disease, for men modelled to progress to metastatic disease we applied the average time trade-off values elicited for these states from a sample of US men.[166]

Although there is uncertainty surrounding the wider applicability of some of the progression rates, treatment effects and utility values applied in the model, the cost inputs were based on the estimation of resource use in UK settings according to current guidelines. National average unit costs were applied to resource-use estimates wherever possible, making individual cost inputs generalisable across the UK. However, there is uncertainty as to how hospitals are reimbursed for TRUS-guided biopsies at the local level and also the true opportunity cost of TRUS/Bx compared with that of running MRS/MRI sequences. It would be useful if future prospective studies could estimate these more accurately using patient-level data.

Strengths and limitations of the analysis

Strengths

Attempts have been made to use the best available evidence to model both the diagnostic pathways and subsequent treatment pathways and outcomes. The model provides a flexible framework allowing the comparison of many different diagnostic strategies in the context of the patient's lifetime. It captures the trade-off between the increased upfront costs of imaging and the reduction in subsequent biopsies, and also the trade-off between earlier diagnosis and potential utility decrements associated with treatment side-effects. Further, the model is risk stratified to allow for comparison of strategies that vary in their ability to differentiate between tumours of different stage and grade. The model can easily be updated to incorporate new, more detailed evidence as it becomes available.

Limitations

The modelling was hampered by limited availability of data on the diagnostic accuracy of alternative diagnostic strategies, comparable cost estimates for alternative procedures, the natural history of cancer detected at repeat biopsy, and also the impact of diagnosis and treatment on disease progression.

The systematic review uncovered limited data on the relative sensitivity (cancer detection rates) of MRI-/MRS-targeted biopsy techniques and systematic TRUS-guided approaches. In particular, there were no identified studies providing head-to-head comparisons of MRI-/MRS-targeted approaches and systematic sampling schemes based on different numbers of cores. Further, it was not possible to obtain pooled estimates for the sensitivity/specificity of alternative MRS/MRI sequences by grade of tumour, which is potentially an important parameter for informing cost-effectiveness. There is therefore a need for a large comparative study assessing the sensitivity of systematic approaches and MRS/MRI sequences for detecting cancer by D'Amico risk strata.

A high degree of uncertainty also exists regarding the impact of a false-negative result at repeat biopsy on the time to final diagnosis, and also on the impact of any delay on disease progression. The base-case analysis relied on the assumption that all patients experience a relative risk reduction for progression to metastatic disease upon referral, but recent data suggest that risk reductions associated with radical treatment for low-risk patients (and even moderate-risk patients) may be small and insignificant.[149] If this is the case it will undermine the cost-effectiveness of strategies that increase cancer detection rates over standard practice.

The more sensitive and more costly enhanced imaging techniques were found to be associated with small cost increases, for even smaller survival and QALY gains compared with T2-MRI and systematic TRUS/Bx. This results in the incremental cost per QALY ratios being very sensitive to the baseline risks of progression and relative treatment effects. Recent data suggest that the underlying risk of progression for low-risk cancer, identified in the PSA era, may be lower than reported for the low-risk subgroup identified by Bill-Axelson *et al.*[148] However, the above point also highlights the potential benefit of utilising a pre-biopsy imaging test that could differentiate between low-, moderate- and high-risk cancer, so that only those patients in the latter categories could be targeted for biopsy. Our modelling suggests that if DW-MRI or MRS could be shown to provide such discrimination in the cohort of patients with elevated PSA but previously negative biopsy, these tests could achieve levels of cost-effectiveness considered acceptable.

More detailed studies are required to assess the diagnostic accuracy of different sequences by stage/grade of cancer in order to address this question.

Finally, a further issue contributing to the uncertainty surrounding the cost-effectiveness of alternative diagnostic approaches, and indeed the cost-effectiveness of radical treatment,[9] is the impact of treatment on health-related QoL. In our base-case specification we have applied utility values that suggest that radical treatment complications do not impact heavily on health-related QoL as measured by the EQ-5D.[163] However, the incremental cost per QALY findings are highly sensitive to changes to the applied utility assumptions. When health-state utilities are adjusted downwards for those patients experiencing treatment complications, the cost-effectiveness of strategies that improve cancer detection rates decreases substantially. This highlights the potential importance of risk stratifying treatment appropriately, so that only those patients likely to experience a significant survival benefit receive radical treatments. However, current data suggest that a substantial proportion of low-risk patients still elect for radical treatment, which undermines the cost-effectiveness of diagnostic strategies that result in more low-risk patients being diagnosed.

Summary/conclusions

To summarise, the level of uncertainty surrounding model inputs and structural assumptions makes it difficult to arrive at a definitive conclusion on the cost-effectiveness of using MRS/MRI techniques to aid the localisation of prostate abnormalities for biopsy. However, our modelling shows that under certain circumstances T2-MRI may be considered cost-effective in comparison with TRUS/Bx, and if MRS and DW-MRI can be shown to have high sensitivity for picking up moderate/high-risk cancer, while negating the need for patients with no cancer or low-risk disease to undergo biopsy, then their use could represent a cost-effective approach to diagnosis. Data from subgroup analysis would also suggest that the use of more sensitive and more expensive sequences is more likely to be cost-effective in subgroups of patients who are more likely to be harbouring cancer. Future research should focus on generating comparable estimates of (1) the sensitivity of MRI-/MRS-directed and systematic approaches to TRUS/Bx; (2) the sensitivity/specificity of MRS/MRI sequences for detecting different grades of localised disease in the repeat biopsy cohort; and (3) the full economic costs of MRI sequences and systematic approaches to TRUS/Bx based on different numbers of cores.

Chapter 6 Assessment of factors relevant to the NHS and other parties

The introduction of MRS and other MRI techniques (T2-MRI, DCE-MRI, DW-MRI) for evaluation of men with a TRUS-guided negative biopsy but in whom there remains suspicion of cancer would have a range of implications for the NHS, patients and other parties. These arise primarily because of a shift in the test–treatment pathway for this group. This shift is caused by changes in the method of making the diagnosis and changes the options and timings of treatments, complications and outcomes of patients. There are consequential effects on service delivery, health-care professionals and wider society.

Factors relevant to the NHS

Increased sensitivity and specificity of the diagnostic pathway would lead to more patients being correctly diagnosed with PC and diagnosed at an earlier stage and fewer patients wrongly diagnosed as having no cancer. This would result in a shift in the numbers and stages of patients diagnosed with PC. For the NHS this change in distribution of disease would have implications for service configuration, cost and training.

Service reconfiguration, including the purchase of high-end MRI scanners, would be needed to ensure that radiology departments have sufficient capacity and the means to offer high-quality MRI testing within adequate timescales. Local diagnostic pathways would require updating to ensure compliance with national targets because of the persistent suspicion of undiagnosed cancers in these subjects. Occasional local disruptions may occur if MRI equipment suffers technical failures although most scanners have up-times of >95%.

The requirements of urological and/or radiological services to undertake targeted biopsies of MRS/MRI-suspicious regions will reduce the number of patients undergoing repeat biopsies. However, there would need to be extra provision for undertaking targeted biopsies, whether MRS/MRI guided (within MRI scanners under direct visualisation as an outpatient procedure) or MRI/MRS directed (outside MRI scanner using MRS/MRI information fused to ultrasound images). The latter could be undertaken as outpatient procedures if only a few targeted biopsies were undertaken (per rectally) or an inpatient procedure if the template transperineal route was chosen. MRI-/MRS-targeted or -directed biopsy will require the purchase of a new generation of hardware equipment and software to enable accurate biopsies to be obtained from all regions of the prostate (particularly from commonly missed anterioapical areas). This equipment is capable of operating within MRI scanners or can be used for biopsy via the transperineal or transrectal routes and is beginning to appear in the marketplace. In the future, the move towards targeted biopsy may reduce the number of biopsy cores taken per biopsy session (approximately two to five cores per session) and this will likely result in cost savings especially when compared with saturation or template biopsies (often 20–30 cores per session).

Earlier positive diagnosis of patients who would also be more accurately staged and whose risk stratification was more definitively known would have the benefit of them being appropriately triaged to several therapy options. It is likely that MRS/MRI will identify more patients with localised disease with intermediate and high risk of progression and this would increase the number of patients who would be eligible for radical therapies (including prostatectomy, brachytherapy and external beam therapy). Therefore, surgical and radiation therapy services may require more resources. Furthermore, MRI would provide more accurate preoperative imaging, which may alter the type of radical therapy being undertaken (e.g. the decision to resect or preserve neurovascular bundles at surgery). Preoperative imaging might prevent positive resection margins around large tumours and might also prevent unnecessary morbidity by predicting the preservation of neurovascular bundles if cancer foci locations permitted this. MRS/MRI

may identify fewer patients with low risk of progression, which would help the problem of over-diagnosis of indolent PCs. More accurate and confident diagnoses of patients with low risk of progression disease will increase the proportion of patients likely to undergo 'active surveillance' programmes. This would have implications for the follow-up of these patients including increased utilisation of repeated PSA-testing, repeated interval biopsies and follow-up clinics (much of this work could be nurse practitioner led). Taken together, earlier, more accurate diagnoses and treatment of PC may improve survival and reduce the requirements on end-of-life and palliative care services.

There will be *cost* implications of these service reconfigurations and for changes in treatment patterns mentioned above. There will be significant cost implications for procuring and maintaining new MRI equipment. Although some centres may already have access to the high-end equipment required for this purpose, other centres may have to upgrade, purchase or rent new equipment because of access considerations. There are several other costs associated with implementing MRI testing, which are outlined in the cost-effectiveness chapter.

Implementation would result in the need for further *training* for radiology staff. Radiographers and radiologists would require additional training to ensure adequate technical skills for performing these tests and diagnostic skills to read the MRS/MRI scans. There is a learning curve effect for all staff when more sophisticated MRS/MRI techniques are being implemented; this is particularly true for MRS and DCE-MRI. Adequate quality control and quality assurance programmes would be needed in order to maintain high standards of data acquisition and reporting. However, these new skills and equipment would be transferable for future use in other PC subgroups (e.g. staging of known PC, therapy planning and suspected relapsed disease), and to other pathologies for which MRS/MRI are known to be useful.

Factors relevant to patients and other parties

Many men find themselves in the difficult situation of having a persistently raised serum PSA level but a negative biopsy. They and their physicians know that there is a substantial risk of an undiagnosed, perhaps life-threatening, PC that has not yet been found and as a consequence cannot be treated. This can cause anxiety for patients and their family. The anxiety and stress may substantially reduce an individual's QoL with many men seeking clarity about their status in order to be able to move forward. Increased certainty of diagnosis influences an individual's decision-making about life choices, such as employment, insurance and family issues. Any test that improves the diagnostic certainty in this group of men may reduce anxiety. Additionally, patients may feel more reassured if they have different tests that point to the same diagnosis. Although earlier diagnosis may reduce the anxiety of uncertainty, it may also cause psychological harm if effective treatments are unavailable or if the discovered cancer is indolent and unlikely to cause health deterioration over the course of an individual's life. DW-MRI and MRS may be better at detecting intermediate and high risk of progression cancers, which may have a positive effect in this regard. Active surveillance programmes for patients with indolent cancer types can have high dropout rates, partly because many patients find it difficult to have a diagnosis of cancer without commencing disease-limiting or curative treatment. If more evidence were to become available that allowed the discrimination between low-risk/less aggressive cancer and intermediate- and high-risk cancer, then urologists would not need to treat asymptomatic men with clinically insignificant cancer, curing them from a disease that might never have harmed them, with collateral morbidity as a result. Perhaps over time clinically insignificant PC may also come to be more accepted by the patient.

Magnetic resonance imaging techniques may reduce the number of patients undergoing several repeat biopsies, avoiding the discomfort, side effects and possible complications of this. Patients who have chosen not to undergo repeat biopsy, because of the unpleasantness of the procedure, may find MRI investigation more acceptable. However, some patients who suffer from claustrophobia may find MRI more unacceptable than repeat biopsy. Patient refusal to undergo MRI scanning is likely to decrease in the future

with the increasing availability of wider, short-bore scanners. MRI cannot always be used in patients who have metallic foreign objects in their bodies or in those with implanted non-MRI compatible pacemakers.

Patients and carers may need to travel further to access appropriate MRI testing in scanners that have the appropriate high levels of sophistication capable of performing high-quality MRS/MRI (T2-MRI, DW-MRI and DCE-MRI) examinations. Inequalities in access may arise as services undergo reconfiguration at different rates, depending on pre-existing equipment age and capability as well as operator and interpretation expertise. If MRI technologies are not implemented across the NHS, income inequalities may arise as some patients seek investigations through private health-care companies. Private UK providers are already preparing to provide this service with some providing MRI detection only and others offering MRI detection and biopsy services. These patients may then re-present to the NHS for their further care.

Health professionals are likely to prefer the increased certainty, reproducibility and anatomic capability of diagnoses made with MRS/MRI. Subsequently, medical staff would be more confident about negative diagnoses, knowing that an intermediate or high risk of progression cancer is unlikely to be present.

Earlier treatment may result in greater medical and societal success and improved patient functioning [physiological (urinary, rectal, erectile) and psychological]. These may, in turn, reduce the requirements on end-of-life and social care.

Chapter 7 Discussion

Diagnostic accuracy

Statement of principal findings

The included diagnostic studies reported sensitivity, specificity or predictive values for the index tests of MRS, DCE-MRI and DW-MRI and the comparator tests of T2-MRI and TRUS against a reference standard of histopathological assessment of biopsied tissue. Studies that reported true/false-positive and true/false-negative results or provided information that allowed these data to be calculated were considered for inclusion in the pooled estimates (meta-analyses). Meta-analyses were performed at both patient and biopsy level. In addition to the meta-analyses models of the diagnostic accuracy of the individual tests, combinations of tests and also of six studies directly comparing MRS with T2-MRI, an indirect comparison of all tests was also undertaken.

In terms of methodological quality, the majority of the 39 full-text studies were considered to have a low risk of bias for the patient selection (29/39, 74%), index test (39/39, 100%) and flow and timing (36/39, 92%) domains. Three studies (8%) were considered at high risk of bias for the flow and timing domain. In the reference standard domain, 25 studies (64%) were considered at high risk of bias because of a lack of follow-up, and in 14 (36%) the risk of bias was considered unclear. In terms of the applicability of the studies to the review question, all studies had low concern for applicability for the reference standard domain, whereas the majority had low concern for applicability for the patient selection (37/39, 95%) and index test (34/39, 87%) domains.

Although biopsy-level analysis was reported by a number of studies, patient-level data are more useful in determining management, and more clinically relevant. Most studies took multiple biopsies from participants, leading to clustering within participants. We were unable to account for this clustering in the biopsy-level analysis and therefore estimates from the biopsy-level analysis will be to some extent artificially precise.

In the patient-level pooled estimates for the individual tests, although both sensitivity and specificity (95% CI) of MRS [92% (86% to 95%), 76% (61% to 87%)] were higher than that of T2-MRI [86% (74% to 93%), 55% (44% to 66%)], the difference was greater for specificity. However, the reverse was the case in the meta-analysis of the six studies that directly compared the two tests, where the sensitivity and specificity of MRS was 89% (95% CI 79% to 95%) and 71% (95% CI 51% to 85%) compared with 77% (95% CI 55% to 90%) and 68% (95% CI 59% to 75%) for T2-MRI, with the difference being greater for sensitivity. There was statistical evidence ($p = 0.004$) that accuracy varied with threshold for the direct comparison analysis of T2-MRI and MRS; however, to make inferences on how these two tests compared with each other would require the assumption that accuracy did not vary with threshold.

A sensitivity analysis for MRS and T2-MRI comparing the pooled estimates for earlier studies (pre 2007) with those published more recently (2007 onwards) found no significant differences between the two time periods for either test (see *Appendices 9* and *10*).

Combining the two tests so that a positive result for either was considered a positive result for the combination led to an increase in sensitivity [96% (95% CI 90% to 98%)] but at the expense of a large decrease in specificity [31% (95% CI 21% to 42%)]. In a meta-analysis of three studies reporting DCE-MRI, the pooled estimates for both sensitivity [79% (95% CI 69% to 87%)] and specificity [52% (95% CI 14% to 88%)] were lower than that reported for either MRS or T2-MRI. DW-MRI was reported only by one small study[96] involving 43 patients, and only for sensitivity, although this was 100%. In pooled estimates for six

studies reporting TRUS as an imaging test,[57,75,80,82,93,111] sensitivity and specificity were 27% (95% CI 16% to 42%) and 81% (95% CI 77% to 85%), respectively.

Across six large-scale population screening studies[81,88,97,99,103,113] that provided information on the performance of systematic biopsies using a TRUS-guided approach on a subset of their patient populations who had a previous negative biopsy ($n = 5771$) sensitivity was 72.5% (range 60.6% to 96.3%). Pepe *et al.*[97] reported that a median of 23 cores (range 20 to 38) were taken.[97] The other studies reported the number of cores to be taken as follows: four to six cores,[88] at least four or six cores,[103] six cores[113] and eight cores.[81] Pinsky *et al.*[99] did not report the number of cores taken.

In the indirect comparison the highest sensitivity was reported for MRS at 93% (95% CI 87% to 97%), whereas the highest specificity was for TRUS (used as an imaging test) at 88% (95% CI 79% to 94%). The combination of tests that produced the highest sensitivity was for 'T2-MRI or MRS' at 97% (95% CI 91% to 99%), whereas the combination of tests that produced the highest specificity was for 'T2-MRI and MRS' at 73% (95% CI 58% to 85%). There was marginal evidence that accuracy varied with threshold in the indirect comparison model ($p = 0.065$); however, to make comparative inferences would require the assumption that accuracy did not vary with threshold.

For the estimates from the indirect comparison model comparing T2-MRI with other tests, in terms of relative sensitivity, the direction of effect favoured (1) MRS, (2) 'T2-MRI or DCE' and (3) 'T2-MRI or MRS' over T2-MRI, while favouring T2-MRI over (1) DCE-MRI, (2) 'T2-MRI and MRS' and (3) TRUS. However, the only results that were statistically significant were for 'T2-MRI or MRS' compared with T2-MRI ('T2 or MRS' better) and T2-MRI compared with TRUS (T2-MRI better). In terms of relative specificity the direction of effect favoured (1) MRS, (2) 'T2-MRI and MRS' and (3) TRUS over T2-MRI, while favouring T2-MRI over (1) DCE-MRI, (2) 'T2-MRI or DCE-MRI' and (3) 'T2-MRI or MRS'. The only results that were statistically significant were for 'T2-MRI and MRS' compared with T2-MRI ('T2-MRI and MRS' better), T2-MRI compared with TRUS (TRUS better) and 'T2-MRI or MRS' compared with T2-MRI (T2-MRI better). However, it should be noted that in practice MRS is acquired in combination with T2-MRI and would not usually be interpreted without taking into account this information.

In summary, the evidence from patient-level pooled estimates suggests that MRS has higher sensitivity (92%) and specificity (76%) than T2-MRI (86%, 55%), while combining both tests so that when either is positive the combination is positive further increases sensitivity (96%) but at the expense of specificity (31%). DCE-MRI has lower sensitivity (79%) and specificity (52%) than either MRS or T2-MRI, although this was based on only three studies.[78,90,105] TRUS used as an imaging test has low sensitivity (27%) but high specificity (81%). Only one small study[96] reported patient-level estimates for DW-MRI and only for sensitivity, which, however, was 100%.

Strengths and limitations of the assessment

In terms of strengths, a broad, robust literature search was undertaken with double screening of titles and double checking of data extraction. Risk of bias was assessed using a modified QUADAS-2 questionnaire, tailored to the needs of this review. A HSROC model was used, which takes account of the trade-off between true/false-positives and models between-study heterogeneity.[172] Pooled estimates were performed at both patient and biopsy level and an indirect comparison of tests was also undertaken. Homogeneity was improved by having a robust inclusion criterion for meta-analysis and indirect comparison, and by performing an additional analysis using only those studies that directly compared tests. Indirect comparison allows relative estimation of sensitivity and specificity for each comparison by including all tests in one model.

In terms of limitations, there was variation in the use of tests, methodology and reporting of included studies. We could not test for the effects of covariates such as the number of previous biopsies on the results because the data captured were not conducive for such analysis. Non-English-language studies were excluded. Few studies were identified reporting DCE-MRI or DW-MRI, and few studies included a

period of follow-up as part of the reference standard, thereby potentially failing to identify a proportion of patients who might have been false-negative on the tests. The index and comparator tests were not independent of the reference standard (incorporation bias), as they provided the biopsy cores for the reference standard to assess for the presence or absence of disease.

Uncertainties

Dichotomising test results where studies reported an 'equivocal' category

Some studies reported suspicious results (test-positives), normal results (test-negatives) and a third category, neither positive nor negative, such as 'equivocal'. In order to incorporate these results into a 2×2 table and for inclusion in meta-analyses they had to be dichotomised as either positive or negative. Our position was to class equivocal results along with positive results rather than with negative results. This approach increased sensitivity and decreased specificity, whereas the reverse would have been the case if equivocal results had been classed along with negative results. In *Appendix 8,* when studies have reported an 'equivocal' category, where possible, we have shown sensitivity and specificity both for equivocal cases classed with positive results and for equivocal cases classed with negative results. For example, in the study by Yuen *et al.*,[112] for MRS, when equivocal was classed as 'suspicious' sensitivity was 71.4% and specificity was 52.9%, whereas when equivocal was classed as 'normal' sensitivity was 57.1% and specificity was 82.4%.

False-positives

Eleven studies[57,74,76,78,79,101,106,108,109,133,137] provided some additional information on the nature of their false-positive results (i.e. the test detected an abnormal area but the histopathological assessment of the biopsy cores taken from that area was negative for cancer). The false-positive rate for patient-level analysis (six studies[74,76,79,101,108,137]) ranged from 2.4% to 100% and for biopsy-level analysis (five studies[57,78,106,109,133]) ranged from 13.0% to 46.2%. High-grade PIN and prostatitis accounted for a substantial proportion of false-positives. One study presented this information separately for MRS and T2-MRI.[79] For MRS (11 false-positives), PIN accounted for six (54.5%), fibrosis for four (36.4%) and normal prostatic tissue for one (9.1%). For T2-MRI (13 false-positives) PIN accounted for three (23.0%), fibrosis for five (38.5%) and normal prostatic tissue for five (38.5%).

True-negatives

An extended TRUS/Bx procedure may miss cancers, as the transrectal approach renders sampling of apex tumours and anterior TZ tumours difficult. Using this as the approach to provide the biopsies for the reference standard has its limitations, especially if not combined with long-term follow-up. The number of true-negatives in these types of study could therefore potentially be lower than reported.

Detection of clinically significant disease

Using comprehensive (saturation) biopsy protocols based on TRUS/Bx may reduce the likelihood of missing cancers. However, although saturation biopsies may improve the detection rate of PC, solely increasing the number of biopsy cores may also lead to an increase in the detection of clinically insignificant disease. In addition, saturation biopsies have the disadvantage of possibly requiring anaesthesia and increasing the risk of adverse events.[105] On the other hand Scattoni *et al.*[173] reported that the detection rates of protocols including 20–38 cores ranged from 14% to 41% without significantly increasing the likelihood of detecting clinically insignificant cancers compared with initial or repeat biopsy.

One of the suggested advantages of MRS and other MRI techniques is the ability to detect clinically significant disease (Gleason score of ≥ 7). An explanation put forward for this in relation to MRS is that it is unable to detect the lowest grade of PC due to partial voluming of healthy surrounding tissue included in a spectroscopic voxel of spatial resolution 0.32 cm.[106]

Twenty-nine studies[74,76,78–84,86,87,90,91,95–98,102–106,108–113,136] reported the Gleason score based on the biopsy results of patients diagnosed with PC. Most studies reported a median Gleason score of ≥ 6 and in the

one study[96] reporting DW-MRI the median Gleason score was 7. Across six MRI studies reporting a median Gleason score of >6,[74,90,96,104,108,109] the percentage of patients with a Gleason score of ≥7 ranged from 50% to 66.7%. The limited evidence suggests that, potentially, a substantial number of cancers detected by MRS and other MRI techniques in patients with raised PSA levels and previous negative biopsy may be clinically significant (Gleason score of ≥7 and/or volume >0.5 ml).

The experience of clinical experts (Anwar Padhani, Mount Vernon Cancer Centre, July 2012, personal communication) suggests that DW-MRI is capable of detecting more clinically significant disease than TRUS/Bx, and that cancers missed on DW-MRI that are detected on TRUS/Bx are generally not clinically significant. However, there is a lack of evidence on the detection of clinically significant disease by DW-MRI in the population of men with a previously negative biopsy who still have raised PSA levels and a continuing suspicion for cancer. There is some evidence on the ability of DW-MRI to detect clinically significant disease in the wider population of men with PC; for example, Hambrock *et al.*[64] undertook DW-MRI of 51 patients before prostatectomy and found that the median ADC in the tumours was negatively correlated with Gleason score in the PZ of the prostate. However, further research is needed to assess the extent to which this finding applies to men with suspected PC but a previously negative biopsy. In the TZ, although there is a small significant difference in ADC between Gleason 3 + 3 and Gleason 4 + 4 cancers, the overlap in ADC between the two cancer groups is so large that discrimination on an individual level is not possible (Tom Scheenen, Radboud University Nijmegen Medical Centre, July 2012, personal communication).

Cancer detection in the transition zone by magnetic resonance spectroscopy and other magnetic resonance imaging techniques

Hoeks *et al.*[87] commented that MRS had problems imaging the TZ and also noted that different choline–creatine ratios were needed for cut-offs for a positive test result for the PZ and TZ. The authors stated that their relatively high detection rates of PC in the TZ in men with one or more negative TRUS-guided biopsies agreed with the results of Hambrock *et al.*[86] (57% in the TZ). However, they noted that, in other reports by Roethke *et al.*[104] and Franiel *et al.*,[84] TZ cancer detection rates (47% and 35%, respectively) were lower than PZ cancer detection rates (53% and 64%, respectively). Testa *et al.*,[106] in a region-based analysis, also reported sensitivity and specificity separately for the PZ and TZ for MRS and T2-MRI. For the PZ, MRS sensitivity and specificity were 64.9% and 85.8%, respectively, compared with 72.2% and 93.3% for the TZ. T2-MRI sensitivity and specificity for the PZ were 27.0% and 95.8% respectively, compared with 61.1% and 98.9% for the TZ.

Heterogeneity across the studies

Across the studies, the prevalence of PC ranged from 9.5%[76] to 100%.[117] The original biopsy scheme used will influence the prevalence of PC in patients with raised PSA and previously negative biopsy; the more cores taken during the original biopsy scheme(s), the more cancers are likely to be detected at this stage and consequently the prevalence of cancer in subsequent biopsies will be lower. The previous biopsy schemes reported by the studies ranged from four or six core[57] to 12 core.[74,78,93,116] The number of previous biopsy sessions reported by the studies for their patient populations ranged from 1 to 9, with different numbers of sessions occurring within studies as well as across studies.

Transrectal ultrasonography: imaging compared with obtaining biopsies

Transrectal ultrasonography is used to either visualise the prostate in order to obtain a systematic, predefined biopsy (TRUS/Bx) or inspect the prostate for evidence of cancer and biopsy highly suspicious areas. Based on advice from clinical experts, the most common use for TRUS in the NHS is to obtain a systematic, predefined biopsy. Therefore, TRUS sensitivity could mean:

- *The proportion of patients with prostate cancer correctly identified on systematic predefined biopsy* This is complicated by the fact that TRUS is not independent from the reference standard, as discussed elsewhere. Therefore, to obtain the false-negatives necessary to calculate sensitivity, at least one repeat biopsy is needed. In studies that use this method, low-risk patients do not usually

undergo repeat biopsies. This can lead to a falsely high sensitivity, as it assumes that all patients who did not undergo a biopsy did not have cancer. Furthermore, if there is a considerable interval between biopsies, there is the potential that an individual may have developed cancer in the intervening period.

Alternatively, TRUS sensitivity could mean:

- *The proportion of patients with prostate cancer correctly identified when TRUS is used to identify suspicious lesions* This scenario is complicated because often both systematic and targeted biopsies are taken and in reported studies is it unclear if the sensitivity refers to the combination or just the targeted lesions.

Systematic biopsies used in conjunction with magnetic resonance spectroscopy and other magnetic resonance imaging techniques

In studies reporting the sensitivity and specificity of MRS or other MRI techniques, a number of cores were targeted for biopsy, based on suspicious areas identified by the imaging test and a systematic (generally 10- or 12-core) TRUS/Bx was also undertaken. In most studies it was unclear how the results from the systematic biopsy contributed to the sensitivity and specificity values reported for the imaging technique, i.e. it was unclear whether the sensitivity and specificity reported were for the imaging test alone or the imaging test plus the systematic biopsies.

Subsidiary questions from the protocol

There was insufficient information from the included studies to address the subsidiary questions of (1) identifying specific patient groups in which MRS and other MRI techniques are most clinically effective; (2) whether or not these techniques can identify cases in which PC is present but further procedures are unnecessary and (3) evidence of use of MRS and other MRI techniques leading to a change in patient management.

Other relevant factors

Ongoing studies

The search strategy identified a few ongoing studies, although none focused on our population of interest – men with suspected PC and elevated PSA level but previously negative biopsy. The largest of the ongoing studies identified was the UK multicentre study 'PROstate MRI Imaging Study: evaluation of multiparametric magnetic imaging (MP-MRI) in the diagnosis and characterisation of PC (PROMIS)' that was anticipated to start in March 2012 and end in April 2015.[171] The objectives of this study are to (1) determine the ability of MP-MRI to identify men who can safely avoid biopsy; (2) assess the ability of the MP-MRI-based diagnostic pathway to improve the rate of detection of clinically significant cancer compared with TRUS/Bx; and (3) estimate the cost-effectiveness of an MP-MRI-based diagnostic pathway. The study design is described as a prospective validating paired cohort study. Participant inclusion criteria are men who (1) are aged ≥ 18 years who are at risk of PC and have been advised to have a prostate biopsy; (2) have a PSA level value of ≤ 15 ng/ml in the last 3 months; (3) have suspected stage of ≤ T2 on rectal examination (organ confined); and (4) are fit for general/spinal anaesthesia and all study procedures. Exclusion criteria include a previous history of prostate biopsy. The intervention is MP-MRI scan and combined prostate biopsy procedure (template prostate mapping biopsy) followed by TRUS/Bx. The primary outcome measures are (1) proportion of men who could safely avoid biopsy; (2) proportion of men correctly identified by MP-MRI to have clinically significant PC; and (3) primary definition of cancer according to biopsy: dominant Gleason pattern of ≥ 4 and/or cancer core length of ≥ 6 mm.

Another ongoing study is the 'Prostate Cancer Localization With a Multiparametric Magnetic Resonance (MR) Approach'.[174] This is a prospective, observational, international, multicentre study that started in June 2010. Its primary objective is to prove the diagnostic accuracy of in vivo 3-T multimodality MRI (high-resolution T2-MRI, DCE-MRI, MRS and DW-MRI techniques) in distinguishing carcinoma from other prostate tissue. Specific objectives include (1) determining the diagnostic accuracy of 3-T multimodality

non-endorectal coil MR imaging in localising PC and (2) proving that multimodality MR data allow for predicting tumour grade. Inclusion criteria include men with biopsy-proven diagnosis of PC in whom radical prostatectomy and histopathological examination are planned.

Comparison of our results with other systematic reviews

Our searches identified four other systematic reviews[70,175–177] that assessed MRI techniques for detecting PC in men, although only the review by Lawrentschuk and Fleshner[176] focused on men with previous negative biopsies and elevated PSA levels.

Umbehr *et al.*[70] undertook a systematic review and meta-analysis of MRI combined with MRS in the diagnosis of PC. Thirty-one studies were included, seven of which recruited participants with a previous negative biopsy. Six[74,76,79,100,101,112] of these seven studies[74,76,79,100,101,112,178] were included in our review; the seventh[178] was excluded as the participants did not have a previous negative biopsy or this was unclear. The authors performed a meta-analysis of seven studies[57,74,76,79,100,101,112] examining patients with suspected PC and found a sensitivity of 82% (95% CI 59% to 95%) and specificity of 88% (95% CI 80% to 95%). However, in this meta-analysis only four[74,76,79,112] of the seven studies[57,74,76,79,100,101,112] involved men with a previously negative biopsy.

Lawrentschuk and Fleshner[176] undertook a review of studies of MRI or MRS which recruited participants with a previous negative biopsy and persistently elevated PSA. Six studies were included, five of which were included in our review;[57,74,79,101,112] the sixth[179] was excluded as the test used was outwith our inclusion criteria. The authors did not statistically pool the results, but rather narratively presented each study. For MRI or combined MRI and MRS, they reported a sensitivity of 57% to 100% and a specificity of 44% to 96%. The authors found that 54% of patients (34/63) were diagnosed with cancer solely on the basis of a MRI-targeted biopsy.

Wang *et al.*[177] undertook a meta-analysis of PC studies that used MRS as a diagnostic tool. The inclusion criteria were not limited to men with suspected PC and previously negative biopsy. Seven studies were included, of which two were included in our review;[101,112] the remaining five[18,51,53,180,181] were excluded as the types of participants were outwith our inclusion criteria. The authors reported the sensitivity and specificity of MRS using a CC/C ratio cut-off of 0.75 as 82% and 68% respectively, and with a cut-off of 0.86 as 64% and 86%, respectively.

Engelbrecht *et al.*[175] performed a systematic review of local staging of PC using MRI. The authors included 76 studies and calculated the area under the ROC curve using trapezium methodology. It was not reported how many of these studies included participants with a previous negative biopsy and raised PSA and the list of included studies was not included in the list of references. On the ROC curve the joint maximum sensitivity and specificity of MRI was at 71%; however, the authors found unexplained heterogeneity throughout the results.

Future technological developments

Magnetic resonance-guided biopsies are not usually carried out in the UK, resulting in challenges in ensuring the correspondence of TRUS/Bx spatial accuracies to suspicious areas identified by MRS/MRI. Hoeks *et al.*[87] stated that the clinical use of MR-guided biopsies was currently restricted by limited availability and long procedure times. They commented that the application of MRI–ultrasound fusion techniques, needle-guided tracking sequences, and implementation of robotics may improve these drawbacks in the near future and that, when these issues were resolved, multiparametric-MRI- and MR-guided biopsies could be applied on a larger scale for PC detection in patients with an elevated PSA level and one or more negative TRUS/Bx sessions.

Cost-effectiveness

Statement of principal findings

The economic modelling found the cost-effectiveness of strategies to be highly sensitive to a number of key parameters and assumptions, as well as context. Our findings suggest that when the average cost of TRUS/Bx is ~£115 greater than the cost of obtaining a T2-MRI + MRS sequence (i.e. ~£300 per patient when holding the base-case T2-MRI + MRS cost estimate constant) then T2-MRI- and MRS-directed approaches dominate the systematic extended-cores approach in both 60- and 70-year-old cohorts (with cancer prevalence at 24%). In addition, the ICER for MRS compared with T2-MRI falls to < £30,000 in the 60-year-old cohort (although not in the 70-year-old cohort). Such a difference in costs between TRUS/Bx and obtaining a MRS/MRI scan might be expected in hospitals where a significant proportion of biopsies are carried out as day-case activity, or if the average outpatient HRG cost significantly underestimates histopathology costs, as some personal communication suggests.

In both the 60- and 70-year-old low-prevalence cohorts, T2-MRI and MRS again dominate extended-cores TRUS/Bx when the cost of biopsies is inflated to £300, although MRS does not achieve an ICER of < £30,000 in either age group. In the high-prevalence cohorts, this biopsy cost increase results in MRS having an ICER of ~£22,000 per QALY in 60-year-old men, whereas the ICER remains above £30,000 per QALY in 70-year-old men.

Under the assumption that all index repeat biopsies are carried out as outpatient procedures, at the lower cost of £212, we found the following:

1. The use of T2-MRI (for directing TRUS/Bx) may be considered cost-effective in comparison with systematic TRUS-guided extended-cores biopsy (60-year-old cohort with prevalence at 24%), but there is a high degree of uncertainty at the £30,000-per-QALY ceiling ratio.
2. T2-MRI dominates extended TRUS/Bx in cohorts in which the prevalence of cancer is low (10%).
3. MRS is borderline cost-effective in comparison with systematic TRUS/Bx in the 60-year-old cohort with prevalence set at 24%, and its cost-effectiveness improves in the high-prevalence 60-year-old cohort. The ICER for MRS compared with systematic TRUS/Bx remains > £30,000 for all 70-year old cohorts.
4. The ICER for MRS compared with T2-MRI is above £30,000 in both the low and the moderate prevalence 60- and 70-year-old cohorts but < £30,000 for the high-prevalence 60-year-old cohort.
5. The findings for point 4 (above) hold when it is assumed that MRI-/MRS-directed biopsies require fewer cores and so are carried out as outpatient procedures, whereas systematic extended-cores biopsies are carried out at higher cost.
6. Threshold cost analysis shows that when the cost of biopsy is on average ~£90 higher than the cost of obtaining an MRS sequence, the ICER for MRS falls to < £30,000 per QALY compared with T2-MRI (60-year-old cohort, cancer prevalence 24%).

When applying the lower outpatient costs to biopsies, the cost-effectiveness of MRS compared with T2-MRI was found to be particularly sensitive to the ability of MRS to discriminate between low-, moderate- and high-risk cancer. Applying the assumption that MRS detects all moderate- and high-risk disease (with false-negatives concentrated in the low-risk group) the ICER for MRS fell to < £30,000. By the same token, reducing the baseline risk of disease progression, and applying lower relative risk reductions for diagnosis and treatment, undermined the cost-effectiveness of MRS.

A probabilistic sensitivity analysis was carried out for the 60-year-old cohort, applying the lower outpatient procedure cost to all index repeat biopsies (MRS/MRI-targeted and non-targeted), with all other parameter distributions centred on their base-case point estimates. Under this scenario, none of the strategies showed a high probability of being preferred on grounds of cost-effectiveness (see *Figure 28*) at a threshold willingness-to-pay ratio of £30,000 per QALY gained. However, increasing the average index repeat biopsy cost (to £298, as described above) and adjusting the sensitivity of MRS by underlying grade of disease demonstrated how these changes would give rise to a higher probability (~57%) of MRS

being cost-effective at the £30,000-per-QALY threshold (assuming that base-case progression rates and diagnoses/treatment effects hold). (Note: the 57% is calculated from the data behind *Figure 29*.)

Finally, while we were unable to accurately assess the diagnostic accuracy of DW-MRI in this cohort, sensitivity analysis demonstrates that its lower cost could make it preferable to MRS if it could be shown to have similar diagnostic accuracy.

Strengths and limitations of the assessment

Strengths

Attempts have been made to use the best available evidence to model both the diagnostic pathways and subsequent treatment pathways and outcomes. The model provides a flexible framework allowing the comparison of many different diagnostic strategies in the context of the patient's lifetime. It captures the trade-off between the increased upfront costs of imaging and the reduction in subsequent biopsies, and also the trade-off between earlier diagnosis and potential utility decrements associated with treatment side-effects. Further, the model is risk stratified to allow for comparison of strategies that vary in their ability to differentiate between tumours of different stage and grade. The model can easily be updated to incorporate new, more detailed evidence as it becomes available.

Limitations

The modelling was hampered by limited availability of data on the diagnostic accuracy of alternative diagnostic strategies, the natural history of cancer detected at repeat biopsy, and the impact of diagnosis and treatment on disease progression and health-related QoL.

The systematic review uncovered limited data on the relative sensitivity (cancer detection rates) of MRI-/MRS-targeted biopsy techniques and systematic TRUS-guided approaches. In particular, there were no identified studies providing head-to-head comparisons of MRI-/MRS-targeted approaches and systematic TRUS-guided sampling schemes based on different numbers of cores. Further, it was not possible to obtain pooled estimates for the sensitivity/specificity of alternative MRS/MRI sequences by grade of tumour, which is potentially an important parameter for informing cost-effectiveness. There is therefore a need for a large comparative study to prospectively assess the sensitivity of systematic approaches and MRS/MRI sequences for detecting cancer by D'Amico risk strata. It would also be beneficial for follow-up to be built into such a cohort study to ascertain how contemporary cohorts are treated, how they progress over time, and how their health-related QoL is affected by diagnosis and subsequent treatment with different modalities.

Although the model attempted to capture all the important clinical and cost events, it was not possible to capture and/or value all the important factors that might influence cost-effectiveness. For example, we were not able to ascertain and assign utility decrements for pain and short-lived complications associated with undergoing biopsy. Further, we did not have a good source of EQ-5D utility weights for a UK-based cohort of patients undergoing repeat biopsy and follow-up, making it necessary to draw on alternative sources. It would be beneficial to incorporate a measure of health-state utility into future cohort studies assessing the accuracy of alternative approaches to diagnosis. In addition, with the survival and QALY gains being so small, and of questionable clinical significance, the choice between strategies might be better informed by patient or public preferences for process of care factors to which the standard QALY model may be insensitive.

Uncertainties

Uncertainty exists regarding the way that hospitals across England and Wales are, or would be, reimbursed for repeat biopsy procedures using the TRUS-guided extended-cores approach and MRI-/MRS-directed approaches. Although it is difficult to ascertain the average picture across the UK, it is clear to see from the analysis that the use of MRS/MRI is likely to be cost-effective if a high proportion of the biopsies averted by its use would otherwise be reimbursed as day-case procedures. Sensitivity analysis suggests that, in settings where the average cost of biopsies averted is ~£115 more than the cost of obtaining a MRS sequence, the

use of MRS might be cost-effective; the greater the saving from biopsies averted, the higher the likelihood of MRS being considered cost-effective.

In contexts/settings where index repeat biopsies averted (using standard TRUS guidance and/or MRS/MRI direction) would otherwise only incur the outpatient procedure cost (£212), there is less certainty surrounding the relative cost-effectiveness of MRI-/MRS-directed approaches.

A high degree of uncertainty exists regarding the impact of a false-negative result at repeat biopsy on the time to final diagnosis, and also on the impact of any delay on disease progression. The base-case analysis relied on the assumption that all patients experience a relative risk reduction for progression to metastatic disease upon referral. However, recent data suggest that risk reductions associated with radical treatment for low-risk patients (and even moderate-risk patients) may be small and insignificant.[149] If this is the case, it might undermine the cost-effectiveness of strategies that increase cancer detection rates and costs over standard practice, unless those strategies are able to discriminate by grade of tumour.

With index repeat biopsies costed as outpatient procedures, the more sensitive and more costly enhanced imaging techniques were found to be associated with small cost increases, for even smaller survival and QALY gains compared with T2-MRI and systematic TRUS/Bx. This results in the incremental cost-per QALY ratios being very sensitive to the baseline risks of progression and relative treatment effects. Recent data suggest that the underlying risk of progression for low-risk cancer, identified in the PSA era, may be lower than that reported for the low-risk subgroup identified by Bill-Axelson *et al.*[148] However, the above point also highlights the potential benefit of utilising a pre-biopsy imaging test that could differentiate between low-, moderate- and high-risk cancer, so that only those patients in the moderate- and high-risk categories could be selected for biopsy. Our modelling suggests that if DW-MRI or MRS could be shown to provide such discrimination in the cohort of patients with elevated PSA level but previously negative biopsy, these tests could achieve levels of cost-effectiveness considered acceptable, even at the lower biopsy procedure costs. More detailed studies are required to assess the diagnostic accuracy of different sequences by stage/grade of cancer in order to address this question.

A key driver in the cost-effectiveness analysis was the high sensitivity/specificity of systematic TRUS-guided extended-core biopsy carried out in the outpatient setting compared with MRS/MRI. As there were no available literature data directly comparing the relative accuracy of MRI-directed biopsies with this method for obtaining biopsies, we were forced to rely on a study in which the sensitivity of the systematic extended-cores biopsy was modelled using the results of a saturation biopsy as the reference standard. There is a degree of uncertainty about the assumption of saturation biopsy as the reference standard in this study because of the following reasons: a large number of cancers modelled were found to be of low risk; there was variable correlation with prostatectomy specimens; and a considerable risk exists of missing apex and anterior TZ tumours. If this derived high level of test accuracy for systematic TRUS-guided extended biopsy is not achieved in actual clinical practice within the NHS then the cost-effectiveness of the approach would be negatively altered and correspondingly the MRS/MRI approach would be improved. To mitigate operator-dependent variability of performing outpatient systematic TRUS-guided extended biopsy, it would be advantageous to be able to record by ultrasound the actual locations where cores are obtained as a quality measure.

Finally, a further issue contributing to the uncertainty surrounding the cost-effectiveness of alternative diagnostic approaches, and indeed the cost-effectiveness of radical treatment,[9] is the impact of treatment on health-related QoL. In our base-case specification, we have applied utility values that suggest radical treatment complications do not impact heavily on health-related QoL as measured by the EQ-5D.[163] However, the incremental cost per QALY findings are highly sensitive to changes to these applied utility assumptions. When health-state utilities are adjusted downwards for those patients experiencing treatment complications, the cost-effectiveness of strategies that improve cancer detection rates, at an increased cost to the health service, decreases substantially. This highlights the potential importance of risk stratifying treatment appropriately, so that only those patients likely to experience a significant survival

benefit receive radical treatments. However, current data suggest that a substantial proportion of low-risk patients still elect for radical treatment, which undermines the cost-effectiveness of diagnostic strategies that result in more low-risk patients being diagnosed. This emphasises the potential benefit of reducing overdiagnosis of low-risk cancers, which MRS/MRI might be able to do.

Other relevant factors

The modelled differences in survival between strategies were found to be extremely small. Despite this, the more sensitive strategies do achieve a high probability of being more effective (in terms of LYs and QALYs) than less sensitive strategies. This is due to the application of a constant and significant relative treatment effect (at least in the 60-year-old cohort). However, the QALY model in this instance may fail to capture other important process-of-care factors that have important influences on patients' preferences for alternative approaches to diagnosis and monitoring. Scope exists to carry out preference elicitation studies to identify and value the key factors influencing patients' preferences for alternative diagnostic, monitoring, and subsequent treatment pathways. For example, one could design a preference elicitation study to directly assess patients' willingness to trade between factors such as chance of a positive diagnosis being made, risk of biopsy complications, treatment options and likely survival benefit if diagnosed, risk of treatment complications, risk of progression if undiagnosed, frequency of monitoring if diagnosed/undiagnosed, and need for repeat biopsies if undiagnosed. If the value ascribed by patients to these alternative attributes could be measured using a common numéraire such as willingness to pay, these values could then be applied within a decision analysis framework to help identify the optimal approach from the patient perspective in the modern NHS.

Chapter 8 Conclusions

Implications for service provision

The evidence from the patient-level pooled estimates suggests that MRS has higher sensitivity (92%; 95% CI 86% to 95%) and specificity (76%; 95% CI 61% to 87%) than T2-MRI [sensitivity 86% (95% CI 74% to 93%), specificity 55% (95% CI 44% to 66%)] in detecting PC in men with elevated PSA level but a previous negative biopsy. Combining both tests so that when either is positive the combination is considered positive further increases sensitivity (96%; 95% CI 90% to 98%) but at the expense of specificity (31%; 95% CI 21% to 42%). The advantages of higher sensitivity (fewer false-negatives) have to be weighed against the disadvantages of lower specificity. As the combination of MR methods works as guidance for biopsies, which need to provide the final positive diagnosis, the lower specificity may be acceptable. The limited evidence for DCE-MRI (three studies) suggests that it has lower sensitivity (79%; 95% CI 69% to 87%) and specificity (52%; 95% CI 44% to 66%) than either MRS or T2-MRI. Only one small study reported patient-level estimates for DW-MRI and only for sensitivity, which, however, was high at 100%. TRUS used as an imaging test has low sensitivity (27%; 95% CI 16% to 42%) but high specificity (81%; 95% CI 77% to 85%). The results from the indirect comparison of tests were broadly reflective of those of the pooled estimates of the individual tests.

Transrectal ultrasonography is no longer routinely used as an imaging test but rather is used to visualise the prostate in order to obtain a systematic predefined set of biopsies (TRUS/Bx). Six large population screening studies[81,88,97,99,103,113] allowed the calculation of the sensitivity of TRUS used in this manner on a subset of their participants with a previously negative biopsy and continuing suspicion of cancer. The reference standard in these studies[81,88,97,99,103,113] was a second, third or more, possibly extended-core, transrectal biopsy session. Across these studies[81,88,97,99,103,113] the median sensitivity was moderately high at 72.5% (range 60.6% to 96.3%). However, it should be borne in mind that in these studies,[81,88,97,99,103,113] patients classed as low risk do not usually proceed to further repeat biopsies. All of the remaining patients, therefore, will have a high suspicion of cancer and this could potentially lead to the sensitivity values reported being artificially high. Moreover, cancer foci that are difficult to sample transrectally in the apex or anteriorly in the TZ of the prostate could remain undetected for quite a long time.

Although saturation biopsies, through removing a higher number of cores than standard or extended biopsy schemes, may potentially improve cancer detection rates compared with these schemes, solely increasing the number of biopsy cores may also lead to an increase in the detection of clinically insignificant disease. Most of the MRS and other MRI imaging studies reported a median Gleason score of ≥6 and the one DW-MRI study[96] reported a median Gleason score of 7. Across six studies[74,90,96,104,108,109] reporting a median Gleason score of >6, the percentage of patients with a Gleason score of ≥7 ranged from 50.0% to 66.7%. The limited evidence suggests that, potentially, a substantial number of cancers detected by MRS and other MRI techniques in men with raised PSA level and previously negative biopsy may be clinically significant (Gleason score of ≥7 and/or volume of >0.5 ml).

The cost-effectiveness modelling showed the relative cost-effectiveness of alternative strategies to be highly sensitive to a number of key parameters and structural assumptions. Given the level of uncertainty surrounding these key inputs, it is difficult to arrive at a definitive conclusion on the cost-effectiveness of using different MRS/MRI sequences to aid the localisation of prostate abnormalities for biopsy. However, our modelling suggests that under certain circumstances T2-MRI may be considered cost-effective in comparison with systematic TRUS/Bx. In addition, if MRS and DW-MRI can be shown to have high sensitivity for detecting moderate/high-risk cancer, while negating the need for patients with no cancer or low-risk disease to undergo biopsy, their use could represent a cost-effective approach to diagnosis.

The cost-effectiveness of using MRS rather than T2-MRI to direct biopsies was also found to be sensitive to the cost of prostate biopsies relative to the cost of obtaining the MRS sequence. Threshold analysis suggests that MRS may be considered cost-effective in moderate prevalence cohorts (24%) in settings where the cost of obtaining the MRS sequence is at least ~£90 less than the average cost of any biopsies averted (holding all other base-case parameter values constant). The greater the cost of biopsies relative to the cost of MRS, the more cost-effective it becomes. Data from subgroup analysis also show that the use of MRS is more likely to be cost-effective in subgroups harbouring a higher prevalence of cancer, and also in younger cohorts. In cohorts harbouring a low prevalence of cancer, T2-MRI may be preferred over TRUS/Bx and MRS. The most sensitive strategy of targeting all patients who are positive on either T2-MRI or MRS for biopsy did not compare favourably in terms of cost-effectiveness compared with using MRS findings alone. This is due to the significant drop in specificity for only a small increase in sensitivity compared with MRS.

The introduction of MRS and other MRI techniques (T2-MRI, DCE-MRI, DW-MRI) for evaluation of men with TRUS-guided negative biopsies but in whom there remains suspicion of cancer would have a range of implications for the NHS. These would arise primarily because of a shift in the test–treatment pathway for this group, with changes in the method of making diagnosis resulting in changes to the types of patients being treated, offered patient options and timings of treatments. This would have consequential effects on service provision, costs and training. If urological and/or radiological services were to undertake targeted biopsies of MRI-/MRS-suspicious regions then extra provision would be required for this. A new generation of equipment and software would be needed to enable accurate, documentable biopsies to be obtained from all regions of the prostate. If MRS/MRI identified more patients with localised disease with intermediate and high risk of progression, this would increase the proportion of patients considered eligible for radical therapies. If MRS/MRI detected few patients with low risk of progression disease then fewer patients in this category would undergo perhaps inappropriate radical therapies. Thus the total number of patients undergoing radical therapies would be appropriately decreased, thus requiring a rebalancing of current resources currently allocated to surgical and radiation therapy services. Furthermore, if MRS/MRI contributed to the more accurate classification of low-risk of progression patients, this would lead to an increase in the proportion of appropriately selected patients likely to undergo 'active surveillance' helping to mitigate the current high dropout rate of this approach. The implications for the follow-up of active surveillance patients would include utilisation of repeated PSA testing, repeated interval biopsies and follow-up clinics (much of this work is protocol driven and could be nurse practitioner led). Taken together, earlier, more accurate diagnoses and more appropriate treatments of PC may improve patient outcomes by reducing treatment-related morbidity, improved survival and, in the longer term, reduce the requirements on end-of-life and palliative care services. There would be cost implications of these service reconfigurations and for changes in treatment patterns mentioned above. Implementation would also result in the need for further training of all staff involved in delivering care to patients with PC.

Suggested research priorities

Although there is some evidence available for the sensitivity and specificity of MRS and standard T2-MRI for the detection of PC in men with suspected PC and elevated PSA level but previously negative biopsy, less evidence is available for DCE-MRI and even less for DW-MRI. More evidence is also needed for all of these tests of the extent to which they can differentiate between clinically significant and insignificant disease.

Therefore, prospective studies are required comparing the utility of the individual and combined components of a multiparametric magnetic resonance (MR) approach (MRS, DCE-MRI and DW-MRI) with both a MR-guided or -directed biopsy session and an extended 14-core TRUS/Bx scheme (the test currently most often used in the UK for a second biopsy where the first was negative but the patient still has a suspicion for PC) against a reference standard of histopathological assessment of biopsied tissue obtained via saturation biopsy, template biopsy or prostatectomy specimens. A follow-up time of 12 months should

be incorporated as part of the reference standard. Investigations of DW-MRI should be encouraged as it is already gaining widespread acceptance in normal radiological practice for investigating prostate diseases. These studies could take the form of fully paired direct (head-to-head) comparisons where all of the study population receives the index test(s), comparator test(s) and reference standard, or a randomised direct comparison in which study participants are randomly allocated to receive the index test or the comparator and all receive the reference standard.

These studies should also report the sensitivity of the tests in detecting clinically significant disease (Gleason score of ≥ 7 and/or volume of > 0.5 ml). In addition to diagnostic outcomes, adverse event data and impact of the tests on subsequent physician attitudes to patient management should also be obtained, and also cost-effectiveness data including impact of testing on health-related QoL.

Uncertainties surrounding cost-effectiveness could be significantly reduced by future research focusing on generating comparable estimates of (1) the sensitivity of MRI-/MRS-directed and systematic approaches to TRUS/Bx (using a robust and common reference standard); (2) the prospective sensitivity/specificity of MRS/MRI sequences for detecting different grades of localised disease in the repeat biopsy cohort; and (3) the full economic costs of MRI sequences and systematic approaches to TRUS/Bx based on different numbers of cores.

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Contributions of authors

Cynthia Fraser developed and ran the search strategies, managed the reference database and formatted references.

Charles Boachie conducted the statistical analysis.

Moira Cruickshank and **John Ford** screened titles and abstracts, assessed full-text papers and undertook data extraction and risk of bias assessment.

Graham Mowatt assessed full-text papers, undertook risk of bias assessment and co-ordinated the project.

Lutfi Kurban, **Thomas Lam**, **Anwar Padhani**, **Justine Royle** and **Tom Scheenen** provided expert advice on clinical aspects of the review.

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Discussion (Graham Mowatt and Graham Scotland).
Conclusions (Graham Mowatt and Graham Scotland).

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Appendix 1 Protocol

17 September 2010 (updated 9 November 2011)

HTA 09/146/01

1. Title of the project

Systematic review of 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

2. Name of TAR team and project 'lead'

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3. Plain English summary

In the UK prostate cancer is the most common cancer in men and the second most common cause of cancer death in men after lung cancer. Cases are rare in men aged under 50 years, but it becomes more common as they grow older. In its early stages prostate cancer usually develops without any symptoms. However, when a tumour causes the prostate gland to become enlarged or cancer spreads beyond the prostate, a range of symptoms can result, including increased frequency of passing urine, problems starting or stopping passing urine, a painful burning sensation or blood in urine.

Techniques commonly used to diagnose prostate cancer include digital rectal examination (DRE), the prostate specific antigen (PSA) blood test, and trans-rectal ultrasound (TRUS)-guided needle biopsy. Although a DRE and the PSA test collectively are able to identify abnormalities that might indicate prostate cancer, a diagnosis can only be confirmed following a prostate biopsy. However, the PSA test can cause false alarms and give false reassurance (15–30% of men with prostate cancer have normal PSA and even in those patients with abnormal PSA results, 7 of 10 men will not have prostate cancer diagnosed in the next two years). Biopsies also have their limitations because prostate cancers cannot be seen during biopsy procedures (so biopsies may miss at least 20–30% of cancers that are present) and biopsy results may not be reliable, underestimating cancer aggressiveness in more than 20–30% of cases. Current diagnostic methods (DRE, TRUS, PSA) are unable to distinguish non-aggressive disease (requiring careful monitoring) from virulent prostate cancer (requiring definitive treatment).

Magnetic resonance imaging (MRI) can be used to assess what stage the prostate cancer is at and in helping to decide whether an operation is needed. MRI relies on identifying tissue changes within the prostate to diagnose the presence and extent of cancer. However, these changes often do not accurately reveal whether cancer is present or its size. MRI can be performed with add-ons including three-dimensional magnetic resonance spectroscopy (MRS), dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI). DCE-MRI is sensitive to differences in the amount of blood and the permeability of blood vessels that can be associated with the development of tumours and is performed by obtaining a sequence of images before, during and following the injection of a contrast agent. DW-MRI measures the diffusion of water molecules in tissue and may help to distinguish between cancerous and normal prostate tissue. MRS measures the level of certain chemicals in the prostate. The concentration of these chemicals may be altered in the presence of prostate cancer, and hence this technique may be helpful in identifying this type of cancer.

Many men find themselves with the dilemma of having a raised PSA level and a negative prostate biopsy, and the best way to manage these patients remains uncertain. Sometimes these men undergo many repeated, blind biopsies which can be painful and may provide little additional yield. DCE-MRI, DW-MRI and MRS may be able to provide better information on tumour location, size and aggressiveness. These techniques may also be able to help identify cases where undertaking invasive biopsy may be avoided because the tumours are small, or not aggressive.

This review will assess the diagnostic accuracy of MRS, DCE-MRI and DW-MRI and the clinical effectiveness and cost-effectiveness of strategies involving their use in men with suspected prostate cancer and elevated PSA but previously negative biopsy.

The analysis will also focus on the impact that MRS, DCE-MRI and DW-MRI have for diagnosis, and what the overall impact of introducing these techniques would be on NHS services and patient morbidity and mortality. Cost-effectiveness will be assessed from the perspective of the NHS and personal social services.

Information on the diagnostic accuracy and population subgroups for which the technique is most clinically effective will be derived by systematically reviewing relevant studies. Information on cost-effectiveness will be derived from an economic model which will be developed and which will use the findings of the diagnostic accuracy review to help provide estimates of the relative cost-effectiveness of diagnostic strategies that involve MRS, DCE-MRI or DW-MRI.

4. Decision problem

In the UK prostate cancer is the most common cancer in men and the second most common cause of cancer death in men after lung cancer.[1] Each year around 35,000 men in the UK are diagnosed with prostate cancer and more than 10,000 die from it.[1] The 5-year survival rate is around 77%.[2] Cases are rare in men aged under 50 years, but it becomes more common as they grow older, and almost 60% of cases

are diagnosed in men aged over 70 years.[1] There is evidence of a higher incidence of prostate cancer in men of African or Caribbean origin.[3]

The prostate is located in the pelvis and in a normal young adult male the gland is approximately 3 cm long and weighs around 20 grams.[4] In its early stages prostate cancer usually develops without exhibiting any symptoms. However when a tumour causes the prostate gland to enlarge to a significant degree, or cancer spreads to areas beyond the prostate, a range of symptoms can result, including increased frequency of urination, problems starting or stopping urination, a painful burning sensation or blood in urine.[5]

Four procedures are commonly used to diagnose prostate cancer: digital rectal examination (DRE), the prostate specific antigen (PSA) blood test, trans-rectal ultrasound (TRUS) and needle biopsy.[6] PSA is a protein produced by cells of the prostate gland, and the test measures the level of PSA in the blood. The PSA test is specific to the prostate but not to prostate cancer, and so serum levels may be elevated in the presence of benign prostatic hyperplasia, prostatitis and other non-malignant conditions. TRUS has two potential roles in the diagnosis of prostate cancer: to identify lesions suspected of malignancy (done rarely as the majority of prostate cancers are not visible by TRUS) and to improve the accuracy of prostate biopsy.[7] TRUS is a blind procedure that involves the clinician taking 10–12 biopsies in a manner that attempts to obtain representative tissue within the peripheral zone of the prostate. However, TRUS has limitations in that several parts of the gland are not well sampled using this approach. The anterior part of the gland may be missed as a result of its greater distance from the rectum, tissue in the midline may be missed due to efforts to avoid the urethra, while the apex of the prostate is often inaccessible by the transrectal route. Collectively a DRE and the PSA test are able to identify abnormalities that could be indicators of prostate cancer. However, neither test is conclusive and a diagnosis can only be confirmed following the examination of cells taken from a biopsy of prostate tissue. The aim of prostate biopsy is to detect those prostate cancers with the potential for causing harm. It has been estimated that, of asymptomatic men in whom prostate cancer is detected by prostate biopsy following PSA measurement, around 50% do not require active treatment.(NICE guideline prostate cancer) The use of these tests in the diagnosis of prostate cancer has led to many thousands more patients being identified at increasingly younger ages and earlier (and therefore potentially treatable) stages of disease than occurred previously.[8]

The stage of prostate cancer is classified using the TNM classification of malignant tumours criteria.[9] This describes the extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of metastasis (M stage). The most commonly used system for grading prostate cancer is the Gleason sum score. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 being the most aggressive,[10] although most pathologists now group scores $1 \leq 6$ as Gleason 6.[11]

Magnetic resonance imaging (MRI) can be used in the local staging of prostate cancer and has acquired a role in pre-operative assessment.[12] Conventional MRI of the prostate relies on abnormal signal intensities that result from morphologic changes within the prostate to define the presence and extent of cancer. However, these changes often do not accurately reflect the presence and extent of active tumour.[13] MRI can be performed with add-ons including three-dimensional magnetic resonance spectroscopy (MRS), dynamic contrast enhanced MRI (DCE-MRI) and diffusion weighted MRI (DW-MRI) in a multifunctional examination that may provide more specific information relating to tumour location, size and aggressiveness. DCE-MRI is sensitive to differences in blood volume and vascular permeability that can be associated with tumour related development of new blood vessels and is performed by obtaining sequential magnetic resonance images before, during and following the injection of a contrast agent.[14] DW-MRI measures the diffusion of water molecules in tissue and may help differentiate between malignant and benign prostatic tissue on the basis of lower apparent diffusion coefficient (ADC) values of prostate cancer compared with normal prostate tissue.[15] MRS measures the level of specific chemicals (including choline, creatine, and citrate) in the targeted tissue. The concentration of these chemicals may be altered in the presence of prostate cancer and this phenomenon may be exploited to identify areas of

tumour activity. MRS may also potentially have a role to play in assessing the aggressiveness of any tumour activity identified.

The management of localised prostate cancer depends on the TNM stage of the disease as well as the PSA level, Gleason score, personal preferences of the patients, their physicians, and other available expertise, equipment and resources. The treatment options for men with localised prostate cancer are: watchful waiting, active surveillance, radical prostatectomy, radical external beam radiotherapy (EBRT), radical brachytherapy, high intensity focused ultrasound (HIFU) and cryotherapy. Treatment of men with localised prostate cancer may be associated with a wide range of significant adverse effects. Adverse effects that are common, long-lasting and that may seriously affect quality of life include rectal problems, sexual dysfunction and urinary incontinence.[16]

Many men find themselves with the dilemma of having an elevated PSA level and a prostatic biopsy with negative findings, and the best way to manage these patients remains uncertain.[17] These men may have enlarged central prostate glands due to benign prostatic hyperplasia, which present sampling problems for TRUS-guided biopsies, or they may have cancer present in locations that are difficult to biopsy.[18] A negative biopsy or biopsies for a persistently raised PSA may have two possible explanations, either a missed cancer (for example through sampling error) or there is no cancer (PSA false positive). The use of MRS and enhanced MRI techniques may help to differentiate between these two situations, thereby avoiding unnecessary further biopsies in the false positives, while at the same time expediting the diagnosis of those men with cancers which are otherwise difficult to diagnose.

Both the National Institute for Health and Clinical Excellence (NICE) and the European Association of Urology (EAU) have issued guidelines on prostate cancer, including diagnosis and staging.[6,7] The NICE guideline states that imaging is not routinely recommended for men in whom no radical treatment is intended. MRS is not recommended for men with prostate cancer except in the context of a clinical trial.[6]

The EAU guidelines state in relation to MRI and MRS for staging prostate cancer:

- Local staging (T-staging of) prostate cancer is based on findings from DRE and possibly MRI.
- In comparison with DRE, TRUS, and CT, MRI demonstrates higher accuracy for the assessment of uni- or bilobar disease (T2), extracapsular extension and seminal vesicle invasion (T3), as well as the invasion of adjacent structures (T4).
- The addition of DCE-MRI can be helpful in equivocal cases.
- The addition of MRS to MRI also increases accuracy and decreases inter-observer variability in the evaluation of extracapsular extension.[7]

This review will assess the diagnostic accuracy of MRS, DCE-MRI and DW-MRI and the clinical effectiveness and cost-effectiveness of strategies involving their use in men with suspected prostate cancer and elevated PSA but previously negative biopsy.

Subsidiary questions to be addressed relating to these techniques include:

- In which patient group are they most clinically effective?
- Can they identify cases where prostate cancer is present but further procedures are unnecessary?
- Does their use lead to changes in patient management?

5. Report methods for synthesis of evidence of clinical effectiveness

Systematic review. A systematic review of the evidence for the diagnostic accuracy of MRS, DCE-MRI and DW-MRI techniques in aiding the localisation of prostate abnormalities for biopsy will be undertaken

following the general principles of the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[19] and reported in accordance with the PRISMA statement.[20]

5.1 Population

The population considered will be men with suspected prostate cancer and elevated prostate specific antigen (PSA) up to 20 ng/ml but previously negative biopsy.

The setting is secondary or tertiary care.

5.2 Index tests

The following tests will be considered, alone or in combination:

- Magnetic resonance spectroscopy (MRS) guided biopsy;
- Dynamic contrast enhanced MRI (DCE-MRI) guided biopsy; and
- Diffusion weighted MRI (DW-MRI) guided biopsy.

If sufficient data are available we may undertake sensitivity analysis around when the studies took place, to assess the effects of changes in the technology over time. For example, for MRS, given sufficient data we will consider the different approaches used, including single voxel and 3D-MRSI (chemical shift imaging).

5.3 Comparator tests

The comparator tests considered will be:

- Standard (T2-weighted) MRI;
- Transrectal ultrasound guided prostate biopsy.

5.4 Reference standard

The reference standard considered will be histopathological assessment of biopsied tissue. Tissue samples may be obtained by transrectal needle biopsy, saturation biopsy, transperineal template biopsy or from prostatectomy specimens.

We will incorporate a follow-up time of 12 months as part of the reference standard, to help distinguish between tumours missed by the index/comparator tests (subsequently detected within this 12 month period) and interval tumours that were not missed (and are subsequently detected after the 12-month follow-up time for histology).

5.5 Outcomes

Included studies must report relevant and interpretable data.

The following outcomes will be considered:

- Diagnostic performance of MRS, DCE-MRI and DW-MRI in the localisation of abnormalities of the prostate.

In studies reporting the above outcome, the following outcomes will also be recorded, if reported:

- Altered treatment as a result of the tests;
- Acceptability of the tests;
- Interpretability of the tests;
- Effect of testing on quality of life (disease-specific and generic instruments);
- Adverse effects of testing.

Studies reporting test performance must report the absolute numbers of true positives, false positives, false negatives and true negatives, or provide information allowing their calculation, and report a per-patient analysis.

5.6 Search strategy

Extensive sensitive electronic searches will be conducted to identify reports of published and ongoing studies on the diagnostic accuracy and cost-effectiveness of MRS, DCE-MRI and DW-MRI techniques in aiding the localisation of prostate abnormalities for biopsy. Highly sensitive search strategies will be designed, including appropriate subject headings and text word terms, interventions under consideration and included study designs. Searches will be restricted to years from 1995 onwards, reflecting the introduction of these techniques for the evaluation of prostate cancer, and restricted to the English language. A draft MEDLINE search is reproduced in *Appendix 1*. Databases to be searched will include MEDLINE, MEDLINE in process, Embase, Science Citation Index, Biosis and the Cochrane Controlled Trials Register. Reports of relevant evidence syntheses will also be sought from the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Review of Effects (DARE), the HTA Database and MEDION.

Conference abstracts for the years 2006 onwards from meetings of the European, American and British Urological Associations will be searched. Ongoing studies will be identified through searching the WHO International Clinical Trials Registry, Current Controlled Trials, Clinical Trials, NIHR Portfolio and NIH National Cancer Institute database. Full text searching of key urology journals will also be undertaken. Websites of manufacturers, professional organisations, regulatory bodies and the HTA agencies will be checked to identify unpublished reports.

Reference lists of all included studies will be scanned in order to identify additional potentially relevant reports. We will also ask our clinical advisers to provide details of any additional potentially relevant reports that they are aware of.

5.7 Inclusion criteria

For diagnostic accuracy of MRS, DCE-MRI and DW-MRI the following types of studies will be included:

- Direct (head-to-head) studies in which index test(s), comparator test(s) and reference standard test are done independently in the same group of people.
- Randomised controlled trials (RCTs) in which people are randomised to the index and comparator test(s) and all receive the reference standard test.

If there is insufficient evidence from direct and randomised studies, we will consider indirect (between-study) comparisons by meta-analysing studies that compare each single test or combination of tests with the reference standard test, and making comparisons between meta-analyses of the different tests. However, this type of study design is less reliable than direct studies as differences in diagnostic accuracy are susceptible to confounding factors between studies. The following types of studies will be considered:

- Observational studies, including case series, in which the sample is created by identifying all people presenting at the point of testing (without any reference to the test results).
- Case-control studies in which two groups are created, one known to have the target disease and one known not to have the target disease, where it is reasonable for all included to go through the tests. We may exclude case-control studies comparing severely diseased people with very healthy controls or studies excluding people with other urological disease such that the spectrum of disease and non-disease is unlike that to be encountered in a diagnostic situation.

If the number of studies meeting our inclusion criteria is sufficiently large, we may limit them by type of study design and taking into account the importance of other factors such as study size.

5.8 Exclusion criteria

The following types of report will be excluded:

- Reviews, editorials and opinions;
- Case reports;
- Reports investigating technical aspects of a test;
- Non-English-language reports.

5.9 Data extraction strategy

One reviewer will screen the titles (and abstracts if available) of all reports identified by the search strategy. Full text copies of all studies deemed to be potentially relevant will be obtained and two reviewers will independently assess them for inclusion. Any disagreements will be resolved by consensus or arbitration by a third party.

A data extraction form will be developed and piloted. Two reviewers will independently extract details from full text studies of study design, participants, index, comparator and reference standard tests and outcome data. Any disagreements will be resolved by consensus or arbitration by a third party.

5.10 Quality assessment strategy

Two reviewers will independently assess the quality of all included diagnostic studies using the quality assessment of diagnostic accuracy studies (QUADAS) checklist. The QUADAS checklist was developed for use in systematic reviews of diagnostic studies[21] and is designed to be adapted to make it more applicable to a specific review topic. QUADAS was developed through a formal consensus method and was based on empirical evidence. The QUADAS tool will be adapted to make it more applicable to assessing the quality of studies of tests for detecting prostate cancer.

Two reviewers will independently assess the quality of any diagnostic studies reporting additional effectiveness outcomes (see section 5.5 above) using one of two separate checklists depending on study design. A 14-question checklist will be used to assess the quality of RCTs. An 18-question checklist will be used to assess non-randomised comparative studies, with the same checklist minus four questions used to assess the methodological quality of case series. The checklist for RCTs was adapted from Verhagen *et al.*[22] and the checklist for non-randomised studies and case series was adapted from several sources, including the Centre for Reviews and Dissemination's guidance for undertaking reviews in health care[19] Verhagen *et al.*,[22] Downs and Black[23] and the Generic Appraisal Tool for Epidemiology (GATE).[24] Both checklists were developed through the Review Body for Interventional Procedures (ReBIP). ReBIP is a joint venture between the Health Services Research Unit, University of Aberdeen and Health Services Research at Sheffield University and works under the auspices of the National Institute for Health and Clinical Excellence (NICE) Interventional Procedures programme. The tools rate bias and generalisability, sample definition and selection, description of the intervention, outcome assessment, adequacy of follow up and performance of the analysis.

For both the QUADAS and ReBIP checklists, each question is worded so that a rating of 'Yes' is always optimal in terms of methodological quality. Any disagreements will be resolved by consensus or arbitration by a third party.

5.11 Methods of analysis/synthesis

The results of the individual diagnostic studies will be tabulated and sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and diagnostic odds ratios (DORs) calculated. If reported in a given study, a separate 2×2 table will be derived for patient-level and prostate site-level analyses.

Summary receiver operating characteristic (SROC) curves will be produced for each test where three or more diagnostic studies report sufficient data in RevMan 5. Where studies report 2×2 data for a number

of different cutoff values then the most frequently used cutoff value across studies will be chosen. Meta-analysis models will be fitted using the hierarchical summary receiver operating characteristic (HSROC) model[25] in SAS 9.1. A symmetric SROC model will be used. This model takes proper account of the diseased and non-diseased sample sizes in each study, and allows estimation of random effects for the threshold and accuracy effects. Summary sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratios (DORs) for each model will be reported as point estimate and 95% confidence interval (CI).

Sensitivity and specificity will be pooled using the weighted average method[26] if numerical difficulties are encountered with the HSROC model and there is no evidence of a threshold effect. Pooled likelihood ratios and DOR will be calculated using the DerSimonian and Laird random effects method.[27] Where a study has an empty cell, a correction of 0.5 will be added to all four cells. These analyses will be carried out using Metadisc software.[28] Heterogeneity will be assessed using the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error. A value greater than 50% may be considered to represent substantial heterogeneity.[29] Where data permit we will explore heterogeneity amongst parameter estimates on a variety of characteristics of the primary studies, e.g. PSA threshold.

For additional non-diagnostic outcomes reported (see section 5.5 above), where appropriate, meta-analysis will be employed to estimate a summary measure of effect. Dichotomous outcome data will be combined using the Mantel-Haenszel relative risk (RR) method and continuous outcomes will be combined using the inverse-variance weighted mean difference (WMD) method. For the estimates of RR and WMD 95% CIs and p-values will be calculated. The results will be reported using a fixed-effect model. Chi-squared tests and I-squared statistics will be used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity will be explored using sensitivity analysis. Where there is no obvious reason for heterogeneity, the implications will be explored using a random-effects model. Where a quantitative synthesis is considered to be inappropriate or not feasible, a narrative synthesis of results will be provided.

6. Report methods for synthesising evidence of cost-effectiveness

The economic objectives are:

- To estimate the costs of standard practice (i.e. transrectal ultrasound-guided biopsy) and alternative guided biopsies in the form of MRS, DCE-MRI and DW-MRI techniques in the diagnosis of prostate abnormalities.
- To estimate the cost-effectiveness of MRS, DCE-MRI and DW-MRI in comparison to standard practice in men with suspected prostate cancer.

An economic model will be developed using data from the literature and expert opinion. The model will be populated using results of the systematic review, other focused reviews for key parameters (e.g. utilities) and if necessary study specific estimates (e.g. for some costs). Bibliographic databases that will be searched include MEDLINE, MEDLINE in process, Embase, Science Citation Index, Health Management Information Consortium (HMIC), NIHR Economic Evaluations Database (NEED) and the HTA database. Using this and other routine information such as the cost of treatment, the effectiveness and cost-effectiveness of alternative methods of diagnosis of prostate cancer will be modelled.

6.1 Economic modelling using the results of the systematic reviews to determine the effectiveness and cost-utility of different options

Diagnostic techniques and any subsequent treatment need not only to be effective but also cost-effective. The proposed research will evaluate, using Markov modelling methods, the clinical effectiveness and cost-effectiveness of various diagnostic technologies to aid the localisation of prostate abnormalities

for biopsy. The economic model will describe the pathway of individuals from the point where a choice exists about the form of biopsy that a patient might receive. It will cover the period of diagnosis using the biopsy, subsequent treatment/management and the consequences during that time period. The structure of the model will be based upon detailed care pathways. To formulate the care pathways we will see how previous economic models in this area have been modelled, and recommendations from current clinical guidelines. We will also seek advice from clinical experts involved in this study to identify pathways for all of the options to be included in the economic model.

The economic model represents a further level of evidence synthesis that will integrate information on the relative effectiveness of diagnostic techniques derived from the systematic review along with information on natural history, costs, and utilities of diagnosing and treating prostate cancer. The economic model will compare the alternative diagnostic techniques for a hypothetical cohort of men with suspected prostate cancer or elevated prostate specific antigen. This cohort will reflect the average population of men presenting with these abnormalities. The time horizon of the model will be the patient's lifetime although shorter time horizons will be explored in a sensitivity analysis.

Data on the resource use and costs incurred for the different diagnostic options and their consequences will be derived from consultation with experts, published literature, including of the existing published economic evidence, manufacturers and other suppliers and other routine sources e.g. NHS reference costs. As noted above, study specific costs will be generated if suitable data from other sources are not available and research resources permit. One area we will investigate is the impact of procedure time of the different MRI techniques and whether any differences in procedure time are reflected in existing cost data or whether we need to devise study specific costs to reflect differences in procedure time. The primary perspective of costs will be the NHS and PSS. Cost data will include the direct health service costs associated with each diagnostic option, treatment and subsequent patient management.

Data on utilities associated with prostate cancer and the possible differences in quality of life of the different options will be derived from the published literature, including a structured review of economic evaluations as well as a search of the CEA Registry.[30]

The results of the model will be presented in terms of a cost-consequence analysis (e.g. costs, number of cases detected, etc). Results will also be presented as incremental cost per quality adjusted life-year gained (QALY). The modelling exercise will use a net benefit framework to combine cost and benefit estimates. The results of the analysis will be presented as point estimates of mean incremental costs, effects, and for any cost utility analysis, incremental cost per QALY. Sensitivity analysis will be used to address parameter and other forms of uncertainty. Cost per QALY data will be presented in terms of cost and effect plots and cost-effective acceptability curves (CEACs).

7. Expertise in this TAR team

The TAR team are experienced in conducting reviews of this nature in both the clinical and technical aspects required to address the commissioning brief. Graham Mowatt, Luke Vale and Cynthia Fraser have been involved in a number of similar studies and the remaining TAR team members are also familiar with and experienced in systematic reviews and economic modelling.

7.1 TAR centre

The Aberdeen Technology Assessment Group has a track record of producing these types of focused reports whilst keeping to tight timescales for various policy customers such as the National Institute for Health and Clinical Excellence (NICE), the National Screening Committee and the NHS R&D HTA programme. In recent years the following similar types of systematic reviews have been completed:

- Screening for open angle glaucoma;
- 64-slice computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease;
- Detection and treatment of staphylococcus aureus infection for patients on peritoneal dialysis for end stage renal disease;
- Rapid point of care tests for the detection of genital Chlamydia;
- Photodynamic diagnosis, urine biomarkers and cytology for the detection and follow-up of bladder cancer.

7.2 Team members' contributions

Pawana Sharma, Research Fellow, will be technical lead on this project and will be responsible for the day-to-day running of the review, as well as undertaking the reviews of test performance and effectiveness, and will be supervised by Graham Mowatt, Senior Research Fellow. Graham Scotland, Research Fellow, Health Economics Research Unit will undertake the economic evaluation. Cynthia Fraser, Information Officer, will develop and run the search strategies and will be responsible for obtaining papers and reference management. Charles Boachie, Statistician, will provide statistical advice and support. Thomas Lam, Specialist Registrar, Department of Urology, Aberdeen Royal Infirmary, Justine Royle, Consultant Urologist, Department of Urology, Aberdeen Royal Infirmary, Lutfi Kurban, Consultant Radiologist and Honorary Senior Lecturer, Department of Radiology, University of Aberdeen, Anwar Padhani, Consultant Radiologist and Head of Imaging Research, Mount Vernon Cancer Centre, Northwood, Middlesex, and Tom Scheenen, MR Physicist, Department of Radiology, Radboud University, Nijmegen Medical Center, Netherlands, will provide clinical support and advice to the team.

8. Competing interests of authors

None.

9. Timetable/milestones

2011:

November–December Develop care pathways, screening, data extraction and quality assessment forms, develop and run searches, assess studies for inclusion, start to develop economic model.

2012:

January–February Data extraction and quality assessment, develop economic model.

March–April Data analysis, develop economic model.

May–July Prepare draft report.

End July Submit report.

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Appendix 1: Draft MEDLINE search strategy

1. exp Diffusion Magnetic Resonance Imaging/
2. Magnetic Resonance Imaging/mt [Methods]
3. magnetic resonance spectroscop$.tw. 1
4. dce-mri.tw.
5. (dynamic contrast enhanced adj3 (MRI or magnetic)).tw.
6. dw-mri.tw.
7. (diffusion weight$ adj3 (MRI or magnetic)).tw.

8. or/1-7 6
9. Prostate-Specific Antigen/
10. Prostatic Neoplasms/
11. psa.tw.
12. (prostat$ adj3 (cancer or carcinoma$ or neoplasm$ or malignan$)).tw.
13. or/9-12
14. 8 and 13
15. "sensitivity and specificity"/
16. roc curve/
17. predictive value of tests/
18. false positive reactions/
19. false negative reactions/
20. du.fs. use mesz
21. sensitivity.tw.
22. distinguish$.tw.
23. differentiat$.tw.
24. identif$.tw.
25. detect$.tw.
26. diagnos$.tw.
27. (predictive adj4 value$).tw
28. accura$.tw.
29. comparison.tw.
30. or/15-29
31. 14 and 30
32. limit 31 to english language
33. limit 32 to yr = "1995 -Current"

Appendix 2 Search strategies

Diagnostic accuracy

MEDLINE 1946 to week 1 March 2012, MEDLINE In-Process Citations 14 March 2012, EMBASE 1980 to week 10 2012

Ovid Multifile Search.

URL: https://shibboleth.ovid.com/

1. prostatic neoplasms/ use mesz
2. exp prostate cancer/ use emez
3. (prostat$ adj3 (cancer or carcinoma$ or neoplasm$ or malignan$)).tw.
4. Prostate-Specific Antigen/
5. psa.tw.
6. prostat$ specific antigen$.tw.
7. or/1-6
8. Magnetic Resonance Imaging/ use mesz
9. Nuclear Magnetic Resonance imaging/ use emez
10. exp Diffusion Magnetic Resonance Imaging/ use mesz
11. Diffusion Weighted Imaging/ use emez
12. exp Magnetic Resonance Spectroscopy/ use mesz
13. Nuclear Magnetic Resonance Spectroscopy/ use emez
14. Prostate/us use mesz
15. Transrectal Ultrasonography/ use emez
16. magnetic resonance imag$.tw.
17. magnetic resonance spectroscop$.tw.
18. mrs.tw.
19. (dynamic contrast enhanced adj3 (MRI or magnetic)).tw.
20. dce-mri.tw.
21. (diffusion weight$ adj3 (MRI or magnetic)).tw.
22. dw-mri.tw.
23. (transrectal adj1 (ultrasound or ultrason$)).tw.
24. trus.tw.
25. (previous$ or initial$) adj3 negative$).tw
26. or/8-25
27. 7 and 26
28. biopsy/
29. biopsy, needle/ or biopsy, fine-needle/ use mesz
30. needle biopsy/ use emez
31. (biopsy or biopsies).tw.
32. (histopathol$ or pathol).tw.
33. (locali?ation or locali?ing).tw.
34. or/28-33
35. 27 and 34
36. exp animals/ not humans/
37. nonhuman/ not human/
38. 35 not (36 or 37)
39. 38 not case report/
40. (comment or editorial or letter or note).pt.

41. 39 not 40
42. limit 41 to english language
43. limit 42 to yr = 1995 - current
44. remove duplicates from 43

Science Citation Index (1995 – 14 March 2012), BIOSIS (1995 – 9 March 2012), Conference Proceedings Citation Index-Science (1995–14 March 2012)

ISI Web of Knowledge. URL: http://wok.mimas.ac.uk/

#1 (TS = (prostat* NEAR/3 (cancer OR carcinoma* OR neoplasm* OR malignan*)))
#2 (TS = PSA)
#3 (TS = (prostat* NEAR/1 specific) AND TS = (specific NEAR/1 antigen*))
#4 #3 OR #2 OR #1
#5 (TS = "magnetic resonance spectroscopy")
#6 (TS = "dce-mri")
#7 (TS = "dynamic contrast enhanced magnetic")
#8 (TS = "dynamic contrast enhanced MRI")
#9 (TS = "dw-mri")
#10 (TS = (Diffusion NEAR/1 weight*) AND TS = (weight* NEAR/1 magnetic))
#11 (TS = (Diffusion NEAR/1 weight*) AND TS = (weight* NEAR/1 MRI))
#12 (TS = "diffusion weighted imaging")
#13 (TS = "magnetic resonance imaging")
#14 (TS = mri)
#15 (TS = mrs)
#16 (TS = (transrectal NEAR/1 ultrasonograph*))
#17 (TS = (transrectal NEAR/1 ultrasound))
#18 (TS = TRUS)
#19 #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5
#20 #19 AND #4
#21 (TS = (localising or localizing or staging))
#22 (TS = (localisation or localization))
#23 (TS = (histapathol* or pathol*))
#24 (TS = (biopsy or biopsies))
#25 #24 OR #23 OR #21 OR #22
#26 #25 AND #20 AND Language = (English)

The Cochrane Library (Issue 3 2012)

URL: http://www3.interscience.wiley.com/

#1 MeSH descriptor Prostatic Neoplasms, this term only
#2 MeSH descriptor Prostate-Specific Antigen, this term only
#3 (psa):ti,ab,kw or (prostat* specific antigen*):ti,ab,kw
#4 (prostat* NEAR/4 cancer):ti,ab,kw or (prostat* NEAR/4 carcinoma*):ti,ab,kw or (prostat* NEAR/4 neoplasm*):ti,ab,kw or (prostat* NEAR/4 malignan*):ti,ab,kw
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Magnetic Resonance Imaging, this term only
#7 MeSH descriptor Diffusion Magnetic Resonance Imaging explode all trees
#8 MeSH descriptor Magnetic Resonance Spectroscopy explode all trees
#9 MeSH descriptor Prostate, this term only with qualifier: US
#10 (magnetic resonance NEAR/4 imag*):ti,ab,kw or (magnetic resonance NEAR/4 spectroscop*):ti,ab,kw or (mrs):ti,ab,kw

#11 (dynamic contrast enhanced NEAR/4 MRI):ti,ab,kw or (dynamic contrast enhanced NEAR/4 magnetic):ti,ab,kw or (dce-mri):ti,ab,kw or (dce mri):ti,ab,kw
#12 (diffusion weight NEAR/4 MRI):ti,ab,kw or (diffusion weight NEAR/4 magnetic):ti,ab,kw or (dw-mri):ti,ab,kw or (dw mri):ti,ab,kw
#13 (transrectal ultrasound):ti,ab,kw or "trus":ti,ab,kw
#14 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 (#5 AND #14)
#16 MeSH descriptor Biopsy, this term only
#17 MeSH descriptor Biopsy, Needle explode all trees
#18 MeSH descriptor Neoplasm Staging this term only
#19 (biopsy):ti,ab,kw or (biopsies):ti,ab,kw or (histopathol*):ti,ab,kw or (pathol*):ti,ab,kw
#20 (localisation):ti,ab,kw or (localization):ti,ab,kw or (localising):ti,ab,kw or (localizing):ti,ab,kw or (staging):ti,ab,kw
#21 (#16 OR #17 OR #18 OR #19)
#22 (#15 AND #21)

Health Technology Assessment/Database of Abstracts of Reviews of Effects databases (March 2012)

Centre for Reviews & Dissemination. URL: http://nhscrd.york.ac.uk/welcome.htm

1. MeSH DESCRIPTOR prostatic neoplasms WITH QUALIFIER undefined 3
2. MeSH DESCRIPTOR Prostate-Specific Antigen EXPLODE ALL TREES
3. #1 OR #2
4. MeSH DESCRIPTOR Magnetic Resonance Imaging EXPLODE ALL TREES
5. MeSH DESCRIPTOR Magnetic Resonance Spectroscopy EXPLODE ALL TREES
6. MeSH DESCRIPTOR Diffusion Magnetic Resonance Imaging EXPLODE ALL TREES
7. MeSH DESCRIPTOR prostate EXPLODE ALL TREES WITH QUALIFIERS undefined, US
8. ("dynamic contrast enhanced") OR (dce-mri) OR ("diffusion weighted") OR (dw-mri)
9. ("transrectal ultrasound") OR ("transrectal ultrasonography") OR (trus)
10. #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. #3 AND #10

Medion (March 2012)

URL: www.mediondatabase.nl/

KW = male genital system OR urology

AND medical imaging

Clinical Trials (March 2012)

URL: http://clinicaltrials.gov/ct/gui/c/r

Disease = prostatic neoplasms Intervention = magnetic

Current Controlled Trials (March 2012)

URL: www.controlled-trials.com/

Prostat% and magnetic

International Clinical Trials Registry Platform (ICTRP) (March 2012)

World Health Organization URL: www.who.int/ictrp/en/

Prostat* AND magnetic

National Institutes of Health Research Portfolio Online Reporting Tool (NIH RePORTER) (March 2012)

URL: http://projectreporter.nih.gov/reporter.cfm

Prostat% and magnetic

Conference proceedings

American Society of Clinical Oncolology.

URL: www.asco.org

- Annual Meeting, Orlando, FL, 29 May to 2 June 2009
- Annual Meeting, Chicago, IL, 4–8 June 2010
- Annual Meeting, Chicago, IL, 3–7 June 2011

Websites consulted

American Society of Clinical Oncology. URL: www.asco.org

American Urological Association. URL: www.auanet.org/

Cancer Research UK. URL: http://info.cancerresearchuk.org/cancerstats/

European Association of Urology. URL: www.uroweb.org/

Economic evaluations

NIHR Economic Evaluations Database (March 2012)

Centre for Reviews & Dissemination. URL: http://nhscrd.york.ac.uk/welcome.htm

1. MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES WITH QUALIFIERS TH, SU,RT,DT IN NHSEED
2. MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES WITH QUALIFIERS DI, RA, RI, US IN NHSEED
3. #1 OR #2

Health Management Information Consortium 1979 – January 2012

Ovid. URL: https://shibboleth.ovid.com/

1	prostate cancer/
2	(prostat$ adj3 (cancer or carcinoma$ or neoplasm$ or malignan$)).tw.
3	1 or 2
4	exp economic analysis/
5	economic models/

6	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).tw.
7	(economics$ or pharmacoeconomic$ or pharmo-economic$).ti.
8	(price$ or pricing$).tw.
9	(financial or finance or finances or financed).tw.
10	(value adj2 (money or monetary)).tw.
11	markov$.tw.
12	monte carlo.tw.
13	(decision$ adj2 (tree? or analy$ or model$)).tw.
14	or/4-13
15	3 and 14

MEDLINE 1966 to March week 1 2012, MEDLINE In-Process Citations 16 March 2012, EMBASE 1980 to 2012 week 11

Ovid Multifile Search. URL: https://shibboleth.ovid.com/

1	prostatic neoplasms/ use mesz
2	exp prostate cancer/ use emez
3	(prostat$ adj3 (cancer or carcinoma$ or neoplasm$ or malignan$)).tw.
4	Prostate-Specific Antigen/
5	psa.tw.
6	prostat$ specific antigen$.tw.
7	or/1-6
8	Magnetic Resonance Imaging/ use mesz
9	Nuclear Magnetic Resonance imaging/ use emez
10	exp Diffusion Magnetic Resonance Imaging/ use mesz
11	Diffusion Weighted Imaging/ use emez
12	exp Magnetic Resonance Spectroscopy/ use mesz
13	Nuclear Magnetic Resonance Spectroscopy/ use emez
14	Prostate/us use mesz
15	Transrectal Ultrasonography/ use emez
16	magnetic resonance imag$.tw.
17	magnetic resonance spectroscop$.tw.
18	mrs.tw.
19	(dynamic contrast enhanced adj3 (MRI or magnetic)).tw.
20	dce-mri.tw.
21	(diffusion weight$ adj3 (MRI or magnetic)).tw.
22	dw-mri.tw.
23	transrectal adj (ultrasound or ultason$).tw.

24	trus.tw.
25	or/8-24
26	7 and 25
27	prostatic neoplasms/di, ra, ri, us use mesz
28	exp prostate cancer/di use emez
29	26 or 27 or 28
30	exp "costs and cost analysis"/ use mesz
31	exp economic evaluation/ use emez
32	economics/
33	health economics/ use emez
34	exp economics,hospital/ use mesz
35	exp economics,medical/ use mesz
36	economics,pharmaceutical/ use mesz
37	exp budgets/
38	exp models, economic/ use mesz
39	exp decision theory/
40	monte carlo method/
41	markov chains/
42	exp technology assessment, biomedical/
43	cost$.ti.
44	(cost$ adj2 (effective$ or utilit$ or benefit$ or minimis$)).ab.
45	economics model$.tw.
46	(economic$ or pharmacoeconomic$).tw.
47	(price or prices or pricing).tw.
48	(value adj1 money).tw.
49	markov$.tw.
50	monte carlo.tw.
51	(decision$ adj2 (tree? or analy$ or model$)).tw.
52	or/30-51
53	29 and 52

Quality of life

MEDLINE 1966 to week 1 March 2012, MEDLINE In-Process Citations 16 March 2012, EMBASE 1980 to week 11 2012

Ovid Multifile Search. URL: https://shibboleth.ovid.com/

1. prostatic neoplasms/ use mesz
2. exp prostate cancer/ use emez

3. (prostat$ adj3 (cancer or carcinoma$ or neoplasm$ or malignan$)).tw.
4. Prostate-Specific Antigen/
5. psa.tw.
6. prostat$ specific antigen$.tw.
7. or/1-6
8. Magnetic Resonance Imaging/ use mesz
9. Nuclear Magnetic Resonance imaging/ use emez
10. exp Diffusion Magnetic Resonance Imaging/ use mesz
11. Diffusion Weighted Imaging/ use emez
12. exp Magnetic Resonance Spectroscopy/ use mesz
13. Nuclear Magnetic Resonance Spectroscopy/ use emez
14. Prostate/us use mesz
15. Transrectal Ultrasonography/ use emez
16. magnetic resonance imag$.tw.
17. magnetic resonance spectroscop$.tw.
18. mrs.tw.
19. (dynamic contrast enhanced adj3 (MRI or magnetic)).tw.
20. dce-mri.tw.
21. (diffusion weight$ adj3 (MRI or magnetic)).tw.
22. dw-mri.tw.
23. transrectal adj (ultrasound or ultason$).tw.
24. trus.tw.
25. or/8-24
26. 7 and 25
27. quality of life/
28. quality adjusted life year/
29. "Value of Life"/ use mesz
30. health status indicators/ use mesz
31. health status/ use emez
32. sickness impact profile/ use mesz
33. disability evaluation/ use mesz
34. disability/ use emez
35. activities of daily living/ use mesz
36. exp daily life activity/ use emez
37. cost utility analysis/ use emez
38. rating scale/
39. questionnaires/
40. (quality adj1 life).tw.
41. quality adjusted life.tw.
42. disability adjusted life.tw.
43. (qaly? or qald? or qale? or qtime? or daly?).tw.
44. (euroqol or euro qol or eq5d or eq 5d).tw.
45. (hql or hqol or h qol or hrqol or hr qol).tw.
46. (hye or hyes).tw.
47. health$ year$ equivalent$.tw.
48. (hui or hui1 or hui2 or hui3).tw.
49. (health adj3 (utilit$ or disutili$)).tw.
50. (health adj3 (state or status)).tw.
51. (sf36 or sf 36 or short form 36 or shortform 36).tw.
52. (sf6 or sf 6 or short form 6 or shortform 6).tw.
53. (sf12 or sf 12 or short form 12 or shortform 12).tw.
54. (sf16 or sf 16 or short form 16 or shortform 16).tw.
55. (sf20 or sf 20 or short form 20 or shortform 20).tw.

56. willingness to pay.tw.
57. standard gamble.tw.
58. trade off.tw.
59. conjoint analys?s.tw.
60. discrete choice.tw.
61. or/27-60
62. (case report or editorial or letter).pt.
63. case report/
64. 61 not (62 or 63)
65. 26 and 64
66. remove duplicates from 65
67. limit 66 to english language

Appendix 3 Quality assessment of diagnostic accuracy studies (version 2) checklist

Magnetic resonance spectroscopy and enhanced MRI techniques in aiding the localisation of prostate abnormalities for biopsy – QUADAS-2 risk of bias tool.

Domain 1: patient selection

A. Risk of bias

	Yes	No	Unclear
Signalling questions:			
1. Was a consecutive or random sample of patients enrolled?			
2. Was a case–control design avoided?			
3. Did the study avoid inappropriate exclusions?			
	Risk		
	Low	**High**	**Unclear**
Could the selection of patients have introduced bias?			

B. Concerns regarding applicability

	Concern		
	Low	**High**	**Unclear**
Is there concern that the included patients do not match the review question?			

Domain 2: index & comparator test(s)

A. Risk of bias

	Yes	No	Unclear
Signalling questions:			
4. Were the index test results interpreted without knowledge of the results of the reference standard?			
5. If a threshold was used, was it pre-specified?			
6. For a test requiring subjective interpretation, was it interpreted by someone experienced in interpreting such tests?			
	Risk		
	Low	**High**	**Unclear**
Could the conduct or interpretation of the index test have introduced bias?			

B. Concerns regarding applicability

	Concern		
	Low	**High**	**Unclear**
Is there concern that the index test, its conduct, or interpretation differ from the review question?			

Domain 3: reference standard

A. Risk of bias

	Yes	No	Unclear
Signalling questions:			
7. Is the reference standard likely to correctly classify the target condition?			
8. Were the reference standard results interpreted without knowledge of the results of the index test?			
9. Were the results of the reference standard test interpreted by someone experienced in interpreting such tests?			
10. Was a follow-up included in the reference standard?			

	Risk		
	Low	High	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?			

B. Concerns regarding applicability

	Concern		
	Low	High	Unclear
Is there concern that the target condition as defined by the reference standard does not match the review question?			

Domain 4: flow and timing

A. Risk of bias

	Yes	No	Unclear
Signalling questions:			
11. Was there an appropriate interval between index test(s) and reference standard?			
12. Did all patients receive a reference standard?			
13. Did patients receive the same reference standard?			
14. Were all patients included in the analysis?			

	Risk		
	Low	High	Unclear
Could the patient flow have introduced bias?			

Appendix 4 List of included studies

Amsellem-Ouazana 2005

Amsellem-Ouazana D, Younes P, Conquy S, Peyromaure M, Flam T, Debre B, *et al.* Negative prostatic biopsies in patients with a high risk of prostate cancer. Is the combination of endorectal MRI and magnetic resonance spectroscopy imaging (MRSI) a useful tool? A preliminary study. *Eur Urol* 2005;**47**:582–6.

Babaian 2000

Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, *et al.* A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. *J Urol* 2000;**163**:152–7.

Beyersdorff 2002

Beyersdorff D, Taupitz M, Winkelmann B, Fischer T, Lenk S, Loening SA, *et al.* Patients with a history of elevated prostate-specific antigen levels and negative transrectal US-guided quadrant or sextant biopsy results: value of MR imaging. *Radiology* 2002;**224**:701–6.

Secondary publication

Winkelmann B, Beyersdorff D, Taupitz M, Deger S, Tuerk I, Loening SA. Value of high-resolution MR-imaging in patients with elevated PSA levels and negative TRUS-guided quadrant or sextant biopsy. *J Urol* 2001;**165**:317.

Bhatia 2007

Bhatia C, Phongkitkarun S, Booranapitaksonti D, Kochakarn W, Chaleumsanyakorn P. Diagnostic accuracy of MRI/MRSI for patients with persistently high PSA levels and negative TRUS-guided biopsy results. *J Med Assoc Thai* 2007;**90**:1391–9.

Calvo 2010

Calvo N, Henriquez L, I, Pujol F, Milia L, Pont A, Grio J, *et al.* Utility of magnetic resonance spectroscopy and guided biopsies in patients with previous negative biopsies and suspicious of prostate cancer. *Radiother Oncol* 2010;**96**(Suppl. 1):419.

Campodonico 2006

Campodonico F, Casarico A, Gavazzi L, Calcagno T, Capponi G, Canepa G, *et al.* Cancer detection with TRUS-guided 10-core biopsy of the prostate. an institutional assessment at the first, repeated and surgical specimen biopsy. *Arch Ital Urol Androl* 2006;**78**:39–43.

Cheikh 2009

Cheikh AB, Girouin N, Colombel M, Marechal JM, Gelet A, Bissery A, *et al.* Evaluation of T2-weighted and dynamic contrast-enhanced MRI in localizing prostate cancer before repeat biopsy. *Eur Radiol* 2009;**19**:770–8.

Chung 2010

Chung MS, Lee SH, Oh CK, Park SU, Rha KH, Oh YT, *et al.* MRI is important before repeat targeted biopsy in men with prior negative prostatic biopsy. *Eur Urol 2010;* **9**(Suppl. 3):501.

Cirillo 2008

Cirillo S, Petracchini M, Della MP, Gallo T, Tartaglia V, Vestita E, *et al.* Value of endorectal MRI and MRS in patients with elevated prostate-specific antigen levels and previous negative biopsies to localize peripheral zone tumours. *Clin Radiol* 2008;**63**:871–9.

Comet-Batlle 2004
Comet-Batlle J, Vilanova-Busquets J, Maroto-Genover A, Bucar-Terrades S, Lopez-Bonet E, Barcelo-Obregon J, *et al.* Targeting prostate cancer in the central gland with endorectal MRI and spectroscopy. *Eur Urol Suppl* 2004;**3**:36.

De La Rosette 2009
De La Rosette JJ, Wink MH, Mamoulakis C, Wondergem N, ten Kate FJ, Zwinderman K, *et al.* Optimizing prostate cancer detection: 8 versus 12-core biopsy protocol. *J Urol* 2009;**182**:1329–36.

Destefanis 2009
Destefanis P, Bosio A, De MC, Bisconti A, Cugiani A, Negro CLA, *et al.* Targeted needle re-biopsy of the prostate after combination of endorectal MRI (ENDOMRI) and magnetic resonance spectroscopy (MRS) in patients with atypical small acinar proliferation (ASAP). *Eur Urol Suppl* 2009;**8**:354.

Djavan 2001
Djavan B, Ravery V, Zlotta A, Dobronski P, Dobrovits M, Fakhari M, *et al.* Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? *J Urol* 2001;**166**:1679–83.

Engelhard 2006
Engelhard K, Hollenbach HP, Kiefer B, Winkel A, Goeb K, Engehausen D. Prostate biopsy in the supine position in a standard 1.5-T scanner under real time MR-imaging control using a MR-compatible endorectal biopsy device. *Eur Radiol* 2006;**16**:1237–43.

Eskicorapci 2007
Eskicorapci SY, Guliyev F, Islamoglu E, Ergen A, Ozen H. The effect of prior biopsy scheme on prostate cancer detection for repeat biopsy population: Results of the 14-core prostate biopsy technique. *Int Urol Nephrol* 2007;**39**:189–95.

Franiel 2011
Franiel T, Stephan C, Erbersdobler A, Dietz E, Maxeiner A, Hell N, *et al.* Areas suspicious for prostate cancer: MR-guided biopsy in patients with at least one transrectal US-guided biopsy with a negative finding – multiparametric MR imaging for detection and biopsy planning. *Radiology* 2011;**259**:162–72.

Ghafoori 2010
Ghafoori M, Moradi M, Shakiba M, Hosseini K, Alavi M. Targeted TRUS-guided biopsy of prostate with the aid of MR spectroscopy in the patients with elevated PSA and negative previous systematic biopsy. *J Med Imag Radiat Oncol 2010;* **54**(Suppl. S1):A19.

Hambrock 2010
Hambrock T, Somford DM, Hoeks C, Bouwense SA, Huisman H, Yakar D, *et al.* Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. *J Urol* 2010;**183**:520–7.

Secondary publications
Hambrock T, Futterer JJ, Huisman HJ, Hulsbergen-van de Kaa C, Van Basten JP, Van Oort I, *et al.* Thirty-two-channel coil 3T magnetic resonance-guided biopsies of prostate tumor suspicious regions identified on multimodality 3T magnetic resonance imaging: technique and feasibility. *Invest Radiol* 2008;**43**:686–94.

Hambrock T, Somford D, Futterer J, Van Oort, I, Van Basten JP, Witjes A, *et al.* Value of 3 TESLA multi-modality directed MR-guided biopsy to detect prostate cancer in patients after at least two previous negative biopsies and elevated PSA. *J Urol* 2009;**181**(Suppl. 1):706.

Hambrock T, Somford DM, Futterer JJ, Hoeks CMA, Hulsbergen-Van De Kaa CA, Van Oort IM, *et al.* Value of 3 tesla multimodality MR-guided biopsy (MRGB) to detect prostate cancer in patients after at least two previous negative biopsies and an elevated PSA. *Eur Urol Suppl* 2009;**8**:195.

Hambrock T, Somford DM, Hoeks H. Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. *J Vascul Intervent Radiol* 2010;**21**:764.

Hoeks 2012
Hoeks CMA, Schouten MG, Bomers JGR, Hoogendoorn SP, Hulsbergen-Van De Kaa CA, Hambrock T, *et al.* Three-Tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. *Eur Urol* 2012. doi.org/10.1016/j.eururo.2012.01.047

Keetch 1994
Keetch DW, Catalona WJ, Smith DS. Serial prostatic biopsies in men with persistently elevated serum prostate specific antigen values. *J Urol* 1994;**151**:1571–4.

Labanaris 2010
Labanaris AP, Engelhard K, Zugor V, Nützel R, Kühn R. Prostate cancer detection using an extended prostate biopsy schema in combination with additional targeted cores from suspicious images in conventional and functional endorectal magnetic resonance imaging of the prostate. *Prostate Cancer Prostat Dis* 2010;**13**:65–70.

Secondary publications
Labanaris AP, Engelhard K, Smiszek R, Nützel R, Kühn R. Prostate cancer detection using an extended prostate biopsy schema in combination with additional targeted cores from suspicious images in conventional and functional endorectal magnetic resonance imaging of the prostate. *J Urol* 2009;**181**(Suppl. 1):711–12.

Labanaris AP, Engelhard K, Nützel R, Smiszek R, Kühn R. Endorectal magnetic resonance imaging of the prostate. A useful tool in the detection of anterior prostate cancer. *J Urol* 2010;**183**(Suppl. 1):e719.

Lattouf 2007
Lattouf JB, Grubb RL III, Lee SJ, Bjurlin MA, Albert P, Singh AK, *et al.* Magnetic resonance imaging-directed transrectal ultrasonography-guided biopsies in patients at risk of prostate cancer. *BJU Int* 2007;**99**:1041–6.

Lee 2011
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Invalid study design (*n* = 57)

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Appendix 6 Characteristics of the included studies

Study	Participants	Tests	Outcomes summary
Amsellem-Ouazana 2005[74] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** April 2003 to April 2004 **Country:** France **Follow-up:** N	**Enrolled:** 42 **Analysed:** 42 **Consecutive:** Y **Age (years):** Mean 62.3, range 54 to 74 **PSA (ng/ml):** Mean 12.1, range 3.87 to 35 **Prostate size:** NR **Previous negative biopsies:** Mean 2, range 1 to 4 **Previous biopsy scheme:** 12-core TRUS **Inclusion criteria:** Persistently increasing PSA, at least one negative 12-core biopsy and normal DRE **Exclusion criteria:** NR	**Index test(s):** MRS Definition of positive test: CC/C ratio ≥0.75 **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Judged as equivocal if homogenously low in signal with conservation of the prostate gland architecture and without mass syndrome. Judged as suspicious if there was a precise area of low signal associated with a mass syndrome **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 42$) **Sensitivity:** MRS 93.3%, T2 60% **Specificity:** MRS 96.3%, T2 66.7% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Babaian 2000[75] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** May 1997 to October 1998 **Country:** USA **Follow-up:** N	**Enrolled:** 277 **Analysed:** 277 **Consecutive:** NR **Age (years):** Mean 63.5, range 39 to 76 **PSA (ng/ml):** Mean 8.3, range 0.7 to 28.1 **Prostate size (cc):** Mean 57.9, range 18 to 177 **Previous negative biopsies:** 1–5 **Previous biopsy scheme:** 11-core TRUS **Inclusion criteria:** Persistently abnormal PSA or change in DRE and/or TRUS **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 277$) **Sensitivity:** TRUS 6-core 39.5%, TRUS 11-core 48.1%, TRUS 6-core with TRUS 11-core as reference standard 66.7 **Specificity:** TRUS 6-core 80.1%, TRUS 11-core 83.7% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Beyersdorff 2002[57,135] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** Germany **Follow-up:** N	**Enrolled:** 44 **Analysed:** 38 **Consecutive:** Y **Age (years):** Mean 64.6, range 46 to 76 **PSA (ng/ml):** Mean 13.9, range 4 to 53 **Prostate size:** NR **Previous negative biopsies:** 1 to 6 **Previous biopsy scheme:** 4- or 6-core (approach NR) **Inclusion criteria:** PSA > 4 ng/ml or free–total PSA ratio < 15%; prior negative TRUS quadrant or sextant biopsy **Exclusion criteria:** Contraindications to MRI or use of endorectal coil	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** T2, TRUS **Definition of positive test:** **T2:** Confluent hypointense areas were classified as suspicious; in homogeneously hypointense areas were classified as inconclusive **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 38$) **Sensitivity:** T2 100%, TRUS 33.3% **Specificity:** T2 26.9%, TRUS 88.5% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Bhatia 2007[76] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 2006 to October 2006 **Country:** Thailand **Follow-up:** N	**Enrolled:** 21 **Analysed:** 21 **Consecutive:** Y **Age (years):** Mean 61.4, range 50 to 77 **PSA (ng/ml):** Mean 13.1, range 4.3 to 46.6 **Prostate size:** NR **Previous negative biopsies:** 1–3 **Previous biopsy scheme:** Sextant TRUS **Inclusion criteria:** PSA persistently > 4 ng/ml and at least one prior sextant TRUS/Bx **Exclusion criteria:** Contraindications to MRI or use of endorectal coil	**Index test(s):** MRS **Definition of positive test:** Score obtained from spectral pattern and adjusted according to the CC/C ratio. Voxel scores of 1 and 2 classified as 'normal'. Voxel score of 3 was 'equivocal'. Voxel scores of 4 and 5 classified as 'suspicious'. 'Suspicious' scores were classed as positive for malignancy for the purposes of determining diagnostic accuracy **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Area of discrete and homogeneously low signal intensity that did not correspond to the haemorrhagic areas with high signal intensity on T1W images classed as suspicious. Area of slightly heterogeneous low signal intensity classed as equivocal **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 21$) **Sensitivity:** MRS 100%, T2 100%, MRS and T2 100% **Specificity:** MRS 73.7%, T2 78.9%, MRS and T2 84.2% **Unit of analysis:** Biopsy ($n = 290$) **Sensitivity:** MRS 78.6%, T2 64.3%, MRS and T2 64.3% **Specificity:** MRS 80.4%, T2 84.1%, MRS and T2 91.7% **Adverse effects:** Most men had transient haematuria after the TRUS biopsy but did not require treatment **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Calvo 2010[115] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** August 2008 to January 2010 **Country:** Spain **Follow-up:** N	**Enrolled:** 59 **Analysed:** 59 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** NR **Inclusion criteria:** Suspicion of PC and previous negative biopsies **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** NR **Comparator test(s):** TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 59$) **Sensitivity:** MRS 100% **Specificity:** MRS 74.4% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Campodonico 2006[77] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 2003 to September 2005 **Country:** Italy **Follow-up:** Y (length NR)	**Enrolled:** 81 **Analysed:** 81 **Consecutive:** NR **Age (years):** < 60, *n* = 20 60– 69, *n* = 37 70– 79, *n* = 24 **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** 10- or 12-core TRUS **Inclusion criteria:** Clinical suspicion of PC based on abnormal DRE, increased PSA or hypoechoic lesion at TRUS **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient (*n* = 81) **Sensitivity:** TRUS 88.9% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Cheikh 2009[78] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** November 2005 to March 2008 **Country:** France **Follow-up:** N	**Enrolled:** 93 **Analysed:** 93 **Consecutive:** NR **Age (years):** Mean 63.2, range 52 to 74 **PSA (ng/ml):** Mean 9.63, range 1.6 to 40 **Prostate size (cc):** Mean 49.8 **Previous negative biopsies:** 1–5 **Previous biopsy scheme:** NR (mean 12.6-cores for 129/173 previous negative biopsies) **Inclusion criteria:** Patients who had undergone MRI before repeat biopsy **Exclusion criteria:** NR	**Index test(s):** DCE **Definition of positive test:** All nodules showing early enhancement in the PZ or SV wall were considered malignant **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** All low-signal-intensity nodules in the PZ were considered malignant. In the central gland, only homogeneous low-signal-intensity areas with ill-defined margins and no visible capsule were interpreted as malignant. All central gland hypointense areas extending into the PZ were also considered malignant **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient (*n* = 93) **Sensitivity:** DCE 82.6%, T2 47.8%, DCE or T2 82.6%, DCE and T2 47.8% **Specificity:** DCE 20%, T2 44.3%, DCE or T2 15.7%, DCE and T2 51.4% **Unit of analysis:** Sector (*n* = 670) **Sensitivity:** DCE 52.3%, T2 31.8%, DCE or T2 52.3%, DCE and T2 31.8% **Specificity:** DCE 83.5%, T2 89.8%, DCE or T2 83.1%, DCE and T2 92.3% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Chung 2010[116] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** July 2008 to December 2009 **Country:** Republic of Korea **Follow-up:** N	**Enrolled:** 57 **Analysed:** 57 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** 12-core (approach NR) **Inclusion criteria:** Persistently increasing serum PSA, at least one previous negative 12-core prostate biopsy and normal DRE **Exclusion criteria:** NR	**Index test(s):** DW **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** NR **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Core ($n = 971$) **Sensitivity:** DW or T2 82.8% **Specificity:** DW or T2 68.9% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Cirillo 2008[79] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** July 2004 to February 2006 **Country:** Italy **Follow-up:** N	**Enrolled:** 54 **Analysed:** 54 **Consecutive:** Y **Age (years):** Mean 65.4 **PSA (ng/ml):** Mean 10.8 **Prostate size (cc):** Mean 76 ml, range 22 to 181 **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR (median eight cores) **Inclusion criteria:** Persistently elevated PSA level (≥ 4 ng/ml) and at least one prior negative TRUS biopsy **Exclusion criteria:** Previous hormonal, surgical or irradiation therapy	**Index test(s):** MRS **Definition of positive test:** If one or more suspicious prostate voxels were identified. Voxels were classified as suspicious if the CC/C ratio was > 0.86 **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** If hypotense on T2-weighted images and isotense on T1-weighted images with a nodular or plaque-like morphology and if observed on at least two different planes. Combined MRS and T2 were classified as normal if both MRS and T2 were normal and suspicious in other cases. Using combined MRS and T2, PC was suspected if one or more suspicious prostate sites were identified **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 54$) **Sensitivity:** MRS 88.2%, T2 100%, MRS or T2 100%, MRS and T2 88.2% **Specificity:** MRS 70.3%, T2 64.9%, MRS or T2 51.4%, MRS and T2 NR **Unit of analysis:** Site ($n = 540$) **Sensitivity:** MRS 81.8%, T2 77.3%, MRS or T2 86.4% **Specificity:** MRS 91.3%, T2 90.7%, MRS or T2 86.3% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Comet-Batlle 2004[117] Abstract **Study type:** Prospective cohort diagnostic **Study start/end dates:** NR **Country:** Spain **Follow-up:** N	**Enrolled:** NR **Analysed:** 5 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR **Inclusion criteria:** Elevated PSA level and repeated negative biopsies **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 5$) **Sensitivity:** MRS or T2 NR **Specificity:** MRS or T2 NR (PPV = 100%) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
De la Rosette 2009[80] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** September 2004 to September 2007 **Country:** The Netherlands **Follow-up:** N	**Enrolled:** 139 **Analysed:** 139 **Consecutive:** NR **Age (years):** Mean 62.3 **PSA (ng/ml):** Median 5.5, range 1.1 to 34.1 **Prostate size (cc):** Median 60 ml, range 18 to 196 **Previous negative biopsies:** 1 **Previous biopsy scheme:** 8- or 12-core TRUS **Inclusion criteria:** Age-dependent increased serum PSA level, positive DRE or suspicious TRUS **Exclusion criteria:** Signs of prostatitis, UTI or acute urinary retention within the previous month; use of PSA level altering medication (5-alpha-reductase inhibitors) within the previous 6 months	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 139$) **Sensitivity:** TRUS 10% **Specificity:** TRUS 73.9% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

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Study	Participants	Tests	Outcomes summary
Destefanis 2009[118] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** November 2005 to September 2008 **Country:** Italy **Follow-up:** N	**Enrolled:** 28 **Analysed:** 26 **Consecutive:** Y **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** TRUS-guided (no. of cores NR) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** CC/C > 0.86 **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Low-intensity signal **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 26$) **Sensitivity:** T2 or MRS 100% **Specificity:** T2 or MRS 11.8% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Djavan 2001[81] Full text **Study type:** Cross-sectional diagnostic (screening study) **Study start/end dates:** January 1997 to March 1999 **Country:** Austria/Belgium/France/Poland **Follow-up:** Y (every 6 or 8 weeks)	**Enrolled:** 1051 **Analysed:** 821 **Consecutive:** Y **Age (years):** Mean 68, range 48 to 76 **PSA (ng/ml):** Mean 7.1, range 4 to 10.7 **Prostate size (cc):** Mean 42.5, range 16 to 119 **Previous negative biopsies:** 1 **Previous biopsy scheme:** 8-core TRUS (sextant + two TZ) **Inclusion criteria:** Referred for either early PC screening or lower urinary tract symptoms; PSA level of between 4 and 10 ng/ml **Exclusion criteria:** History of PC, acute or chronic prostatitis and histological evidence of PIN at any grade, urinary retention, indwelling urinary catheter or confirmed UTI	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 820$) **Sensitivity:** TRUS 67.5% **Specificity:** TRUS NR **Adverse effects:** Minor or no discomfort 89% Mild haematuria 57% Recurrent mild haematuria 16.6% UTI 11.3% Delayed haematospermia 10.2% Persistent dysuria 6.8% Rectal bleeding 2.4% Delayed fever 2.3% Vasovagal episodes 1.4% Severe haematuria 0.5% Major rectal bleeding 0.1% **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Engelhard 2006[82] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** December 2003 to May 2005 **Country:** Germany **Follow-up:** N	**Enrolled:** 37 **Analysed:** 37 **Consecutive:** Y **Age (years):** Mean 66, range 46 to 75 **PSA (ng/ml):** Mean 10.8, range 4 to 48 **Prostate size:** NR **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** Sextant TRUS **Inclusion criteria:** Elevated PSA level (≥4 ng/ml), negative or inconclusive TRUS or at least one negative TRUS/Bx **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** T2 **Definition of positive test:** Visible signal changes; asymmetric hypointense lesions within the normally high-signal PZ were classed as profoundly suspect. Low-signal lesions in the front gland (TZ and CZ) were classed as moderately suspect **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 37$) **Sensitivity:** T2 NR **Specificity:** T2 NR (PPV 37.8%) **Unit of analysis:** Biopsy ($n =$ NR) **Sensitivity:** T2 NR **Specificity:** T2 NR (PPV 57.7%) **Adverse effects:** There were no collateral effects or complications caused by the biopsy **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Eskicorapci 2007[83] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** March 2001 to December 2005 **Country:** Turkey **Follow-up:** N	**Enrolled:** 211 **Analysed:** 211 **Consecutive:** NR **Age (years): median (IQR)** Sextant group: 62 (56 to 69) 10-core group: 64 (55 to 70) **PSA (ng/ml): median (IQR)** Sextant group: 7.8 (5.9 to 12.3) 10-core group: 7.5 (5.9 to 11.7) **Prostate size (cc): median (IQR)** Sextant group: 50 cc (39.9 to 70) 10-core group: 54 cc (41.5 to 68) **Previous negative biopsies:** At least one **Previous biopsy scheme:** Sextant or 10-core TRUS **Inclusion criteria:** Serum PSA level > 4 ng/ml, increasing serum PSA level and/or abnormal DRE and/or presence of HGPIN **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 211$) **Sensitivity:** TRUS 18.5% **Specificity:** TRUS 78.3% **Adverse effects:** All patients tolerated the biopsy procedure well and none needed intravenous sedation or narcotic analgesics **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Franiel 2011[84] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** December 2008 to December 2009 **Country:** Germany **Follow-up:** N	**Enrolled:** 55 **Analysed:** 54 **Consecutive:** Y **Age (years):** Median 68, range 49 to 78 **PSA (ng/ml):** Median 12.1, range 3.3 to 65.2 **Prostate size:** NR **Previous negative biopsies:** 1–6 **Previous biopsy scheme:** Systematic TRUS (no. of cores NR) **Inclusion criteria:** At least one negative systematic TRUS/Bx and continued suspicion of PC, i.e. PSA level > 4 ng/ml, suspicious DRE, abnormal PSA velocity **Exclusion criteria:** Presence of a cardiac pacemaker or other electronic implant, reported claustrophobia, known allergy to gadolinium-based contrast agents and failure to give written informed consent	**Index test(s):** MRS, DCE, DW **Definition of positive test:** Diagnostic MR imaging examinations were classified as benign, inconclusive or suspicious on T2 images using published criteria and taking account of the corresponding T1 images for signal intensity changes caused by bleeding. All areas classed as inconclusive or suspicious on T2 images were evaluated further for the CC/C ratio at ^{1}H-MRS, the ADC from DW imaging and exchange constants K^{trans} and k_{ep} from pharmacokinetic parameter maps **Comparator test(s):** T2 **Definition of positive test:** Inconclusive: In the PZ, ill-defined area of diffuse and inhomogeneous mild hypointensity. In the TZ, areas with homogeneous low T2 signal intensity with preserved capsule Suspicious: In the PZ, mass-like region of confluent hypointense area; in the TZ, region of homogeneous low T2 signal intensity with lenticular shape or absence of a capsule and ill-defined margins **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 54$) **Sensitivity:** T2 85.7%; T2 or MRS 95.2%; T2 or DW 100%; T2 or DCE 85.7%; T2 or MRS or DW 100%; T2 or MRS or DCE 95.2%; T2 or DW or DCE 100%; T2 or MRS or DW or DCE 100% **Specificity:** T2 33.3%; T2 or MRS 24.2%; T2 or DW 3%; T2 or DCE 9.1%; T2 or MRS or DW 3%; T2 or MRS or DCE 9.1%; T2 or DW or DCE 0%; T2 or MRS or DW or DCE 0% **Unit of analysis:** Region ($n = 178$) **Sensitivity:** T2 69.8%; T2 or MRS 81.1%; T2 or DW 84.9%; T2 or DCE 83%; T2 or MRS or DW 94.3%; T2 or MRS or DCE 90.6%; T2 or DW or DCE 94.3%; T2 or MRS or DW or DCE 100% **Specificity:** T2 58.4%; T2 or MRS 37.6%; T2 or DW 36.8%; T2 or DCE 33.6%; T2 or MRS or DW 19.2%; T2 or MRS or DCE 14.4%; T2 or DW or DCE 16%; T2 or MRS or DW or DCE 0% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Ghafoori 2010[120] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** NR **Follow-up:** N	**Enrolled:** 46 **Analysed:** 46 **Consecutive:** NR **Age (years):** Mean 68.1, range 53 to 88 **PSA (ng/ml):** Mean 14.1, range 4.5 to 36.8 **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR **Inclusion criteria:** Elevated PSA level and previous negative systematic biopsy results **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** NR **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 46$) **Sensitivity:** MRS 88.9%, TRUS 66.7% **Specificity:** MRS 92.9%, TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Hambrock 2010[85,86,121–123] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** August 2006 to March 2007 **Country:** The Netherlands **Follow-up:** N	**Enrolled:** 71 **Analysed:** 68 **Consecutive:** Y **Age (years):** Mean 63, range 48 to 74 **PSA (ng/ml):** Median 13, range 4 to 243 **Prostate size:** NR **Previous negative biopsies:** 2 to 7 **Previous biopsy scheme:** At least 8- to 10-core TRUS, including TZ sampling **Inclusion criteria:** PSA level of > 4 ng/ml and two or more negative TRUS-guided biopsies **Exclusion criteria:** NR	**Index test(s):** DCE, DW **Definition of positive test:** NR **Comparator test(s):** T2 **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 68$) **Sensitivity:** T2 or DCE or DW NR **Specificity:** T2 or DCE or DW NR (PPV 100%) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Hoeks 2012[87] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** March 2008 to February 2011 **Country:** The Netherlands **Follow-up:** Y (5 months)	**Enrolled:** 438 **Analysed:** 264 **Consecutive:** Y **Age (years):** Median 66 **PSA (ng/ml):** Median 11.4 **Prostate size (cc):** Median 67 **Previous negative biopsies:** At least one **Previous biopsy scheme:** TRUS (median nine cores in $n = 123$ participants) **Inclusion criteria:** Patients who underwent multiparametric MRI and/or MR-guided biopsy and had PSA level > 4 ng/ml and at least one previous negative biopsy **Exclusion criteria:** Existent PC, use of endorectal coil (in MRI) and MRI for indications other than cancer detection	**Index test(s):** DCE, DW **Definition of positive test:** **DCE:** After identification of TSRs on T2 images, the ADC maps and multiparametric pharmacokinetic colour maps and washout were analysed in a colour overlay mode on the T2 images **DW:** In addition to ADC maps, DWI-calculated b1400 images were used to determine CSRs. A lesion was defined as a CSR on DWI in cases of focal restriction on the ADC map combined with an iso- to hyper-signal intensity on the calculated b1400 image. Additionally, after the functional data from DW and DCE imaging were evaluated in relation to the TSS findings on the T2 images, the DW and DCE images were viewed separately and in combination to determine additional TRSs not evident on T2 images **Comparator test(s):** T2 **Definition of positive test:** The generally known tumour criteria were used to detect TSRs, including (1) low signal intensity areas in the PZ, (2) in the TZ, a homogeneous low T2 signal intensity area with ill-defined margins or a lenticular shape, and (3) in the CZ, areas of homogeneous low signal intensity with an ill-defined margin. All other imaging modalities were interpreted in relation to the T2 images **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 264$) **Sensitivity:** T2 or DCE or DW NR **Specificity:** T2 or DCE or DW NR (PPV 40.9%) **Adverse effects:** Sepsis with hospitalisation, $n = 1$; vasovagal reaction, $n = 4$ **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Keetch 1994[88] Full text **Study type:** Cross-sectional diagnostic (screening study) **Study start/end dates:** NR **Country:** USA **Follow-up:** Y (every 6 months)	**Enrolled:** 10,249 **Analysed:** 427 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml): median (SD)** No cancer on biopsy: 5.4 (1.5) Cancer on biopsy: 6.4 (2.8) **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** 4- to 6-core TRUS **Inclusion criteria:** PSA level > 4 ng/ml on two occasions 2 weeks apart **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 427$) **Sensitivity:** TRUS 78.8% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Labanaris 2010[89,124,125] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** 2004–8 **Country:** Germany **Follow-up:** N	**Enrolled:** 260 **Analysed:** 260 (group A, suspicious MRI, $n = 170$; group B, non-suspicious MRI, $n = 90$) **Consecutive:** Y **Age (years):** Median 67.2 (group A) Median 67.1 (group B) **PSA (ng/ml):** Median 8.3, range 1.3 to 45.3 (group A) Median 9.1, range 1.8 to 41.6 (group B) **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR **Inclusion criteria:** Increased PSA level (> 4 ng/ml), suspicious DRE and at least one previous negative biopsy **Exclusion criteria:** Age > 75 years, cardiac pacemaker, history of pelvic surgery, inflammatory bowel disease (Crohn's disease or ulcerative colitis), external beam radiation to the pelvis, anal stricture or severe haemorrhoids interfering with endorectal receiver positioning	**Index test(s):** DCE, DW **Definition of positive test:** **DCE/DW:** Areas within the prostate exhibiting an early enhancement on DCE or DW were interpreted as cancer. Early enhancement within the SV or extension of the enhancement from the prostate to the SVs was presumed to be SVI **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Areas within the prostate showing a low signal intensity and obliteration of the rectoprostatic angle were interpreted as cancer. Irregular bulging of the prostatic contour, contiguous tumour signal intensity within the periprostatic fat and vanishing of the NVB were presumed to be ECE. Diagnostic criteria for NVB involvement include their vanishing and/or asymmetry **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 260$) **Sensitivity:** T2 and DCE and DW 88.1% **Specificity:** T2 and DCE and DW 62.4% **Adverse effects:** Macroscopic haematuria ($n = 190$), mean duration 4 days, range 1 to 18 Haematospermia ($n = 146$), mean duration 11 days, range 1 to 30 Minor rectal bleeding ($n = 96$), mean duration 1.3 days, range 0 to 15 Prostatic infection requiring hospitalisation ($n = 2$) **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Lattouf 2007[90] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** March 2003 to November 2005 **Country:** USA **Follow-up:** N	**Enrolled:** 26 **Analysed:** 26 **Consecutive:** Y **Age (years):** Median 62, range 32 to 76 **PSA (ng/ml):** Median 8.4, range 2.1 to 85.9 **Prostate size (cc):** Median 54.9, range 11.9 to 133 **Previous negative biopsies:** 1 to 12 **Previous biopsy scheme:** NR **Inclusion criteria:** At least one set of prostate biopsies that were negative for cancer **Exclusion criteria:** Previous positive biopsies	**Index test(s):** DCE **Definition of positive test:** Abnormally enhancing regions **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Hypointense regions **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 26$) **Sensitivity:** DCE 71.4%, T2 92.9% **Specificity:** DCE 33.3%, T2 16.7% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Lee 2011[126] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** Republic of Korea **Follow-up:** N	**Enrolled:** 87 **Analysed:** 87 **Consecutive:** NR **Age (years):** No cancer ($n = 41$): median 68, range 50 to 84 Cancer ($n = 46$): median 66, range 48 to 76 **PSA (ng/ml):** *Prebiopsy values* No cancer: median 7.9, mean 11.24 Cancer: median 9.48, mean 12.78 **Prostate size (cc):** No cancer: median 40.8, mean 33.9 Cancer: median 35.4, mean 33.1 **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** 12-core **Inclusion criteria:** Persistently increasing serum PSA, at least one previous set of negative 12-core biopsies and normal DRE **Exclusion criteria:** NR	**Index test(s):** DW **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 87$) **Sensitivity:** T2 or DW 95.7% **Specificity:** T2 or DW 7.3% **Unit of analysis:** Biopsy ($n = 1421$) **Sensitivity:** T2 or DW NR **Specificity:** T2 or DW NR (PPV = 28.8%) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Lin 2008[91] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 2000 to May 2005 **Country:** Taiwan, Province of China **Follow-up:** Y (18 months)	**Enrolled:** 366 **Analysed:** 366 **Consecutive:** Y **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** 6-core TRUS **Inclusion criteria:** PSA level > 4 ng/ml or abnormal DRE **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 366$) **Sensitivity:** TRUS 68.1% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Lopez-Corona 2003[92] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** August 1999 to September 2001 **Country:** USA **Follow-up:** Y (97 months)	**Enrolled:** 343 **Analysed:** 343 **Consecutive:** Y **Age (years):** Mean 62.1, range 38 to 81 **PSA (ng/ml):** Mean 8.4, range 0.28 to 123 **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** NR **Inclusion criteria:** Patients undergoing prostate biopsy with at least one previous negative biopsy **Exclusion criteria:** Cancer diagnosed on initial biopsy	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 343$) **Sensitivity:** TRUS 66.3% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Ozden 2005[93] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** Turkey **Follow-up:** N	**Enrolled:** 60 **Analysed:** 60 **Consecutive:** Y **Age (years):** Mean 64, range 55 to 74 **PSA (ng/ml):** Mean 8.4, range 4.6 to 27 **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** 12-core TRUS **Inclusion criteria:** One previous negative 12-core TRUS/Bx; persistently elevated PSA level (> 4 ng/ml) after the negative biopsy **Exclusion criteria:** More than 12 months since negative biopsy	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 60$) **Sensitivity:** TRUS 43.8% **Specificity:** TRUS 81.8% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Panebianco 2011[95,114,119] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** September 2009 to February 2010 **Country:** Italy **Follow-up:** N	**Enrolled:** 43 **Analysed:** 41 **Consecutive:** Y **Age (years):** Mean 60.3, range 48 to 69 **PSA (ng/ml):** Mean 6.37 **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** NR **Inclusion criteria:** Prior TRUS/Bx negative for PC and HGPIN; persistent elevated PSA level (≥ 4 ng/ml and < 10 ng/ml); negative DRE **Exclusion criteria:** More than 12 months since negative biopsy	**Index test(s):** MRS, DCE **Definition of positive test:** NR **Comparator test(s):** TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 41$) **Sensitivity:** MRS or DCE 92.9% **Specificity:** MRS or DCE 86.6% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Park 2008[96] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** December 2006 to October 2007 **Country:** Republic of Korea **Follow-up:** N	**Enrolled:** 43 **Analysed:** 43 **Consecutive:** NR **Age (years):** Mean 62.6, range 40 to 80 **PSA (ng/ml):** Mean 12, range 2.6 to 66.4 **Prostate size (cc):** Range 22 to 129 ml (patients with positive cores) **Previous negative biopsies:** 1–5 **Previous biopsy scheme:** 10-core TRUS **Inclusion criteria:** At least one previous set of 10-core biopsy; negative DRE; persistently elevated PSA level 6–24 months after initial biopsy **Exclusion criteria:** NR	**Index test(s):** DW **Definition of positive test:** The most hyperintense area was localised qualitatively and superimposed on the ADC maps using MRIcro software, version 1.37.[182] On the ADC maps, the most hypointense lesion was defined as suspicious for tumour **Comparator test(s):** TRUS **Definition of positive test:** It was determined if any hypointense or hypoechoic lesion corresponded to a lesion that was considered a tumour on DW **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 43$) **Sensitivity:** DW 100%, TRUS 70.6% **Specificity:** DW NR, TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Pepe 2010[97] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** July 2001 to December 2009 **Country:** Italy **Follow-up:** Y (22 months)	**Enrolled:** 2358 **Analysed:** 423 **Consecutive:** NR **Age (years):** **Second biopsy:** median 62.8, range 45 to 74 **Third biopsy:** median 64, range 50 to 73 **PSA (ng/ml):** **Second biopsy:** median 12.8, range 2.7 to 56 **Third biopsy:** median 19.5, range 5.6 to 84 **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** Median nine cores in the PZ of each lobe **Inclusion criteria:** Abnormal DRE; PSA level > 10 ng/ml and PSA level of between 4.1 and 10 ng/ml or 2.6 and 4 ng/ml with free–total PSA level ≤25 and 20%, respectively **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 423$) **Sensitivity:** TRUS 96.3% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Perotti 2002[127,128] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** USA **Follow-up:** N	**Enrolled:** 82 **Analysed:** 74 **Consecutive:** Y **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1– 7 **Previous biopsy scheme:** NR **Inclusion criteria:** Elevated PSA level and at least one prior negative TRUS biopsies **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** endorectal MR images were interpreted as being of low, moderate or high suspicion for PC based upon T1 and T2 characteristics **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 74$) **Sensitivity:** T2 94.1% **Specificity:** T2 70.2% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Philip 2006[98] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** UK **Follow-up:** Y (3 and 6 months)	**Enrolled:** 241 **Analysed:** 241 **Consecutive:** NR **Age (years):** Mean 63.4, range 43 to 84 **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** NR **Inclusion criteria:** Persistently high age-specific PSA of 2.5–10 ng/ml and initial benign biopsy **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 241$) **Sensitivity:** TRUS 95.2% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Pinsky 2007[99] Full text **Study type:** Cross-sectional diagnostic (screening study) **Study start/end dates:** November 1993 to July 2001 **Country:** USA **Follow-up:** Y (every 12 months)	**Enrolled:** 38,350 **Analysed:** 2761 **Consecutive:** NR **Age (years):** Mean 65, range 55 to 79 **PSA (ng/ml):** > 4 ng/nl $n = 1739$ ≤ 4 ng/ml $n = 1022$ **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** NR **Inclusion criteria:** PSA level of > 4 ng/ml or nodularity or induration on DRE **Exclusion criteria:** History of PC, surgical removal of entire prostate, taking finasteride (Proscar, Merck) in the previous 6 months and, from 1995, more than one PSA blood test in the previous 3 years	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 2761$) **Sensitivity:** TRUS 71.6% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Portalez 2010[100,129] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** November 2007 to July 2008 **Country:** France **Follow-up:** N	**Enrolled:** 68 **Analysed:** 68 **Consecutive:** Y **Age (years):** Mean 62.4, range 49 to 76 **PSA (ng/ml):** Mean 9.16, range 1.6 to 25 **Prostate size:** NR **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** Mean 17 cores **Inclusion criteria:** Elevated PSA level and at least one prior negative TRUS biopsies **Exclusion criteria:** NR	**Index test(s):** MRS, DCE, DW **Definition of positive test:** **MRS:** A voxel was considered suspicious for malignant tissue when the CC/C ratio was > 0.86 **DCE:** Short time to peak, peak enhancement and washout were considered evocative of PC in the PZ. In the TZ, suspicion was based upon the combination of shorter time to peak, higher peak enhancement and more rapid washout than in the rest of the TZ **DW:** Mean values minus SD for ADC were used as the cut-off (≤ 1.24 for PZ and ≤ 1.11 in the TZ). Lower values were considered suspicious for PC **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Hypointense ovoid mass-like or nodular subcapsular foci of reduced signal intensity in the PZ were considered suspicious for PC. In the TZ, homogeneous low T2 signal intensity with ill-defined margins and lack of capsule or invasion of the anterior fibromuscular stroma were considered significant **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** PZ segment ($n = 408$) **Sensitivity:** MRS 29.3%, DCE 29.3%, DW 39%, T2 48.8% **Specificity:** MRS 90.2%, DCE 93.5%, DW 96%, T2 87% **Unit of analysis:** PZ and TZ segment ($n = 544$) **Sensitivity:** Overall MRI NR **Specificity:** Overall MRI NR (PPV 36.3) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Prando 2005[101] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** July 2002 to October 2003 **Country:** Brazil **Follow-up:** N	**Enrolled:** 42 **Analysed:** 42 **Consecutive:** Y **Age (years):** Median 65, range 45 to 75 **PSA (ng/ml):** Mean 6.8, range 4.1 to 15.3 **Prostate size:** NR **Previous negative biopsies:** 2–6 **Previous biopsy scheme:** TRUS-guided, at least six cores **Inclusion criteria:** Elevated PSA level and prior negative biopsy findings **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** Primary scores of 1–5 were assigned to voxels on the basis of the mean healthy ratio of the CC/C ratio. Scores were then adjusted on the basis of choline–creatine ratio, the loss of polyamines on the basis of increased resolvability of choline and creatine, and spectral signal–noise ratio. Scores of 4 and 5 were considered abnormal **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Hypointense areas **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 42$) **Sensitivity:** MRS (voxel score of 4 and/or 5) 100%, MRS (voxel score of 5) 70.6% **Specificity:** MRS (voxel score of 4 and/or 5) 44%, MRS (voxel score of 5) 84% **Unit of analysis:** Sextant ($n = 348$) **Sensitivity:** MRS 84.6% **Specificity:** MRS 89% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Quinlan 2009[102] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** 2001–5 **Country:** Ireland **Follow-up:** Y (mean 50 months)	**Enrolled:** 111 **Analysed:** 111 **Consecutive:** NR **Age (years):** First repeat biopsy ($n = 16$) mean age 68.7, range 57 to 78 Second repeat biopsy ($n = 4$) mean age 69.5, range 54 to 80 Third repeat biopsy ($n = 4$) mean age 69.8, range 64 to 78 Fourth repeat biopsy ($n = 3$) mean age 66, range 60 to 74 **PSA (ng/ml):** First repeat biopsy ($n = 16$) median PSA 9.8, range 5.6 to 18.95 Second repeat biopsy ($n = 4$) median PSA 39.15, range 10.6 to 103 Third repeat biopsy ($n = 4$) median PSA 19.5, range 14.2 to 57 Fourth repeat biopsy ($n = 3$) median PSA 15, range 13 to 26.7 **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR **Inclusion criteria:** NR **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Biopsy ($n = 175$) **Sensitivity:** TRUS 59.3% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Rahman 2003[130] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** USA **Follow-up:** N	**Enrolled:** 56 **Analysed:** 56 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least two **Previous biopsy scheme:** NR **Inclusion criteria:** Elevated PSA level and at least two previous negative biopsies **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** NR **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 56$) **Sensitivity:** MRS or T2 95.5% **Specificity:** MRS or T2 17.6% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Roehl 2002[103] Full text **Study type:** Cross-sectional diagnostic (screening study) **Study start/end dates:** May 1991 to July 2000 **Country:** USA **Follow-up:** Y (every 6 months)	**Enrolled:** 24,902 **Analysed:** 634 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** 4- or 6-core **Inclusion criteria:** **In screening study:** ≥50 years and no history of PC or ≥40 years if family history of PC and/or African American descent **To be biopsied:** Until May 1995: serum PSA level > 4 ng/ml or suspicious DRE. After May 1995: serum PSA level > 2.5 ng/ml or suspicious DRE **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 634$) **Sensitivity:** TRUS 60.6% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Roethke 2012[104] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** May 2005 to December 2009 **Country:** Germany **Follow-up:** N	**Enrolled:** 100 **Analysed:** 100 **Consecutive:** Y **Age (years):** Median 66, range 48 to 81 **PSA (ng/ml):** Median 8.7, range 3.9 to 65 **Prostate size (cc):** Median 41, range 13 to 183 **Previous negative biopsies:** 1–9 **Previous biopsy scheme:** NR **Inclusion criteria:** At least one prior negative TRUS/Bx, persistently elevated or rising PSA level and at least one lesion suspicious for PC in previous endorectal coil MRI **Exclusion criteria:** History of radiation therapy of the prostate or current hormone deprivation therapy	**Index test(s):** MRS, DCE, DW **Definition of positive test:** MRS: NR DCE: NR DW: NR **Comparator test(s):** T2 **Definition of positive test:** **T2:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 56$) **Sensitivity:** MRS or DCE or DW or MRS NR **Specificity:** MRS or DCE or DW or MRS NR (PPV 52%) **Adverse effects:** All procedures were well tolerated by patients **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Sciarra 2010[94,105,131,132] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 2007 to January 2009 **Country:** Italy **Follow-up:** N	**Enrolled:** 180 (group A: $n = 90$, group B: $n = 90$) **Analysed:** 140 **Consecutive:** Y **Age (years):** Overall ($n = 180$) Mean 63.5, range 48 to 74 **PSA (ng/ml):** Group A: median 6, range 4 to 9 Group B: median 6.22, range 4 to 9.3 **Prostate size (cc):** Group A: median 45, range 30 to 60 Group B: median 45.5, range 30 to 63 **Previous negative biopsies:** 1 **Previous biopsy scheme:** 10-core laterally directed random TRUS-guided biopsies **Inclusion criteria:** First negative biopsy, persistent total PSA level ≥ 4 ng/ml and < 10 ng/ml and negative DRE **Exclusion criteria:** Previous hormonal, surgical or radiation therapies for prostate diseases and cases in which a MRI with complete MRS and DCE was not possible	**Index test(s):** MRS, DCE **Definition of positive test:** **MRS:** Voxels were classed as suspicious if the CC/C ratio was > 0.8. PC was suspected if one or more suspicious voxels were identified **DCE:** Regions of PC within the PZ were identified based on decreased signal intensity on T2 and higher enhancing values on subtracted DCE images. When multiple enhancing regions were identified, the SI-T of the most enhancing region was considered significant for subsequent analysis. Functional dynamic imaging parameters were estimated via the SI-T curves modelled with three main enhancement records: onset time of signal enhancement, time to peak and peak enhancement **Comparator test(s):** TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 90$), one previous biopsy (group B) **Sensitivity:** MRS 88.6%, DCE 79.5%, MRS and DCE 75%, MRS or DCE 93.2% **Specificity:** MRS 93.5%, DCE 91.3%, MRS and DCE 93.5%, MRS or DCE 91.3% **Unit of analysis:** Patient ($n = 50$), two previous biopsies (group A) **Sensitivity:** MRS 92.3%, DCE 84.6%, MRS and DCE 80.8%, MRS or DCE 96.2% **Specificity:** MRS 79.2%, DCE 91.7%, MRS and DCE 91.7%, MRS or DCE 79.2% **Unit of analysis:** Voxel ($n =$ NR), one previous biopsy (group B) **Sensitivity:** MRS NR, DCE NR, MRS and DCE NR, MRS or DCE NR **Specificity:** MRS NR, DCE NR, MRS and DCE NR, MRS or DCE NR (PPV: MRS 94.4, DCE 91.6, MRS and DCE 94.7, MRS or DCE 91.6) **Unit of analysis:** Biopsy ($n =$ NR), one previous biopsy (group B) **Sensitivity:** MRS 83.3%, DCE 75.6%, MRS and DCE 89.7%, MRS or DCE NR **Specificity:** MRS 72.7%, DCE 76.7%, MRS and DCE 80.4%, MRS or DCE NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Testa 2010[106] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** February 2007 to July 2007 **Country:** Italy **Follow-up:** N	**Enrolled:** 58 **Analysed:** 54 **Consecutive:** Y **Age (years):** Mean 63.9, range 52 to 76 **PSA (ng/ml):** Mean 11.4, range 3 to 42 **Prostate size (cc):** Mean 59.3, range 30 to 150 **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** Extended TRUS biopsy (mean no. of cores 16, range 12 to 22) **Inclusion criteria:** Persistently elevated PSA level (> 4 ng/ml) and/or positive DRE; one extended negative TRUS biopsy between 6 and 12 months earlier or two or more negative TRUS biopsies with the last one within the previous 6–24 months **Exclusion criteria:** Previous diagnosis of PC; treatment with 5-alpha-reductase inhibitors or anti-androgen therapy	**Index test(s):** MRS **Definition of positive test:** Regions of PC were metabolically identified based on the CC/C peak area ratios. In the PZ, a score of 0 was assigned to voxels when CC/C was ≤3 SD above the mean healthy value (0.22 ± 0.13); a score of 1 was assigned when CC/C was between 3 and 4 SD above the mean healthy value or when both CC/C was between 2 and 3 SD above the mean healthy value and the CC/C ratio ≥1. A score of 2 was assigned to voxels where CC/C was 4 SD above the mean healthy value. Scores 1 and 2 were regarded as malignant. In the TZ, the same three-point scale was used but voxels were regarded as malignant only when CC/C was at least 4 SD above the mean healthy value **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** In the PZ, regions presenting T2 hypointensities and regions with nodular T2 hypointensities were considered test positive. In the TZ, imaging features considered indicative of cancer were the presence of homogeneous low T2 signal intensity, an absent capsule and ill-defined margins **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 54$) **Sensitivity:** MRS 90.9%, T2 72.7%, MRS and T2 72.7%, MRS or T2 90.9% **Specificity:** MRS 43.8%, T2 62.5%, MRS and T2 71.9%, MRS or T2 34.4% **Unit of analysis:** Region ($n = 648$) **Sensitivity:** MRS ($n = 630$) 67.3%, T2 38.2%, MRS and T2 34.5%, MRS or T2 70.9% **Specificity:** MRS ($n = 630$) 87%, T2 96.3%, MRS and T2 98.8%, MRS or T2 84.7% **Unit of analysis:** Region: PZ only ($n = 540$) **Sensitivity:** MRS ($n = 522$) 64.9%, T2 27%, MRS and T2 21.6%, MRS or T2 70.3% **Specificity:** MRS ($n = 522$) 85.8%, T2 95.8%, MRS and T2 98.6%, MRS or T2 83.3% **Unit of analysis:** Region: TZ only ($n = 108$) **Sensitivity:** MRS 72.2%, T2 61.1%, MRS and T2 61.1%, MRS or T2 72.2% **Specificity:** MRS 93.3%, T2 98.9%, MRS and T2 100%, MRS or T2 92.2% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Ukimura 1997[107] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** December 1987 to February 1996 **Country:** USA **Follow-up:** Y (length NR)	**Enrolled:** 193 **Analysed:** 193 **Consecutive:** NR **Age (years):** Mean 66.5, range 42 to 83 **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** NR **Inclusion criteria:** Initial negative biopsy and re-biopsied during study period **Exclusion criteria:** Diagnosis of PIN at initial biopsy	**Index test(s):** N/A **Definition of positive test:** NR **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 1993$) **Sensitivity:** TRUS 64.7% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Valentini 2010[133] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** Italy **Follow-up:** N	**Enrolled:** 11 **Analysed:** 11 **Consecutive:** Y **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** TRUS-guided (no. of cores NR) **Inclusion criteria:** Persistent elevation of PSA level (> 4 ng/ml) and previous negative TRUS-guided biopsies **Exclusion criteria:** NR	**Index test(s):** DCE, DW **Definition of positive test:** DCE: NR DW: NR **Comparator test(s):** TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transperineal approach	**Unit of analysis:** Biopsy ($n = NR$) **Sensitivity:** DCE 80%, DW 60%, DCE or DW NR **Specificity:** DCE NR, DW NR, DCE and DW NR (PPV: DCE and DW 17.2) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Wefer 2000[134] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** USA **Follow-up:** N	**Enrolled:** 24 **Analysed:** 24 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** NR **Inclusion criteria:** Clinical suspicion of PC and elevated PSA level **Exclusion criteria:** NR	**Index test(s):** MRS **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** Based on low signal intensity on T2-weighted images **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 24$) **Sensitivity:** T2 70%, MRS and T2 50% **Specificity:** T2 85.7%, MRS and T2 85.7% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Wetter 2005[108] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** June 2003 to January 2004 **Country:** Germany **Follow-up:** N	**Enrolled:** 103 **Analysed:** 6 **Consecutive:** Y **Age (years):** Median 64.5, range 50 to 73 **PSA (ng/ml):** Median 8.2, range 6 to 20 **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** Sextant biopsy ($n = 4$); NR ($n = 2$) **Inclusion criteria:** Elevated PSA level (> 3.5 ng/ml) and previous negative biopsy(ies) or no previous biopsy **Exclusion criteria:** Previous hormonal, surgical or irradiation therapies; prostate biopsy within 4 weeks before MRI/MRS	**Index test(s):** MRS **Definition of positive test:** CC/C ratio > 0.6 **Comparator test(s):** T2 **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transgluteal approach	**Unit of analysis:** Patient: any suspicion classed as positive ($n = 6$) **Sensitivity:** MRS 100%, T2 100%, MRS and T2 50%, MRS or T2 100% **Specificity:** MRS 75%, T2 0%, MRS and T2 75%, MRS or T2 50% **Unit of analysis:** Patient: only highest level of suspicion classed as positive ($n = 6$) **Sensitivity:** MRS 50%, T2 50%, MRS and T2 50%, MRS or T2 50% **Specificity:** MRS 75%, T2 50%, MRS and T2 75%, MRS or T2 50% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Yakar 2011[109] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** September 2009 to March 2010 **Country:** The Netherlands **Follow-up:** N	**Enrolled:** 12 **Analysed:** 9 **Consecutive:** NR **Age (years):** Median 69, range 59 to 72 **PSA (ng/ml):** Median 19.5, range 10 to 26 **Prostate size:** NR **Previous negative biopsies:** 1–4 **Previous biopsy scheme:** Transverse US guided **Inclusion criteria:** PSA ≥4 ng/ml and at least one negative biopsy **Exclusion criteria:** Contraindications to MR imaging, e.g. cardiac pacemakers, intracranial clips	**Index test(s):** DCE, DW **Definition of positive test: DCE:** A focally enhancing region on the DCE volume transfer constant map and/or washout map **DW:** A focally low-signal-intensity region in combination with a high-signal-intensity region on the image obtained with a *b*-value of 800 s/mm^2 on the ADC map **Comparator test(s):** T2 **Definition of positive test:** A relatively low-signal-intensity region **Reference standard:** Histopathological assessment of biopsied tissue obtained by T2-guided biopsy **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 9$) **Sensitivity:** DCE or DW or T2 NR **Specificity:** DCE or DW or T2 NR (PPV 55.6) **Unit of analysis:** CSR ($n = 13$) **Sensitivity:** DCE or DW or T2 NR **Specificity:** DCE or DW or T2 NR (PPV 46.2) **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Yanke 2006[110] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 1993 to June 2003 **Country:** USA **Follow-up:** Y (mean 30 months)	**Enrolled:** 416 **Analysed:** 416 **Consecutive:** NR **Age (years):** Black men, mean (SD): 67.3 (6.8) White men, mean (SD): 67.5 (6.9) **PSA (ng/ml):** Black men, mean (SD): 13.1 (12.9) White men, mean (SD): 10.1 (7.3) **Prostate size (cc):** Black men, mean (SD): 49.8cc (32) White men, mean (SD): 49.7cc (28.3) **Previous negative biopsies:** 1 **Previous biopsy scheme:** 6- or 12-core **Inclusion criteria:** Persistently increased PSA level, PSA velocity > 0.75 ng/ml yearly, ASAP or HGPIN, abnormal DRE or patient preference **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** NR **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Unclear if patient or biopsy-level analysis **Sensitivity:** TRUS 67.4% **Specificity:** TRUS NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR
Yao 2009[136] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** January 2003 to January 2008 **Country:** USA **Follow-up:** N	**Enrolled:** 1053 **Analysed:** 41 **Consecutive:** NR **Age (years):** Mean 66, range 48 to 79 **PSA (ng/ml):** Mean 16, range 2 to 104 **Prostate size:** NR **Previous negative biopsies:** 2–8 **Previous biopsy scheme:** Mean cores 15, range 6 to 24 **Inclusion criteria:** At least two negative biopsies and persistent abnormal PSA **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 41$) **Sensitivity:** T2 (and TRUS) 93.3%; targeted T2 80% **Specificity:** T2 (and TRUS) 61.5%, Targeted T2 NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Younes 2001[137] Abstract **Study type:** Cross-sectional diagnostic **Study start/end dates:** NR **Country:** France **Follow-up:** N	**Enrolled:** 27 **Analysed:** 27 **Consecutive:** NR **Age (years):** Mean 62, range 48 to 73 **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** At least one **Previous biopsy scheme:** Sextant **Inclusion criteria:** Previous negative biopsies and increasing PSA level **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** NR **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 27$) **Sensitivity:** T2 100% **Specificity:** T2 53.9% **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Yuen 2004[111] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** February 2000 to April 2001 **Country:** Singapore **Follow-up:** N	**Enrolled:** 57 **Analysed:** 57 **Consecutive:** Y **Age (years):** Biopsy 2 ($n = 45$): mean 65, range 53 to 80 Biopsy 3 ($n = 12$): mean 66, range 58 to 75 **PSA (ng/ml):** Biopsy 2: mean 11.9, range 1 to 34.8 Biopsy 3: mean 29.6, range 7.1 to 131 **Prostate size (cc):** Biopsy 2: mean 41.7, range 11 to 90 Biopsy 3: mean 49.5, range 20 to 96 **Previous negative biopsies:** 1 or 2 **Previous biopsy scheme:** First negative biopsy ($n = 45$): sextant TRUS ($n = 39$), 10-core TRUS ($n = 6$) Second negative biopsy ($n = 12$): 10-core TRUS **Inclusion criteria:** PSA level > 4 ng/ml and/or abnormal DRE **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** NR **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 57$) **Sensitivity:** TRUS 13.3% **Specificity:** TRUS 92.9% **Adverse effects:** Haematuria ($n = 3$), fever ($n = 5$), urinary retention ($n = 5$), rectal bleeding ($n = 1$) **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Yuen 2004[112] Full text **Study type:** Cross-sectional diagnostic **Study start/end dates:** July 2002 to December 2002 **Country:** Singapore **Follow-up:** N	**Enrolled:** 24 **Analysed:** 24 **Consecutive:** Y **Age (years):** Mean 64.5, range 58 to 69 **PSA (ng/ml):** **Negative biopsy:** mean 8.17, range 6.1 to 16.4 **Positive biopsy:** mean 20.36, range 7.1 to 31.8 **Prostate size:** NR **Previous negative biopsies:** **Negative:** 1–2 **Positive:** 1–3 **Previous biopsy scheme:** NR **Inclusion criteria:** At least one prior negative TRUS biopsy, PSA level persistently increased between 4 and 40 ng/ml and/or abnormal DRE **Exclusion criteria:** > 70 years of age; contraindications for MRI	**Index test(s):** MRS **Definition of positive test:** **Equivocal spectra:** Height of combined choline + creatinine peak was lower than citrate peak **Abnormal spectra:** Height of combined choline + creatinine peak was higher than citrate peak **Comparator test(s):** T2, TRUS (part of reference standard only) **Definition of positive test:** **T2:** An abnormal area was judged suspicious if it was discrete and homogeneously low in signal and if it did not correspond to haemorrhagic areas with a high signal on T1-weighted scans **TRUS:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient: equivocal classed as normal ($n = 24$) **Sensitivity:** MRS 57.1%, T2 57.1%, MRS and T2 14.3%, MRS or T2 100% **Specificity:** MRS 82.4%, T2 88.2%, MRS and T2 100%, MRS or T2 70.6% **Unit of analysis:** Patient: equivocal classed as suspicious ($n = 24$) **Sensitivity:** MRS 71.4%, T2 57.1%, MRS and T2 28.6%, MRS or T2 100% **Specificity:** MRS 52.9%, T2 76.5%, MRS and T2 76.5%, MRS or T2 52.9% **Unit of analysis:** Core ($n = 296$) **Sensitivity:** MRS 40%, T2 40% **Specificity:** MRS 94.7%, T2 97.9% **Adverse effects:** Most patients had transient haematuria and haemospermia, which were self-resolving. There were no cases of sepsis or severe bleeding that required inpatient treatment **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

Study	Participants	Tests	Outcomes summary
Zackrisson 2004[113] Full text **Study type:** Cross-sectional diagnostic (screening study) **Study start/end dates:** 1995, until men reached 70 years of age **Country:** Sweden **Follow-up:** Y (every 2 years)	**Enrolled:** 9839 **Analysed:** 706 **Consecutive:** NR **Age (years):** NR **PSA (ng/ml):** NR **Prostate size:** NR **Previous negative biopsies:** 1 **Previous biopsy scheme:** Sextant **Inclusion criteria:** **In screening study:** All men born from 1 January 1930 to 31 December 1944 and living in Göteborg, Sweden **Men randomised to screening group:** Invited to undergo further examination if tPSA level > 3 ng/ml **Exclusion criteria:** NR	**Index test(s):** N/A **Definition of positive test:** N/A **Comparator test(s):** TRUS **Definition of positive test:** NR **Reference standard:** Histopathological assessment of biopsied tissue obtained by TRUS/Bx **Biopsies taken by:** Transrectal approach	**Unit of analysis:** Patient ($n = 706$) **Sensitivity:** TRUS 73.4% **Specificity:** NR **Adverse effects:** NR **Altered treatment as a result of tests:** NR **Interpretability/readability of tests:** NR **Acceptability of tests:** NR **Effects of testing on QoL:** NR

[1]H-MRS, proton magnetic resonance spectroscopy; CSR, cancer-suspicious region; DCE, dynamic contrast-enhanced magnetic resonance imaging; DW, diffusion-weighted magnetic resonance imaging; ECE, extracapsular extension; IQR, interquartile range; N, no; NR, not reported; NVB, neurovascular bundle; SI-T, signal intensity time; SV, seminal vesicle; SVI, seminal vesicle invasion; T2, T2-weighted magnetic resonance imaging; tPSA, total PSA; TSR, tumour suspicious region; Y, yes.

Appendix 7 Results of risk of bias and applicability for the individual full-text studies ($n = 39$)

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Amsellem-Ouazana 2005[74]	☺	☺	☹	☺	☺	☺	☺
Babaian 2000[75]	?	☺	☹	☺	☺	☺	☺
Beyersdorff 2002[57]	☺	☺	☹	☹	☺	☺	☺
Bhatia 2007[76]	☺	☺	☹	☺	☺	?	☺
Campodonico 2006[77]	?	☺	?	☺	☺	☺	☺
Cheikh 2009[78]	☺	☺	☹	☺	☺	☺	☺
Cirillo 2008[79]	☺	☺	☹	☺	☺	☹	☺
De la Rosette 2009[80]	☺	☺	☹	☺	☺	☺	☺
Djavan 2001[81]	☺	☺	?	☺	☺	☺	☺
Engelhard 2006[82]	?	☺	☹	☺	☺	☺	☺
Eskicorapci 2007[83]	?	☺	☹	☺	☺	☺	☺
Franiel 2011[84]	☺	☺	☹	☺	☺	☺	☺
Hambrock 2010[86]	☺	☺	☹	☺	☺	☺	☺
Hoeks 2012[87]	☺	☺	?	☹	☺	☺	☺
Keetch 1994[88]	?	☺	?	☺	☺	☺	☺
Labanaris 2010[89]	☺	☺	☹	☺	☹	☺	☺
Lattouf 2007[90]	☺	☺	☹	☺	☺	☺	☺
Lin 2008[91]	☺	☺	?	☺	☺	☺	☺
Lopez-Corona 2003[92]	☺	☺	?	☺	☺	☺	☺
Ozden 2005[93]	☺	☺	☹	☺	☺	☺	☺
Panebianco 2011[95]	☺	☺	☹	☺	☺	☺	☺
Park 2008[96]	?	☺	☹	☺	☺	☺	☺
Pepe 2010[97]	☺	☺	?	☺	☺	☺	☺
Philip 2006[98]	?	☺	?	☺	☺	☺	☺
Pinsky 2007[99]	☺	☺	?	☺	☺	☺	☺
Portalez 2010[100]	☺	☺	☹	☺	☺	☹	☺
Prando 2005[101]	☺	☺	☹	☺	☺	☹	☺
Quinlan 2009[102]	?	☺	?	☺	☺	☺	☺
Roehl 2002[103]	?	☺	?	☺	☺	☺	☺
Roethke 2012[104]	☺	☺	☹	☺	☺	☺	☺
Sciarra 2010[105]	☺	☺	☹	☺	☺	☺	☺
Testa 2010[106]	☺	☺	☹	☺	☺	☺	☺

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ukimura 1997[107]	☺	☺	?	☺	☺	☺	☺
Wetter 2005[108]	☺	☺	☹	☺	☺	☺	☺
Yakar 2011[109]	☺	☺	☹	☹	☺	☺	☺
Yanke 2006[110]	?	☺	?	☺	☹	☺	☺
Yuen 2004[111]	☺	☺	☹	☺	☺	☹	☺
Yuen 2004[112]	☺	☺	☹	☺	☺	☺	☺
Zackrisson 2004[113]	☺	☺	?	☺	☺	☺	☺

☹, high risk; ☺, low risk; ?, unclear.

Appendix 8 Individual study results ($n = 51$)

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Amsellem-Ouazana 2005[74]	1–4	Patient	**MRI-/MRS-directed TRUS-guided:** 10-core TRUS (PZ) + 1–4 targeted cores on MRI/MRS equivocal or suspicious zones	T2-MRI or MRS	42	14	21	1	6	93.3	22.2	Equivocal T2 or MRS classed as suspicious
				T2-MRI or MRS	42	11	1	4	26	73.3	96.3	Equivocal T2 or MRS classed as normal
				MRS	42	14	1	1	26	93.3	96.3	Equivocal classed as suspicious. Of the 14 patients with suspicious or equivocal MRS findings, all but one locations resulted in positive biopsies (24/25)
				T2-MRI	42	9	9	6	18	60.0	66.7	Equivocal classed as suspicious. Of the nine patients with suspicious MRI findings, all suspicious locations resulted in positive biopsies (15/15)
Babaian 2000[75]	At least one (71/277 had PIN; 34/277 had atypical cells)	Patient	**TRUS-guided:** 11-core (sextant + R&L anterior horn, R&L TZ, midline)	6-core TRUS	277	32	39	49	157	39.5	80.1	Results of ultasound findings
				11-core TRUS	277	39	32	42	164	48.1	83.7	Results of ultrasound findings
				6-core TRUS	277	54	NR	27	NR	66.7	NR	11-core TRUS as reference standard

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Beyersdorff 2002[57] (Winkelman 2001 abstract[135])	1–6	Patient	**MRI-directed TRUS-guided:** sextant ($n = 3$; from basal, intermediate and apical parts on each side) or octant ($n = 34$; as sextant + two specimens obtained laterally) or quadrant ($n = 1$; from basal area and from intermediate to apical area on each side) (TRUS) + at least one from suspected MRI lesions	T2-MRI	38	10	10	2	16	83.3	61.5	MRI suspicious
				TRUS	38	4	3	8	23	33.3	88.5	TRUS used to detect suspicious areas, to locate MRI-suspicious areas and to guide systematic biopsies
				T2-MRI	38	12	19	0	7	100.0	26.9	MRI suspicious and inconclusive
		Biopsy	As above	T2-MRI	272	15	115	8	134	65.2	53.8	
Bhatia 2007[76]	1–3	Patient	**MRI-/MRS-directed TRUS-guided:** systematic 12-core TRUS (PZ: two cores per sextant) + four cores from equivocal and suspicious MRI/MRS areas	T2-MRI	21	2	4	0	15	100.0	78.9	Bhatia *et al.*[76] categorised normal and equivocal as negative for malignancy and suspicious as positive for malignancy. It was not possible to re-categorise equivocal as suspicious. Results relate to MRI/MRS plus systematic TRUS-guided biopsies. Not reported if positive biopsies resulted from suspicious MRI/MRS areas or were TRUS guided
				MRS	21	2	5	0	14	100.0	73.7	
				MRS and T2-MRI	21	2	3	0	16	100.0	84.2	
		Biopsy	As above	T2-MRI	290	9	44	5	232	64.3	84.1	
				MRS	290	11	54	3	222	78.6	80.4	
				MRS and T2-MRI	290	9	23	5	253	64.3	91.7	
Calvo 2010[115]	1–4	Patient	**MRS-directed TRUS-guided:** 12-core sextant TRUS (areas sampled not reported) + targeted MRS	MRS	59	16	11	0	32	100.0	74.4	Not reported if positive biopsies resulted from suspicious MRS areas or were TRUS guided
Campodonico 2006[77]	1	Patient	**TRUS-guided:** 10-core (sextant + 4 from lateral PZ)	TRUS	81	16	NR	2	NR	88.9	NR	Results for second and third biopsies combined

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Cheikh 2009[78]	1–5	Patient	**MRI-directed TRUS-guided:** at least 12 systematic TRUS (PZ) + additional samples from suspicious MRI sectors	T2-MRI	93	11	39	12	31	47.8	44.3	All back calculated from reported sensitivity and specificity
				DCE	93	19	56	4	14	82.6	20.0	In one patient with PC, DCE images could not be interpreted
				T2-MRI or DCE	93	19	59	4	11	82.6	15.7	Either T2 or DCE suspicious
				T2-MRI and DCE	93	11	34	12	36	47.8	51.4	T2 and DCE suspicious. For all reported results, not reported if positive biopsies resulted from suspicious MRI areas or were TRUS guided
		Sector	As above	T2-MRI	670	14	64	30	562	31.8	89.8	
				DCE	670	23	103	21	523	52.3	83.5	
				T2-MRI or DCE	670	23	106	21	520	52.3	83.1	
				T2-MRI and DCE	670	14	48	30	578	31.8	92.3	
Chung 2010[116]	At least one	Core	**MRI-directed TRUS-guided:** 12-core TRUS (areas sampled not reported) + up to 14 cores from MRI suspicious lesions	T2-MRI or DW[a]	971	106	262	22	581	82.8	68.9	31/57 participants positive for PC; 106/368 cores from targeted lesions and 22/603 from standard biopsies were positive for PC

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Cirillo 2008[79]	At least one (10/54 had PIN)	Patient	**MRI-/MRS-directed TRUS-guided:** systematic 10 cores TRUS (two from basal portion, two mid-gland, one apex, on each side) + up to three from each MRI-/MRS-suspicious area (maximum 16 cores in total)	T2-MRI	54	17	13	0	24	100.0	64.9	Not reported if positive biopsies resulted from suspicious MRI/MRS areas or were TRUS guided
				MRS	54	15	11	2	26	88.2	70.3	
				T2-MRI or MRS	54	17	18	0	19	100.0	51.4	
				T2-MRI and MRS	54	15	NR	2	NR	88.2	NR	
		Site	As above	T2-MRI	540	34	46	10	450	77.3	90.7	
				MRS	540	36	43	8	453	81.8	91.3	
				T2-MRI or MRS	540	38	68	6	428	86.4	86.3	
Comet-Batlle 2004[117]	At least one	Patient	**MRI-/MRS-directed TRUS-guided:** sextant TRUS (MRI/MRS targeting not reported)	T2-MRI or MRS[a]	5	5	0	NR	NR	NR	NR	All patients had normal MRI but clear metabolic abnormalities at MRS; PPV = 100
De la Rosette 2009[80]	1	Patient	**TRUS-guided:** 8-core lateral or 12-core lateral and parasagittal (including four TZ)	TRUS	139	2	31	18	88	10.0	73.9	Unable to extract results separately for 8- and 12-core biopsy groups
Destefanis 2009[118]	At least one	Patient	**MRI-/MRS-directed TRUS-guided:** 12-core TRUS (areas sampled or no. of cores for targeted lesions not reported)	T2-MRI or MRS[a]	26	9	15	0	2	100.0	11.8	Suspicious and equivocal classed as positive; patients all diagnosed with ASAP on initial negative biopsy; in all patients, cancer was found in suspicious zones at MRI/MRS where targeted biopsies were performed
Djavan 2001[81]	1	Patient	**TRUS-guided:** 8 cores (sextant + two TZ)	TRUS	820	83	NR	40	NR	67.5	NR	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Engelhard 2006[82]	1 to 4	Patient	**MRI-guided:** 4–9 biopsies from tumour-suspicious areas per patient	T2-MRI	37	14	23	NR	NR	NR	NR	PPV = 37.8
		Biopsy	As above	T2-MRI	NR	12	2	NR	NR	NR	NR	Strongly suspicious (PZ); PPV = 85.7
				T2-MRI	NR	15	11	NR	NR	NR	NR	Strongly (PZ lesions) and moderately suspicious (TZ and CZ lesions); PPV = 57.7
Eskicorapci 2007[83]	At least one	Patient	**TRUS-guided:** 14 cores (sextant + four from lateral peripheral regions of base and mid-prostate + 4 from both sides of TZ from mid-glandular and base)	TRUS	211	10	34	44	123	18.5	78.3	58 patients diagnosed with HGPIN on initial biopsy

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Franiel 2011[84]	1 to 6	Patient	**MRI-guided:** 1–9 specimens per patient	T2-MRI	54	18	22	3	11	85.7	33.3	
				T2-MRI or MRS	54	20	25	1	8	95.2	24.2	
				T2-MRI or DW	54	21	32	0	1	100.0	3.0	
				T2-MRI or DCE	54	18	30	3	3	85.7	9.1	
				T2-MRI or MRS or DW	54	21	32	0	1	100.0	3.0	
				T2-MRI or MRS or DCE	54	20	30	1	3	95.2	9.1	
				T2-MRI or DW or DCE	54	21	33	0	0	100.0	0.0	
				T2-MRI or MRS or DW or DCE	54	21	33	0	0	100.0	0.0	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
			Region by region	T2-MRI	178	37	52	16	73	69.8	58.4	
				T2-MRI or MRS	178	43	78	10	47	81.1	37.6	
				T2-MRI or DW	178	45	79	8	46	84.9	36.8	
				T2-MRI or DCE	178	44	83	9	42	83.0	33.6	
				T2-MRI or MRS or DW	178	50	101	3	24	94.3	19.2	
				T2-MRI or MRS or DCE	178	48	107	5	18	90.6	14.4	
				T2-MRI or DW or DCE	178	50	105	3	20	94.3	16.0	
				T2-MRI or MRS or DW or DCE	178	53	125	0	0	100.0	0.0	
Ghafoori 2010[120]	At least one	Patient	**MRS-directed TRUS-guided:** systematic 12-core TRUS (areas sampled not reported) + 'multiple' biopsies from MRS suspicious areas	MRS	46	16	2	2	26	88.9	92.9	
			As above	TRUS (systematic biopsies)	46	12	NR	6	NR	66.7	NR	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
[a]Hambrock 2010[86] (Hambrock 2008[85]) (Hambrock 2009 abstracts[121,122]) (Hambrock 2010 abstract[123])	2–7	Patient	**MRI-directed MRI-guided:** TSR-directed biopsies only and no random biopsies	T2-MRI or DCE or DW[a]	68	40	0	NR	NR	NR	NR	PPV = 100
Hoeks 2012[87]	At least one	Patient	**MRI-guided:** only CSRs were targeted, median 2 cores per CSR	T2-MRI or DCE or DW[a]	264	108	156	NR	NR	NR	NR	After first biopsy; PPV = 40.9. Only 51/156 of negative patients were subsequently followed up and nine had prostate cancer (seven were clinically significant). Thus, total with cancer = 117
		CSR	As above	As above	368	123	245	NR	NR	NR	NR	After first biopsy; PPV = 33.4
		Patient	**MRI- or TRUS-guided:** (areas sampled not reported)	As above ($n = 10$) or TRUS ($n = 4$)	51	NR	NR	9	42	NR	NR	After repeat biopsy (5-month follow-up); NPV = 17.6
Keetch 1994[88]	At least one	Patient	**TRUS-guided:** 4–6 cores (directed biopsies of abnormal or suspicious TRUS areas)	TRUS	427	82	NR	22	NR	78.8	NR	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Labanaris 2010[89] (Labanaris 2010 abstract[125]) (Labanaris 2009 abstract[124])	At least one	Patient	**MRI-directed TRUS-guided:** 18-core TRUS + three samples from each MRI suspicious area	DCE and DW and T2-MRI	260	126	44	17	73	88.1	62.4	Group A (suspicious MRI) and group B (non-suspicious MRI)
					15	NR	NR	NR	NR	71.1	NR	Group A: PSA level = 0–4 Detection rates: Targeted 67.9% 18-core 1.4% Targeted + 18 core 71.1%
					98	NR	NR	NR	NR	72.2	NR	Group A: PSA level = 4–10 Detection rates: Targeted 52.3% 18-core 20.2% Targeted + 18 core 72.5%
					47	NR	NR	NR	NR	76.2	NR	Group A: PSA level = 10–20 Detection rates: Targeted 57.6% 18-core 18.6% Targeted + 18 core 76.2%
					10	NR	NR	NR	NR	81.5	NR	Group A: PSA level > 20 Detection rates: Targeted 76.8% 18-core 4.7% Targeted + 18-core 81.5%

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
					170	NR	NR	NR	NR	73.9	NR	Group A: PSA level > 0 Detection rates: Targeted 56.4% 18-core 17.5% Targeted + 18 core 73.9%
					8	NR	NR	NR	NR	NR	100.0	Group B: PSA level = 0–4 Detection rate: 18-core 0%
					58	NR	NR	NR	NR	NR	81.8	Group B: PSA level = 4–10 Detection rate: 18-core 18.2%
					17	NR	NR	NR	NR	NR	77.4	Group B: PSA level = 10–20 Detection rate: 18-core 22.6%
					7	NR	NR	NR	NR	NR	72.6	Group B: PSA level > 20 Detection rate: 18-core 27.4%
					90	NR	NR	NR	NR	NR	80.8	Group B: PSA level > 0 Detection rate: 18-core 19.2%

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Lattouf 2007[90]	1–12	Patient (six had ASAP on initial negative biopsy)	**MRI-directed TRUS-guided:** systematic 12-core TRUS (according to standard sextant anatomy) + targeted MRI lesions	T2-MRI	26	13	10	1	2	92.9	16.7	Reported in paper: Sensitivity = 40% Specificity = 69.5% Not reported whether positive biopsies resulted from systematic TRUS or directed MRI
				DCE	26	10	8	4	4	71.4	33.3	Reported in paper: Sensitivity = 28% Specificity = 79.3%
				T2-MRI and DCE	26	9	8	5	4	64.3	33.3	
				T2-MRI or DCE	26	14	10	0	2	100.0	16.7	Reported in paper: Sensitivity = 40% Specificity = 66.4%
Lee 2011[126]	1-4	Patient	**MRI-directed TRUS-guided:** TRUS (no. of cores and areas sampled NR) + targeted MRI biopsy	T2-MRI or DW[a]	87	44	38	2	3	95.7	7.3	
		Biopsy	Targeted MRI suspicious lesions	T2-MRI or DW[a]	518	149	369	NR	NR	NR	NR	PPV = 28.8
			TRUS + targeted MRI suspicious lesions	T2-MRI or DW[a]	1421	181	1240	NR	NR	NR	NR	PPV = 12.7
			Standard TRUS	TRUS	903	32	871	NR	NR	NR	NR	PPV = 3.5
Lin 2008[91]	1	Patient	**TRUS-guided:** 6-core (areas sampled NR; some follow-up biopsies were TURP biopsies)	TRUS	366	32	NR	15	NR	68.1	NR	12 months' follow-up; assumed that all with positive diagnoses were TP in the second biopsy

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Lopez-Corona 2003[92]	At least one	Patient	**TRUS-guided:** 6–22 cores (sextant + two TZ + directed biopsy on suspicious TRUS areas or 12 TZ + 2 TZ)	TRUS	343	67	NR	34	NR	66.3	NR	
Ozden 2005[93]	1	Patient	**TRUS-guided:** 15 cores (12-core + 2 TZ + 1 midline) + sampling of suspicious PZ lesions	TRUS	60	7	8	9	36	43.8	81.8	
Panebianco 2011[95] (de Silverio 2011 abstract[119]) (Busetto 2011 abstract)[114]	1 (had to be negative for both PC and HGPIN for inclusion in this study)	Patient	**MRI-/MRS-directed TRUS-guided:** 10-core TRUS [two basal (lateral and paramedial), two mid-gland (lateral and paramedial), one apex, on each side] + three from each MRS suspicious lesion	MRS or DCE[a]	41	26	2	2	11	92.9	86.6	Values calculated from reported sensitivity and specificity
Park 2008[96]	1–5	Patient	**MRI-directed TRUS-guided:** at least two cores from suspicious DW areas followed by 6-, 8- or 10-core systematic TRUS/Bx (depending on prostate volume; areas sampled not reported)	TRUS systematic biopsies	43	12	NR	5	NR	70.6	NR	Three participants had history of radiation therapy for prostate cancer
				DW	43	17	NR	0	NR	100.0	NR	
		Core	As above	DW	NR	30	8	NR	NR	NR	NR	PPV = 78.9
Pepe 2010[97]	1	Patient	**TRUS-guided:** 20–38 cores (PZ and TZ)	TRUS	423	79	NR	3	NR	96.3	NR	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Perrotti 2002[127] (Perrotti 2000 abstract[128])	1–7	Patient	**MRI-directed TRUS-guided:** areas sampled and no. of cores NR	T2-MRI	74	16	17	1	40	94.1	70.2	Reported in paper: Sensitivity = 85.7 Specificity = 65.4 Assumes moderate or high suspicion MRI is positive test and low suspicion is negative test
Philip 2006[98]	1	Patient	**TRUS-guided:** 12 cores (sextant + six laterally directed cores)	TRUS	241	40	NR	2	NR	95.2	NR	
Pinsky 2007[99]	1	Patient	**TRUS-guided:** no. of cores NR	TRUS	2761	854	NR	338	NR	71.6	NR	
Portalez 2010[100] (Portalez 2010 abstract[129])	1 to 4	Segment (PZ only)	**MRI-/MRS-directed TRUS-guided:** 12–34 TRUS (base, middle and apex of R&L PZ lateral to the parasagittal plane + two TZ) + two biopsies of suspicious MRI areas	T2-MRI	408	20	48	21	319	48.8	87.0	28/68 participants had cancer
				DW	408	16	15	25	352	39.0	96.0	
				DCE	408	12	24	29	343	29.3	93.5	
				MRS	408	12	36	29	331	29.3	90.2	
		Segment (PZ and TZ)	As above	Overall MRI including sextant	544	45	79	NR	NR	NR	NR	PPV = 36.3
				Overall MRI excluding sextant	62	20	42	NR	NR	NR	NR	PPV = 32.3

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Prando 2005[101]	2–6	Patient	**MRI-/MRS-directed TRUS-guided:** direct voxel-guided biopsy (only for MRS abnormalities) and systematic TRUS biopsy (for all patients; 12 cores, two from each sextant)	MRS	42	17	14	0	11	100.0	44.0	Voxel score of 4 and/or 5 T2 information used only where associated with an abnormal MRS area
				MRS	42	12	4	5	21	70.6	84.0	At least one voxel score of 5. For all of these findings, not reported whether positive biopsies were from MRI/MRS directed or TRUS-guided biopsies
				T2-MRI	42	15	18	2	7	88.2	28.0	
		Sextant level	As above	MRS	348	44	32	8	264	84.6	89.0	Findings combining extended pattern biopsy and MRS-guided biopsy
Quinlan 2009[102]	At least one	Biopsy	**TRUS-guided:** sextant from the PZ bilaterally	TRUS	175	16	NR	11	NR	59.3	NR	
Rahman 2003[130]	At least two	Patient	**MRI-/MRS-directed TRUS-guided:** 12 from posterior + 6 from anterior (TRUS) + 2 or 3 from MRI-/MRS-suspicious sextants	T2-MRI or MRS[a]	56	21	28	1	6	95.5	17.6	These values back calculated Reported in paper: Sensitivity = 95 Specificity = 18 Not reported whether positive biopsies were from MRI-/MRS-suspicious areas or standard TRUS biopsy
Roehl 2002[103]	1	Patient	**TRUS-guided:** 4 cores (2 apex and 2 base) or sextant	TRUS	634	114	NR	74	NR	60.6	NR	
Roethke 2012[104]	1–9	Patient	**MRI-guided:** at least two from each MRI suspicious area (range 2 to 8)	T2-MRI or MRS or DCE or DW[a]	100	52	48	NR	NR	NR	NR	PPV = 52

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Sciarra 2010[105] (Panebianco 2010[94]) (Sciarra 2010 abstracts[131,132])	1 (Had to be negative for both PC and HGPIN for inclusion in this study.)	Patient	**MRI-/MRS-directed TRUS-guided:** 10-core TRUS [two basal (lateral and paramedial), two mid-gland (lateral and paramedial), one apex, on each side] + additional two cores from targeted MRI/MRS lesions	MRS	90	39	3	5	43	88.6	93.5	For all of these results, not reported whether positive biopsies were from MRI-/MRS-directed or random TRUS biopsies Reported in paper: Sensitivity = 92.3 Specificity = 88.2
				DCE	90	35	4	9	42	79.5	91.3	Reported in paper: Sensitivity = 84.6 Specificity = 82.3
				MRS and DCE	90	33	3	11	43	75.0	93.5	Both suspicious; reported in paper: Sensitivity = 92.6 Specificity = 88.8
				MRS or DCE	90	41	4	3	42	93.2	91.3	Either suspicious. Not reported in paper
	2	Patient	As above	MRS	50	24	5	2	19	92.3	79.2	
				DCE	50	22	2	4	22	84.6	91.7	
				MRS and DCE	50	21	2	5	22	80.8	91.7	Reported in paper: Sensitivity = 93.1 Specificity = 90.4
				MRS or DCE	50	25	5	1	19	96.2	79.2	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
	1	Voxel	As above	MRS	NR	136	8	NR	NR	NR	NR	PPV = 94.4
				DCE	NR	153	14	NR	NR	NR	NR	PPV = 91.6
				MRS and DCE	NR	125	7	NR	NR	NR	NR	PPV = 94.7
				MRS or DCE	NR	164	15	NR	NR	NR	NR	PPV = 91.6
	1	Core	As above	MRS	NR	NR	NR	NR	NR	83.3	72.7	Values reported in paper
				DCE	NR	NR	NR	NR	NR	75.6	76.7	
				MRS and DCE	NR	NR	NR	NR	NR	89.7	80.4	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Testa 2010[106]	1-4	Patient	**MRI-/MRS-directed TRUS-guided:** 1–3 cores from each region with abnormal MRI or MRS + one core from each of the remaining regions (TRUS; four basal, four mid-gland, two apex, two TZ)	T2-MRI	54	16	12	6	20	72.7	62.5	Prostate was divided on the basis of a 12-region scheme
				MRS	54	20	18	2	14	90.9	43.8	Not reported whether positive biopsies were from MRI-/MRS-suspicious areas or from standard TRUS biopsies
				T2-MRI and MRS	54	16	9	6	23	72.7	71.9	
				T2-MRI or MRS	54	20	21	2	11	90.9	34.4	
		Region	As above	T2-MRI	648	21	22	34	571	38.2	96.3	
				MRS	630	37	75	18	500	67.3	87.0	
				T2-MRI and MRS	648	19	7	36	586	34.5	98.8	
				T2-MRI or MRS	648	39	91	16	502	70.9	84.7	
			PZ only	T2-MRI	540	10	21	27	482	27.0	95.8	
				MRS	522	24	69	13	416	64.9	85.8	
				T2-MRI and MRS	540	8	7	29	496	21.6	98.6	
				T2-MRI or MRS	540	26	84	11	419	70.3	83.3	
			TZ only	T2-MRI	108	11	1	7	89	61.1	98.9	
				MRS	108	13	6	5	84	72.2	93.3	
				T2-MRI and MRS	108	11	0	7	90	61.1	100.0	
				T2-MRI or MRS	108	13	7	5	83	72.2	92.2	

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Ukimura 1997[107]	1	Patient	**TRUS-guided (directed and/or systematic):** no. of cores NR	TRUS	193	33	NR	18	NR	64.7	NR	
Valentini[133] 2010	At least one	Biopsy	**MRI-directed TRUS-guided:** 24-random-core TRUS (transperineal) + additional biopsies of suspicious MRI areas	DCE	NR	4	25	1	NR	80.0	NR	11 participants
				DW	NR	3	26	2	NR	60.0	NR	
				DCE or DW[a]	NR	5	24	NR	NR	NR	NR	PPV = 17.2
Wefer 2000[134]	At least one	Patient	**MRI-/MRS-directed TRUS-guided:** sextant biopsy (TRUS) using MRI/MRS road map	T2-MRI	24	7	2	3	12	70.0	85.7	Not reported whether positive biopsies were from MRI/MRS road map or TRUS-guided sextant
				T2-MRI and MRS	24	5	2	5	12	50.0	85.7	Reported in paper: Sensitivity = 46 Specificity = 85

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Wetter 2005[108]	1	Patient	**MRS-directed MRI-guided transgluteal biopsies:** no. of samples taken not reported	MRS	6	2	1	0	3	100.0	75.0	Borderline and pathological metabolite classed as positive test
				MRS	6	1	1	1	3	50.0	75.0	Only pathological metabolite classed as positive test
				T2-MRI	6	1	2	1	2	50.0	50.0	Suspected PC classed as positive test
				T2-MRI	6	2	4	0	0	100.0	0.0	Suspected PC and hypoechoic lesions classed as positive test
				T2-MRI and MRS	6	1	1	1	3	50.0	75.0	Borderline and pathological metabolite classed as positive test
				T2-MRI and MRS	6	1	1	1	3	50.0	75.0	Pathological metabolite classed as positive test
				T2-MRI or MRS	6	2	2	0	2	100.0	50.0	Borderline and pathological metabolite classed as positive test
				T2-MRI or MRS	6	1	2	1	2	50.0	50.0	Pathological metabolite classed as positive test
Yakar 2011[109]	1–4	Patient	**Transrectal robot-assisted MRI-guided biopsy:** no. of samples per CSR was based on certainty of correct needle positioning	T2-MRI or DCE or DW[a]	9	5	4	NR	NR	NR	NR	PPV = 55.6
		CSR	As above	T2-MRI or DCE or DW[a]	13	6	7	NR	NR	NR	NR	PPV = 46.2

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Yanke 2006[110]	1	Unclear if patient or biopsy-level analysis	**TRUS-guided:** 6 core (1993–8) or 12 core (1998–2003)	TRUS	416	97	NR	47	NR	67.4	NR	On initial biopsy: 56 men had HGPIN and 129 had ASAP
Yao 2009[136]	2–8	Patient	**MRI-directed TRUS-guided:** systematic and targeted biopsy	T2-MRI or systematic TRUS[a]	41	14	10	1	16	93.3	61.5	'Systematic'/'systemic' biopsy interpreted as saturation biopsy
				Targeted T2-MRI	41	12	NR	3	NR	80.0	NR	Reported in paper for MRI: Sensitivity = 93 Specificity = 62
Younes 2001[137]	At least one	Patient	**MRI-directed TRUS-guided:** no. of cores NR	T2-MRI	27	14	6	0	7	100.0	53.9	Assumed that T2 was type of MRI used
Yuen 2004[111]	1 or 2	Patient	**TRUS-guided:** 10-core [three on each side of mid-lobar paramedian sagittal area (base, mid-gland and apex) + two from far lateral zone on each side] + additional samples from hypoechoic lesions	TRUS	57	2	3	13	39	13.3	92.9	Results relate to presence or absence of hypoechoic lesions rather than systematic TRUS. Median 12 months between biopsy 2 and 3

Study ID	Previous negative biopsy	Unit of analysis	Method of biopsy	Test	No. analysed	TP	FP	FN	TN	Sensitivity	Specificity	Note
Yuen 2004[112]	1–3	Patient	**MRI-/MRS-directed TRUS-guided:** 10-core TRUS (PZ including sextant paramedian and far lateral PZ) + up to four from equivocal or suspicious MRI/MRS areas plus biopsy of abnormal hyperechoic areas on TRUS if present	T2-MRI	24	4	2	3	15	57.1	88.2	No patients had abnormal or hypoechoic areas on TRUS. Equivocal classed as normal
				MRS	24	4	3	3	14	57.1	82.4	Not reported if positive biopsies were from targeted or standard TRUS biopsies. Equivocal classed as normal
				T2-MRI and MRS	24	1	0	6	17	14.3	100.0	Equivocal classed as normal
				T2-MRI or MRS	24	7	5	0	12	100.0	70.6	Equivocal classed as normal
				T2-MRI	24	4	4	3	13	57.1	76.5	Equivocal classed as suspicious
				MRS	24	5	8	2	9	71.4	52.9	Equivocal classed as suspicious
				T2-MRI and MRS	24	2	4	5	13	28.6	76.5	Equivocal classed as suspicious
				T2-MRI or MRS	24	7	8	0	9	100.0	52.9	Equivocal classed as suspicious
		Core	As above	T2-MRI	296	6	6	9	275	40.0	97.9	Reported in paper: Sensitivity = 42.9% Specificity = 97.9%
				MRS	296	6	15	9	266	40.0	94.7	Reported in paper: Sensitivity = 38.5% Specificity = 94.3%
Zackrisson 2004[113]	1	Patient	**TRUS-guided:** sextant biopsies	TRUS	706	124	NR	45	NR	73.4	NR	

R&L, right and left; TURP, transurethral resection of the prostate.

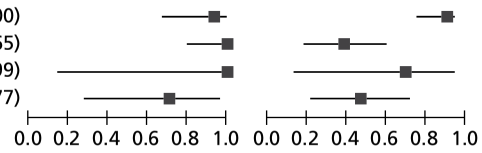
a For these combinations of tests, it was unclear whether, for a result to be considered positive, all tests had to be positive or just one had to be positive. It was assumed that one of the combination had to be positive for an overall positive result.

Appendix 9 Sensitivity analysis of magnetic resonance spectroscopy subgrouped into year of publication

Sensitivity and specificity – individual study results

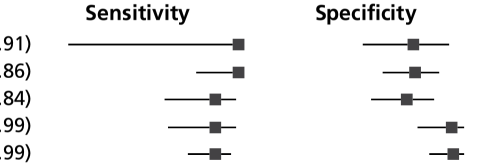
MRS pre 2007

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Amsellem-Ouazana 2005[74]	14	1	1	26	0.93 (0.68 to 1.00)	0.96 (0.81 to 1.00)
Prando 2005[101]	17	14	0	11	1.00 (0.80 to 1.00)	0.44 (0.24 to 0.65)
Wetter 2005[108]	2	1	0	3	1.00 (0.16 to 1.00)	0.75 (0.19 to 0.99)
Yuen 2004[112]	5	8	2	9	0.71 (0.29 to 0.96)	0.53 (0.28 to 0.77)



MRS 2007 onwards

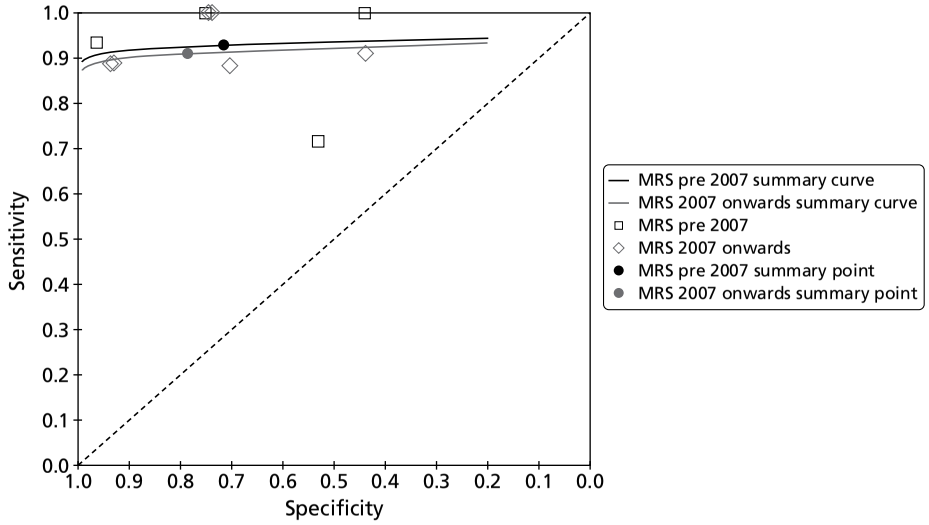
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bhatia 2007[76]	2	5	0	14	1.00 (0.16 to 1.00)	0.74 (0.49 to 0.91)
Calvo 2010[115]	16	11	0	32	1.00 (0.79 to 1.00)	0.74 (0.59 to 0.86)
Cirillo 2008[79]	15	11	2	26	0.88 (0.64 to 0.99)	0.70 (0.53 to 0.84)
Ghafoori 2010[120]	16	2	2	26	0.89 (0.65 to 0.99)	0.93 (0.76 to 0.99)
Sciarra 2010[105]	39	3	5	43	0.89 (0.75 to 0.96)	0.93 (0.82 to 0.99)
Testa 2010[106]	20	18	2	14	0.91 (0.71 to 0.99)	0.44 (0.26 to 0.62)



Pooled estimates (95% CI)

MRS pre 2007	
Sensitivity	0.93 (0.80 to 0.98)
Specificity	0.71 (0.43 to 0.89)
DOR	32.07 (6.39 to 160.89)
LR+	3.25 (1.38 to 7.64)
LR–	0.10 (0.03 to 0.31)
MRS 2007 onwards	
Sensitivity	0.91 (0.84 to 0.95)
Specificity	0.79 (0.60 to 0.90)
DOR	37.07 (13.14 to 104.60)
LR+	4.23 (2.11 to 8.51)
LR–	0.11 (0.06 to 0.21)

SROC curve

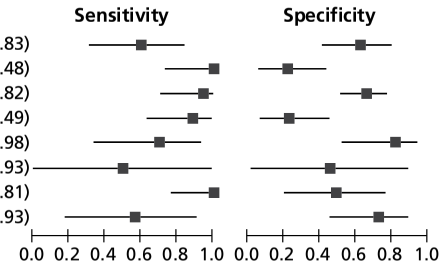


Appendix 10 Sensitivity analysis of T2-weighted magnetic resonance imaging subgrouped into year of publication

Sensitivity and specificity – individual study results

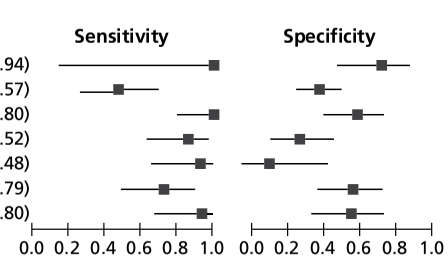
MRI pre 2007

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Amsellem-Ouazana 2005[74]	9	9	6	18	0.60 (0.32 to 0.84)	0.67 (0.46 to 0.83)
Babaian 2000[75]	12	19	0	7	1.00 (0.74 to 1.00)	0.27 (0.12 to 0.48)
Perotti 2002[127]	16	17	1	40	0.94 (0.71 to 1.00)	0.70 (0.57 to 0.82)
Prando 2005[101]	15	18	2	7	0.88 (0.64 to 0.99)	0.28 (0.12 to 0.49)
Wefer 2000[134]	7	2	3	12	0.70 (0.35 to 0.93)	0.86 (0.57 to 0.98)
Wetter 2005[108]	1	2	1	2	0.50 (0.01 to 0.99)	0.50 (0.07 to 0.93)
Younes 2001[137]	14	6	0	7	1.00 (0.77 to 1.00)	0.54 (0.25 to 0.81)
Yuen 2004[112]	4	4	3	13	0.57 (0.18 to 0.90)	0.76 (0.50 to 0.93)



MRI 2007 onwards

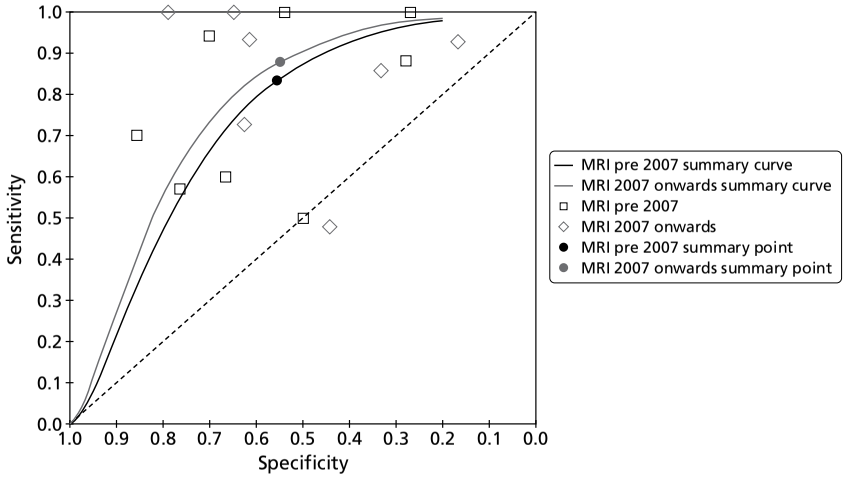
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bhatia 2007[76]	2	4	0	15	1.00 (0.16 to 1.00)	0.79 (0.54 to 0.94)
Cheikh 2009[78]	11	39	12	31	0.48 (0.27 to 0.69)	0.44 (0.32 to 0.57)
Cirillo 2008[79]	17	13	0	24	1.00 (0.80 to 1.00)	0.65 (0.47 to 0.80)
Franiel 2011[84]	18	22	3	11	0.86 (0.64 to 0.97)	0.33 (0.18 to 0.52)
Lattouf 2007[90]	13	10	1	2	0.93 (0.66 to 1.00)	0.17 (0.02 to 0.48)
Testa 2010[106]	16	12	6	20	0.73 (0.50 to 0.89)	0.63 (0.44 to 0.79)
Yao 2009[136]	14	10	1	16	0.93 (0.68 to 1.00)	0.62 (0.41 to 0.80)



Pooled estimates (95% CI)

MRI pre 2007	
Sensitivity	0.83 (0.63 to 0.94)
Specificity	0.56 (0.39 to 0.71)
DOR	6.30 (1.91 to 20.73)
LR+	1.88 (1.26 to 2.79)
LR–	0.30 (0.12 to 0.74)
MRI 2007 onwards	
Sensitivity	0.88 (0.72 to 0.95)
Specificity	0.55 (0.41 to 0.69)
DOR	8.92 (2.97 to 26.79)
LR+	1.95 (1.41 to 2.70)
LR–	0.22 (0.09 to 0.54)

SROC curve



Appendix 11 Transrectal ultrasonography individual study results (patient-level analysis)

Study ID	No. of cores taken	Use of TRUS	No. analysed	Sensitivity (%)	Specificity (%)	Follow-up?
Babaian 2000[75]	11	Anatomical and imaging	277	48.1	83.7	N
Beyersdorff 2002[57]	34	Anatomical and imaging	38	33.3	88.5	N
Campodonico 2006[77]	12	Anatomical	81	88.9	100.0	Y
De la Rosette 2009[80]	8 or 12	Anatomical and imaging	139	10.0	73.9	N
Djavan 2001[81]	8	Anatomical and imaging	820	67.5	NR	Y
Eskicorapci 2007[83]	14	Anatomical and imaging	211	18.5	78.3	N
Ghafoori 2010[120]	12	Anatomical	46	66.7	NR	N
Keetch 1994[88]	4 to 6	Anatomical	427	78.8	NR	Y
Lin 2008[91]	6	Anatomical	366	68.1	NR	Y
Lopez-Corona 2003[92]	6 to 22	Anatomical and imaging	343	66.3	NR	Y
Ozden 2005[93]	15	Anatomical and imaging	60	43.8	81.8	N
Park 2008[96]	6, 8 or 10	Anatomical and imaging	43	70.6	NR	N
Pepe 2010[97]	16 to 21	Anatomical	423	96.3	NR	Y
Philip 2006[98]	12	Anatomical	241	95.2	NR	Y
Pinsky 2007[99]	NR	Anatomical	2761	71.6	NR	Y
Quinlan 2009[102]	6	Anatomical	111	59.3	NR	Y
Roehl 2002[103]	4 or 6	Anatomical and imaging	634	60.6	NR	Y
Ukimura 1997[107]	NR	Anatomical and imaging	193	64.7	NR	Y
Yanke 2006[110]	6 or 12	Anatomical	416	67.4	NR	Y
Yuen 2004[111]	10	Anatomical and imaging	57	13.3	92.9	N
Zackrisson 2004[113]	6	Anatomical	706	73.4	NR	Y

N, no; NR, not reported; Y, yes.

Appendix 12 Studies directly comparing two or more tests

Study ID	MRS	DCE	DW	T-2 MRI	TRUS	MRS/T2	MRS/DCE	MRS/DCE/T2	MRS/DW/T2	MRS/DCE/ DW/T2	DCE/DW	DCE/T2	DCE/ DW/T2	DW/T2
Amsellem-Ouazana 2005[74]	✗			✗		✗								
Beyersdorff 2002[57]				✗	✗									
Bhatia 2007[76]	✗			✗		✗								
Cheikh 2009[78]		✗		✗								✗		
Cirillo 2008[79]	✗			✗		✗								
Franiel 2011[84]				✗		✗		✗	✗	✗		✗	✗	✗
Ghafoori 2010[120]	✗				✗									
Lattouf 2007[90]		✗		✗								✗		
Park 2008[96]			✗		✗									
Portalez 2010[100]	✗	✗	✗	✗										
Sciarra 2010[105]	✗	✗					✗							
Testa 2010[106]	✗			✗		✗								
Valentini 2010[133]		✗	✗								✗			
Wefer 2000[134]				✗		✗								
Wetter 2005[108]	✗			✗		✗								
Yao 2009[136]				✗	✗									
Yuen 2004[112]	✗			✗		✗								

Appendix 13 Results of the indirect comparison

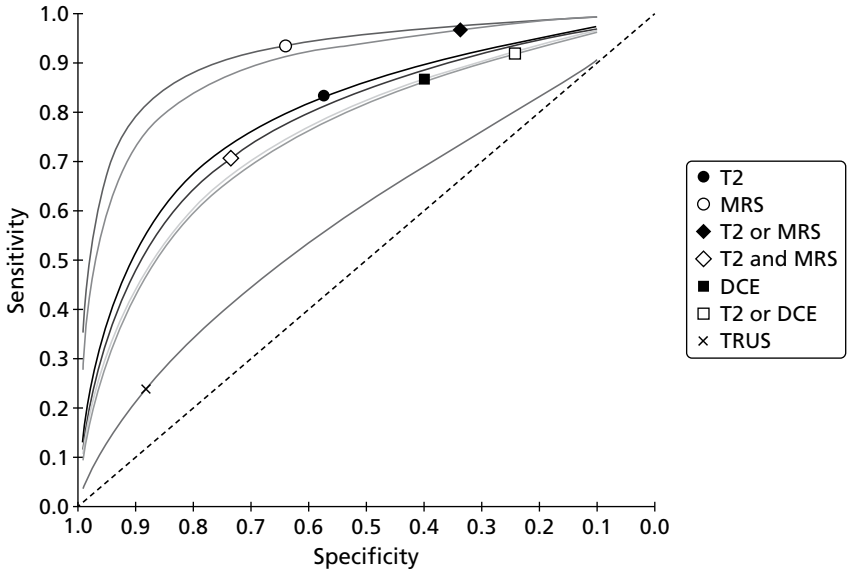
Appendix 13.1: Biopsy-level pooled estimates from indirect comparison: comparing the sensitivity and specificity of T2-weighted magnetic resonance imaging with the other tests

Parameter	Estimate, % (95% CI)	Ratio (95% CI)	*p*-value
Sensitivity for T2-MRI	83 (75 to 89)	1	
Sensitivity for DCE	87 (74 to 94)	1.04 (0.93 to 1.17)	0.499
Sensitivity for MRS	93 (87 to 97)	1.12 (1.03 to 1.22)	0.008
Sensitivity for T2 and MRS	71 (50 to 85)	0.85 (0.67 to 1.07)	0.172
Sensitivity for T2 or DCE	92 (81 to 97)	1.10 (1.00 to 1.21)	0.046
Sensitivity for T2 or MRS	97 (91 to 99)	1.16 (1.07 to 1.26)	0.001
Sensitivity for TRUS	24 (13 to 39)	0.28 (0.16 to 0.50)	< 0.001
Specificity for T2-MRI	57 (47 to 67)	1	
Specificity for DCE	40 (25 to 56)	0.70 (0.49 to 0.98)	0.041
Specificity for MRS	64 (52 to 75)	1.12 (0.95 to 1.32)	0.194
Specificity for T2 and MRS	73 (58 to 85)	1.28 (1.06 to 1.55)	0.011
Specificity for T2 or DCE	24 (13 to 39)	0.42 (0.26 to 0.68)	< 0.001
Specificity for T2 or MRS	34 (23 to 46)	0.59 (0.44 to 0.78)	< 0.001
Specificity for TRUS	88 (79 to 94)	1.54 (1.27 to 1.86)	< 0.001

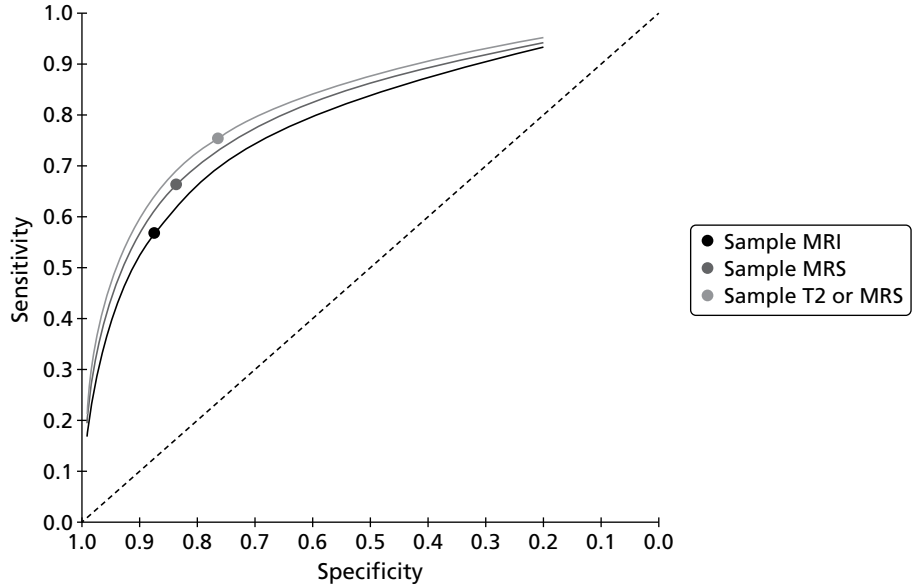
Appendix 13.2: Patient-level pooled estimates from indirect comparison: comparing the sensitivity and specificity of T2-weighted magnetic resonance imaging with the other tests

Parameter	Estimate, % (95% CI)	Ratio (95% CI)	*p*-value
Sensitivity for MRI	57 (43 to 69)	1	
Sensitivity for MRS	66 (53 to 78)	1.23 (1.02 to 1.49)	0.03
Sensitivity for T2 or MRS	75 (61 to 86)	1.35 (1.15 to 1.60)	0.00
Specificity for MRI	87 (78 to 93)	1	
Specificity for MRS	84 (72 to 91)	0.98 (0.94 to 1.03)	0.40
Specificity for T2 or MRS	76 (62 to 86)	0.86 (0.77 to 0.95)	0.00

Appendix 13.3: Hierarchical summary receiver operating characteristic plot comparing tests at patient level, assuming no underlying difference in the shape parameter



Appendix 13.4: Hierarchical summary receiver operating characteristic plot comparing tests at biopsy level, assuming no underlying difference in the shape parameter



Appendix 13.5: Sensitivity analysis of the patient-level pooled estimate from the indirect comparison, assuming there is no common underlying shape

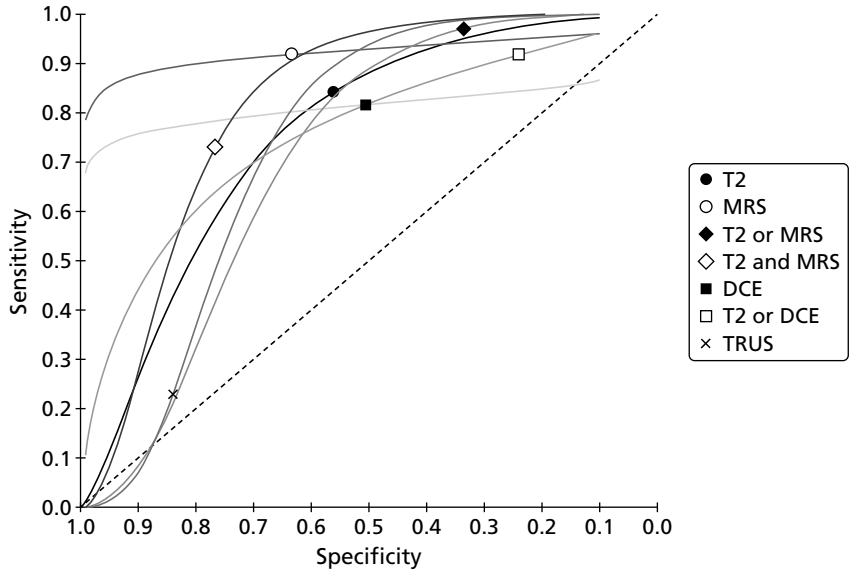
		95% CI	
Parameter	Estimate	Lower	Upper
Sensitivity for T2-MRI	0.84	0.75	0.90
Sensitivity for DCE	0.82	0.70	0.89
Sensitivity for MRS	0.92	0.86	0.95
Sensitivity for T2 and MRS	0.73	0.44	0.90
Sensitivity for T2 or DCE	0.92	0.78	0.97
Sensitivity for T2 or MRS	0.97	0.91	0.99
Sensitivity for TRUS	0.23	0.11	0.42
Specificity for T2-MRI	0.56	0.48	0.64
Specificity for DCE	0.50	0.24	0.77
Specificity for MRS	0.63	0.45	0.78
Specificity for T2 and MRS	0.77	0.65	0.85
Specificity for T2 or DCE	0.24	0.09	0.49
Specificity for T2 or MRS	0.33	0.25	0.42
Specificity for TRUS	0.84	0.76	0.89
DOR for MRI	6.78	3.58	12.84
DOR for DCE	4.49	1.23	16.43
DOR for MRS	19.51	7.51	50.69
DOR for T2 and MRS	8.85	2.23	35.06
DOR for T2 or DCE	3.51	1.05	11.74
DOR for T2 or MRS	16.55	4.80	57.04
DOR for TRUS	1.53	0.55	4.29
LR+ for MRI	1.92	1.57	2.33
LR+ for DCE	1.64	0.90	2.99
LR+ for MRS	2.50	1.58	3.96
LR+ for T2 and MRS	3.11	1.77	5.48
LR+ for T2 or DCE	1.21	0.95	1.53
LR+ for T2 or MRS	1.46	1.28	1.66
LR+ for TRUS	1.41	0.63	3.17
LR– for MRI	0.28	0.17	0.46
LR– for DCE	0.36	0.12	1.06
LR– for MRS	0.11	0.05	0.23
LR– for T2 and MRS	0.42	0.12	1.42
LR– for T2 or DCE	0.37	0.12	1.10
LR– for T2 or MRS	0.08	0.02	0.29
LR– for TRUS	1.44	0.24	8.84

Appendix 13.6: Patient-level comparative estimates from indirect comparison model, comparing estimates of T2-weighted magnetic resonance imaging with other tests

Parameter	Estimate	*p*-value	95% CI	
			Lower	Upper
TP odds ratio DCE vs T2	0.83	0.65	0.38	1.83
TP odds ratio MRS vs T2	2.14	0.06	0.97	4.69
TP odds ratio T2 and MRS vs T2	0.51	0.26	0.16	1.66
TP odds ratio T2 or DCE vs T2	2.11	0.22	0.64	6.91
TP odds ratio T2 or MRS vs T2	6.21	0.00	1.94	19.89
TP odds ratio TRUS vs T2	0.06	< 0.0001	0.02	0.16
TN odds ratio DCE vs T2	0.80	0.68	0.27	2.33
TN odds ratio MRS vs T2	1.35	0.35	0.72	2.51
TN odds ratio T2 and MRS vs T2	2.56	0.00	1.41	4.65
TN odds ratio T2 or DCE vs T2	0.25	0.01	0.08	0.73
TN odds ratio T2 or MRS vs T2	0.39	< 0.0001	0.26	0.60
TN odds ratio TRUS vs T2	4.06	< 0.0001	2.30	7.18
Relative sensitivity DCE vs T2	0.97	0.65	0.85	1.11
Relative sensitivity MRS vs T2	1.09	0.08	0.99	1.20
Relative sensitivity T2 and MRS vs T2	0.87	0.38	0.63	1.19
Relative sensitivity T2 or DCE vs T2	1.09	0.14	0.97	1.23
Relative sensitivity T2 or MRS vs T2	1.15	0.00	1.06	1.26
Relative sensitivity TRUS vs T2	0.27	0.00	0.13	0.55
Relative specificity DCE vs T2	0.90	0.70	0.52	1.54
Relative specificity MRS vs T2	1.13	0.30	0.90	1.42
Relative specificity T2 and MRS vs T2	1.37	0.00	1.15	1.62
Relative specificity T2 or DCE vs T2	0.43	0.04	0.18	0.98
Relative specificity T2 or MRS vs T2	0.60	< 0.0001	0.46	0.76
Relative specificity TRUS vs T2	1.50	< 0.0001	1.27	1.76
RDOR DCE vs T2	0.66	0.53	0.19	2.37
RDOR MRS vs T2	2.88	0.04	1.05	7.86
RDOR T2 and MRS vs T2	1.30	0.70	0.34	4.99
RDOR T2 or DCE vs T2	0.52	0.27	0.16	1.66
RDOR T2 or MRS vs T2	2.44	0.15	0.73	8.16
RDOR TRUS vs T2	0.23	0.01	0.07	0.75

RDOR, relative diagnostic odds ratio.

Appendix 13.7: Hierarchical summary receiver operating characteristic plot comparing tests at patient level



Appendix 13.8: Biopsy-level pooled estimates from indirect comparison model

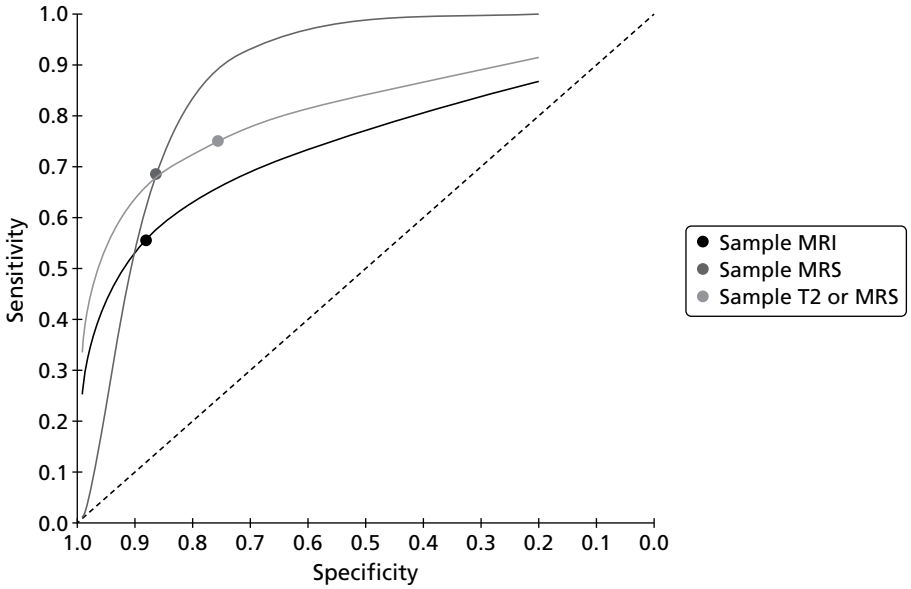
		95% CI	
Parameter	Estimate	Lower	Upper
Sensitivity for MRI	0.55	0.45	0.66
Sensitivity for MRS	0.68	0.49	0.83
Sensitivity for T2 or MRS	0.75	0.63	0.84
Specificity for MRI	0.88	0.78	0.94
Specificity for MRS	0.86	0.81	0.90
Specificity for T2 or MRS	0.75	0.59	0.87
DOR for MRI	9.04	4.53	18.05
DOR for MRS	13.52	6.27	29.17
DOR for T2 or MRS	9.23	4.21	20.24
LR+ for MRI	4.58	2.53	8.32
LR+ for MRS	4.96	3.48	7.06
LR+ for T2 or MRS	3.05	1.79	5.20
LR– for MRI	0.51	0.41	0.63
LR– for MRS	1.79	0.31	10.26
LR– for T2 or MRS	0.34	0.21	0.54

Appendix 13.9: Biopsy-level comparative estimates from indirect comparison model, comparing estimates of T2-weighted magnetic resonance imaging with other tests

Parameter	Estimate	*p*-value	95% CI	
			Lower	Upper
TP odds ratio MRS vs T2	1.74	0.07	0.95	3.20
TP odds ratio T2 or MRS vs T2	2.42	0.00	1.48	3.95
TN odds ratio MRS vs T2	0.86	0.47	0.57	1.30
TN odds ratio T2 or MRS vs T2	0.42	< 0.0001	0.33	0.54
Relative sensitivity MRS vs T2	1.23	0.03	1.02	1.49
Relative sensitivity T2 or MRS vs T2	1.35	0.00	1.15	1.60
Relative specificity MRS vs T2	0.98	0.40	0.94	1.03
Relative specificity T2 or MRS vs T2	0.86	0.00	0.77	0.95
RDOR MRS vs T2	1.50	0.34	0.66	3.40
RDOR T2 or MRS vs T2	1.02	0.94	0.59	1.76

RDOR, relative diagnostic odds ratio.

Appendix 13.10: Hierarchical summary receiver operating characteristic plot comparing tests at biopsy level



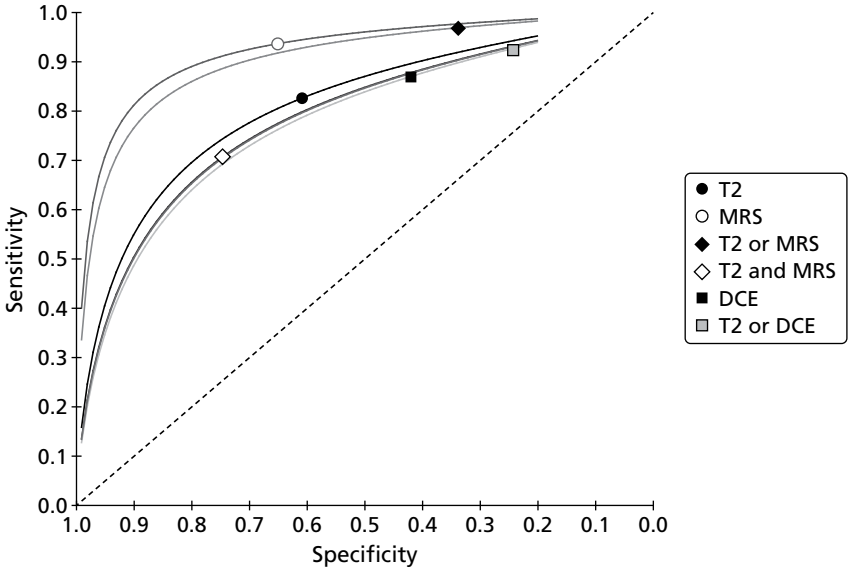
Appendix 13.11: Patient-level pooled estimates from indirect comparison after removing the Franiel study[84]

		95% CI	
Parameter	Estimate	Lower	Upper
Sensitivity for T2-MRI	0.85	0.74	0.92
Sensitivity for DCE	0.82	0.70	0.90
Sensitivity for MRS	0.92	0.85	0.96
Sensitivity for T2 and MRS	0.76	0.45	0.92
Sensitivity for T2 or DCE	0.95	0.69	1.00
Sensitivity for T2 or MRS	0.98	0.91	0.99
Sensitivity for TRUS	0.35	0.18	0.58
Specificity for T2-MRI	0.57	0.48	0.65
Specificity for DCE	0.52	0.24	0.79
Specificity for MRS	0.63	0.44	0.79
Specificity for T2 and MRS	0.77	0.64	0.86
Specificity for T2 or DCE	0.21	0.09	0.44
Specificity for T2 or MRS	0.33	0.24	0.44
Specificity for TRUS	0.90	0.81	0.95
DOR for MRI	7.54	3.25	17.51
DOR for DCE	4.97	1.22	20.23
DOR for MRS	19.26	6.61	56.16
DOR for T2 and MRS	10.20	2.18	47.79
DOR for T2 or DCE	5.75	0.93	35.46
DOR for T2 or MRS	21.31	4.44	102.37
DOR for TRUS	4.91	1.37	17.60
LR+ for MRI	1.97	1.55	2.52
LR+ for DCE	1.71	0.89	3.30
LR+ for MRS	2.49	1.51	4.10
LR+ for T2 and MRS	3.23	1.78	5.85
LR+ for T2 or DCE	1.21	1.01	1.46
LR+ for T2 or MRS	1.47	1.26	1.72
LR+ for TRUS	3.53	1.34	9.27
LR– for MRI	0.26	0.14	0.50
LR– for DCE	0.34	0.11	1.06
LR– for MRS	0.11	0.05	0.26
LR– for T2 and MRS	0.35	0.12	1.02
LR– for T2 or DCE	0.21	0.03	1.68
LR– for T2 or MRS	0.07	0.01	0.33
LR– for TRUS	0.64	0.14	2.89

Appendix 13.12: Patient-level pooled estimates from indirect comparison after removing the Franiel study[84] and also TRUS as test

Parameter	Estimate	95% CI	
		Lower	Upper
Sensitivity for T2-MRI	0.83	0.73	0.89
Sensitivity for DCE	0.87	0.73	0.94
Sensitivity for MRS	0.94	0.87	0.97
Sensitivity for T2 and MRS	0.71	0.50	0.85
Sensitivity for T2 or DCE	0.92	0.80	0.97
Sensitivity for T2 or MRS	0.97	0.90	0.99
Specificity for T2-MRI	0.61	0.49	0.72
Specificity for DCE	0.42	0.26	0.59
Specificity for MRS	0.65	0.52	0.76
Specificity for T2 and MRS	0.75	0.59	0.86
Specificity for T2 or DCE	0.26	0.14	0.44
Specificity for T2 or MRS	0.34	0.22	0.48
DOR for MRI	7.31	3.70	14.41
DOR for DCE	4.78	1.64	13.93
DOR for MRS	26.76	10.90	65.71
DOR for T2 and MRS	7.05	2.34	21.24
DOR for T2 or DCE	4.31	1.14	16.33
DOR for T2 or MRS	15.11	4.31	53.02
LR+ for MRI	2.10	1.56	2.83
LR+ for DCE	1.50	1.10	2.03
LR+ for MRS	2.67	1.88	3.79
LR+ for T2 and MRS	2.77	1.56	4.95
LR+ for T2 or DCE	1.25	1.00	1.57
LR+ for T2 or MRS	1.46	1.20	1.78
LR– for MRI	0.29	0.18	0.46
LR– for DCE	0.31	0.14	0.72
LR– for MRS	0.10	0.05	0.21
LR– for T2 and MRS	0.39	0.21	0.75
LR– for T2 or DCE	0.29	0.09	0.92
LR– for T2 or MRS	0.10	0.03	0.31

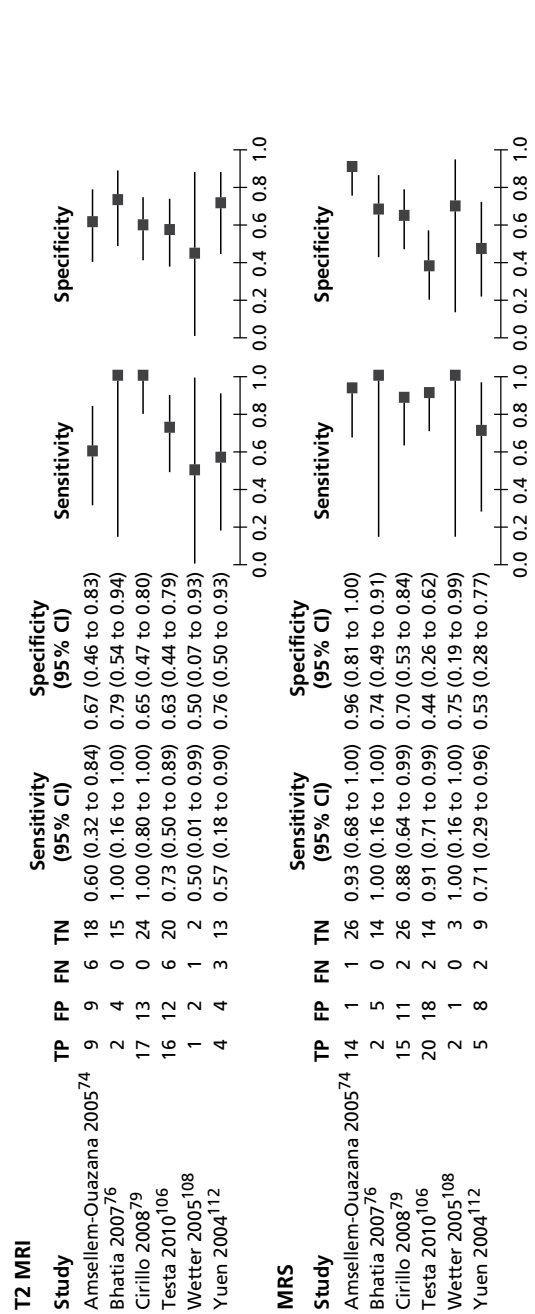
Appendix 13.13: Hierarchical summary receiver operating characteristic plot comparing tests at patient level, assuming no underlying difference in the shape parameter

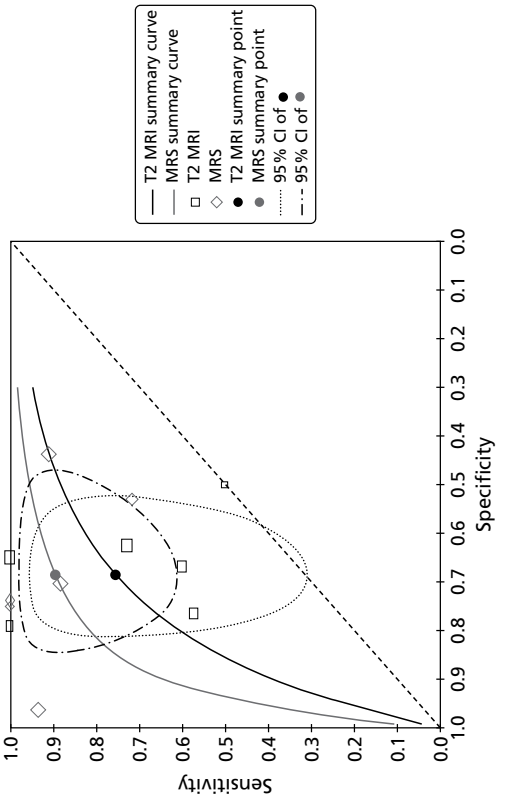


Appendix 13.14: Patient-level pooled estimates from indirect comparison after removing the Franiel study[84] and also TRUS as test, assuming accuracy does not vary with threshold

		95% CI	
Parameter	Estimate	Lower	Upper
Sensitivity for T2-MRI	0.84	0.73	0.91
Sensitivity for DCE	0.82	0.71	0.90
Sensitivity for MRS	0.92	0.86	0.96
Sensitivity for T2 and MRS	0.76	0.45	0.92
Sensitivity for T2 or DCE	0.94	0.65	0.99
Sensitivity for T2 or MRS	0.97	0.90	0.99
Specificity for T2-MRI	0.58	0.49	0.66
Specificity for DCE	0.51	0.24	0.78
Specificity for MRS	0.65	0.47	0.79
Specificity for T2 and MRS	0.77	0.65	0.86
Specificity for T2 or DCE	0.20	0.07	0.44
Specificity for T2 or MRS	0.33	0.25	0.44
DOR for MRI	7.29	3.56	14.96
DOR for DCE	4.95	1.33	18.39
DOR for MRS	22.13	8.37	58.53
DOR for T2 and MRS	10.26	2.37	44.48
DOR for T2 or DCE	4.14	0.77	22.15
DOR for T2 or MRS	18.26	4.34	76.77
LR+ for MRI	2.00	1.62	2.48
LR+ for DCE	1.69	0.91	3.14
LR+ for MRS	2.61	1.63	4.15
LR+ for T2 and MRS	3.25	1.86	5.66
LR+ for T2 or DCE	1.18	0.99	1.41
LR+ for T2 or MRS	1.46	1.26	1.70
LR– for MRI	0.27	0.16	0.49
LR– for DCE	0.34	0.11	0.99
LR– for MRS	0.10	0.04	0.21
LR– for T2 and MRS	0.37	0.13	1.08
LR– for T2 or DCE	0.29	0.04	2.02
LR– for T2 or MRS	0.08	0.02	0.34

Appendix 13.15: Magnetic resonance spectroscopy compared with T2-weighted magnetic resonance imaging patient-level analysis: sensitivity, specificity, pooled estimates and summary receiver operating characteristic curve, assuming an underlying common shape





MRS pooled estimates (95% CI)	
Sensitivity	0.89 (0.78 to 0.95)
Specificity	0.69 (0.57 to 0.78)
DOR	18.37 (6.80 to 49.59)
LR+	2.84 (1.67 to 3.44)
LR–	0.15 (0.07 to 0.35)
T2-MRI pooled estimates (95% CI)	
Sensitivity	0.75 (0.60 to 0.86)
Specificity	0.69 (0.57 to 0.78)
DOR	6.66 (2.92 to 15.15)
LR+	2.39 (1.67 to 3.44)
LR–	0.36 (0.21 to 0.61)

Appendix 14 False-positives

Study ID	Tests	Unit of analysis	No. analysed	FPs	TNs	FP rate (%)	Reasons
Amsellem-Ouazana 2005[74]	T2-MRI; MRS	Patient	42	1	26	3.7	Both MRI and MRS showed concordant suspicious zones; targeted biopsies found HGPIN
Beyersdorff 2002[57]	T2-MRI; TRUS	Biopsy	272	115	134	46.2	Prostatitis, fibrosis or PIN in 86 (75%); normal prostatic tissue in 29 (25%)
Bhatia 2007[76]	T2-MRI; MRS	Patient	21	5	14	26.3	Patients whose MRI/MRS imaging showed FP had either BPH or chronic prostatitis
Cheikh 2009[78]	T2-MRI; DCE-MRI	Sector	670	106	520	16.9	When inflammation was present at biopsy, specificity of T2-MRI and DCE-MRI decreased significantly compared with sextants with normal biopsy findings
Cirillo 2008[79]	T2-MRI; MRS	Patient	54	13	24	35.1	T2-MRI: PIN in three (23%), fibrosis in five (38.5%), normal prostate tissue in five (38.5%)
				11	26	29.7	MRS: PIN in six (54.5%), fibrosis in four (36.4%), normal prostatic tissue in one (9.1%)
Prando 2005[101]	T2-MRI; MRS	Patient	42	14	11	56.0	MRS: Four (29%) had focal prostatic atrophy
Testa 2010[106]	T2-MRI; MRS	Region	630	75	500	13.0	MRS: HGPIN in seven (9.3%), ASAP in one (1.3%), BPH in seven (9.3%), prostatitis in 55 (73.3%) and post-inflammation atrophy in five (6.7%)
Valentini 2010[133]	DCE-MRI; DW-MRI	Biopsy	NR	24	NR	NC	ASAP in three (12.5%), chronic inflammation in five (20.8%), glandular atrophy/fibrosis in 12 (50.0%), atrophy alone in two (8.3%) and microabscess in two (8.3%)
Wetter 2005[108]	T2-MRI; MRS	Patient	6	1	3	25.0	MRS: no sign of malignancy in one (16.7%)
				4	0	100.0	T2-MRI: no sign of malignancy in two (33.3%), chronic prostatitis in two (33.3%)
Yakar 2011[109]	T2-MRI; DCE-MRI; DW-MRI	CSR	13	7	NR	NC	Prostatitis in three (42.9%), hyperplasia in two (28.6%), HGPIN in two (28.6%)
Younes 2001[137]	T2-MRI	Patient	27	6	7	46.2	Inflammatory lesions

BPH, benign prostatic hyperplasia; CSR, cancer-suspicious region; NC, not calculable; NR, not reported.

Appendix 15 Gleason scores reported by the studies

Study ID	Test(s)	No. analysed	No. with PC	Prevalence (%)	Median (range) Gleason score	Percentage with Gleason score ≥7
Amsellem-Ouazana 2005[74]	T2-MRI/MRS	42	15	35.7	6.6 (5–9)	NR
Bhatia 2007[76]	T2-MRI/MRS	21	2	9.5	(6, 6)	0.0
Cheikh 2009[78]	T2-MRI/DCE	93	23	24.7	6 (5–9)	30.4
Cirillo 2008[79]	T2-MRI/MRS	54	17	31.5	6 (4–8)	29.4
De la Rosette 2009[80]	TRUS	139	20	14.4	6 (4–8)	NR
Djavan 2001[81]	TRUS	820	123	15.0	See notes	NR
Engelhard 2006[82]	T2-MRI	37	14	37.8	4.5 (3–7)	21.4
Eskicorapci 2007[83]	TRUS	211	54	25.6	See notes	NR
Franiel 2011[84]	T2-MRI/MRS/DCE/DW	54	21	38.9	6 (6–10)	47.6
Hambrock 2010[86]	T2-MRI/DCE/DW	68	40	58.8	6 (5–9)	20.3
Hoeks 2012[87]	T2-MRI/DCE/DW	264	117	44.3	NR	NR See notes
Lattouf 2007[90]	T2-MRI/DCE	26	14	53.8	6.5 (5–9)	50.0
Lin 2008[91]	TRUS	366	47	12.8	6.7 (SD 1.0) 7.6 (SD 1.3)	NR
Panebianco 2011[95]	MRS/DCE	41	28	68.3	NR	46.4
Park 2008[96]	DW-MRI	43	17	39.5	7 (6–9)	NR
Pepe 2010[97]	TRUS	423	82	19.4	See notes	NR
Philip 2006[98]	TRUS	241	42	17.4	6.5 (6–8)	NR
Quinlan 2009[102]	TRUS	111	27	24.3	See notes	NR
Roehl 2002[103]	TRUS	634	188	29.7	See notes	23.0
Roethke 2011[104]	T2-MRI/MRS/DCE/DW	100	52	52.0	7 (5–9)	59.7
Sciarra 2010[105]	MRS/DCE	90	44	48.9	NR	61.6
Testa 2010[106]	T2-MRI/MRS	54	22	40.7	6 (1–9)	27.3
Wetter 2005[108]	T2-MRI/MRS	6	2	33.3	(6, 7)	50.0
Yakar 2011[109]	T2-MRI/DCE/DW	9	5	55.6	7 (6–8)	66.7
Yanke 2006[110]	TRUS	416	144	34.6	See notes	51.0
Yao 2009[136]	T2-MRI	41	15	36.6	NR	NR See notes

Study ID	Test(s)	No. analysed	No. with PC	Prevalence (%)	Median (range) Gleason score	Percentage with Gleason score ≥7
Yuen 2004[111]	TRUS	57	15	26.3	5.4 (2.5–6.0) 6.8 (4.0–8.0)	NR
Yuen 2004[112]	T2-MRI/MRS	24	7	29.2	6 (6–7)	42.9
Zackrisson 2004[113]	TRUS	706	169	23.9	See notes	NR

MRGB, MR-guided biopsy; NR, not reported; TCCL, total cancer core length.

Notes

Amsellem-Ouazana 2005:[74] mean Gleason score reported.

Djavan 2001:[81] mean (SD) Gleason biopsy scores: biopsy 2, 5.7 (0.5); biopsy 3, 4.6 (0.4); biopsy 4, 4.4 (0.7). Mean (SD) Gleason radical prostatectomy scores: biopsy 2, 4.9 (0.8), biopsy 3, 4.2 (0.3); biopsy 4, 4.0 (0.4).

Eskicorapci 2007:[83] 35 men underwent radical prostatectomy. 32/35 had clinically important cancer (T2a, $n = 7$; T2b, $n = 20$; T3a, $n = 6$; T3b, $n = 2$).

Hoeks 2012:[87] when prostatectomy was not performed, clinical significance of MRGB-detected prostate cancer was defined by (1) a PSA level > 10ng/ml and a PSA density > 0.15 ng/ml per ml; (2) clinical stage ≥T2b; (3) a Gleason grade 4 or 5 within the biopsy specimen; or (4) a TCCL ≥ 10 mm, where TCCL is the total cancer length in all MRGB cores from one cancer-suspicious region (definition based on Epstein and D'Amico criteria). In case of performed prostatectomy, PC was considered clinically significant when PC volume was ≥ 0.5 ml or a stage ≥ pT3 or a Gleason grade 4 or 5 was present. Hoeks *et al.*[87] reported that the majority of detected cancers were clinically significant: a total of 87% (94 of 108) met the clinical criteria and 93% (26 of 28) met radical prostatectomy specimen criteria.

Lin 2008:[91] reported Gleason scores as mean plus SD [6.7 (SD 1.0) for the second session and 7.6 (SD 1.3) for the third session].

Pepe 2010:[97] mean (range) Gleason scores: PZ cancer ($n = 76$) 6.5 (6–8); PZ + TZ cancer ($n = 4$) 6.8 (6–8); TZ cancer ($n = 2$) 6.

Philip 2006:[98] mean (range) Gleason score reported. All but three had a Gleason score ≥ 6.

Quinlan 2009:[102] mean (range) Gleason scores reported by biopsy number: biopsy 1, 6.1 (6–8); biopsy 2, 6.5 (6–7); biopsy 3, 6.25 (6–7); biopsy 4, 6.3 (6–7).

Roehl 2002:[103] Gleason 2–4: $n = 48$ (8%); Gleason 5–6: $n = 397$ (69%); Gleason 7: $n = 107$ (19%); Gleason 8–10: $n = 25$ (4%).

Yakar 2011:[109] Gleason scores reported are for six cancer-suspicious regions of five patients.

Yanke 2006:[110] Gleason 4 to 6: $n = 30$ (49%); Gleason 7: $n = 26$ (43%); Gleason 8–10: $n = 5$ (8%).

Yao 2009:[136] reported that cancers detected by MRI were generally clinically significant with a Gleason score > 6 in 10 of 12 tumours (83%).

Yuen 2004:[111] mean (range) Gleason score reported. Yuen *et al.* reported that the mean (range) Gleason score was 5.4 (2.5 to 6.0) for biopsy 2 and 6.8 (4.0 to 8.0) for biopsy 3.

Zackrisson 2004:[113] number (%) of Gleason score ≤ 3 reported by biopsy: biopsy 1, $n = 322$ (84%); biopsy 2, $n = 104$ (87%); biopsy 3, $n = 32$ (97%); biopsy 4, $n = 5$ (83%).

Appendix 16 Adverse events related to transrectal ultrasonography-guided biopsy

Study ID	No. analysed	No. (%) experiencing event	Type of event
Beyersdorff 2002[57]	38	2 (5%)	Haemorrhage in the prostate
Bhatia 2007[76]	21	Most patients	Transient haematuria (self-resolving) after TRUS biopsy
		None	Sepsis
		None	Severe bleeding
Djavan 2001[81]	820	57%	Mild haematuria
		16.6%	Recurrent mild haematuria
		11.3%	UTI
		10.2%	Delayed haematospermia
		6.8%	Persistent dysuria
		2.4%	Rectal bleeding
		2.3%	Delayed fever
		1.4%	Moderate to severe vasovagal episodes
		0.5%	Severe haematuria
		0.1%	Major rectal bleeding
Engelhard 2006[82]	37	None	Collateral effects or complications
Hambrock 2010[86]	68	1 (1.5%)	Transurethral haemorrhage (self-limiting)
		1 (1.5%)	UTI (uncomplicated)
Hoeks 2012[87]	264	1 (0.4%)	Sepsis with hospitalisation
		4 (1.5%)	Vasovagal reaction
[a]Labanaris 2010[89]	260	190 (73%)	Macroscopic haematuria lasting an average of 4 days (range 1–18 days)
		146 (56%)	Haematospermia lasting an average 11 days (range 1–30 days)
		96 (37%)	Minor rectal bleeding lasting an average of 1.3 days (range 0–15 days)
	173	2 (1.2%)	Prostatic infection (fever and required hospitalisation)
Yakar 2011[109]	9	None	Complications relating to the biopsy procedure in terms of bleeding, infection, sepsis or other medical conditions
Yuen 2004[111]	57	3 (1.4%)	Macroscopic haematuria (treated conservatively as inpatient)
		5 (2.3%)	Fever (treated conservatively as inpatient)
		5 (2.3%)	Acute retention of urine (treated conservatively as inpatient)
		1 (0.5%)	Bleeding per rectum (admitted to hospital)
		Not stated	Transient haematuria, haematospermia and orchitis (treated in the outpatient setting)
Yuen 2004[112]	24	Most patients	Transient haematuria and haematospermia (self-resolving)
		None	Sepsis requiring inpatient treatment
		None	Severe bleeding requiring inpatient treatment

a Nos of those experiencing adverse events calculated from the percentages reported.

Appendix 17 Supplementary results from cost-effectiveness analysis

TABLE 39 Costs of diagnosis and pre-diagnosis monitoring, biopsy complications and cancer treatment by diagnostic strategy: 60-year-old cohort

	Costs (£)			
Strategy	Diagnosis and prediagnosis monitoring	Biopsy complications	Cancer treatment	Total
TRUS	773	11	3111	3895
MRI	780	7	3115	3902
MRS	822	5	3125	3952
DCE	873	7	3104	3984
MRI or MRS	892	9	3130	4031
MRI or DCE	928	10	3118	4056

TABLE 40 Costs of diagnosis and pre-diagnosis monitoring, biopsy complications and cancer treatment by diagnostic strategy: 70-year-old cohort

	Costs (£)			
Strategy	Diagnosis and pre-diagnosis monitoring	Biopsy complications	Cancer treatment	Total
TRUS	595	11	2593	3199
MRI	603	7	2596	3206
MRS	644	5	2607	3256
DCE	694	7	2586	3287
MRI or MRS	714	9	2613	3336
MRI or DCE	750	10	2600	3360

TABLE 41 Expected numbers of unnecessary and appropriate biopsies: 60-year-old cohort

Strategy	Expected no. of unnecessary biopsies[a]	Expected no. of appropriate biopsies[b]	Total expected no. of biopsies
TRUS	0.758	0.378	1.137
MRI	0.341	0.338	0.679
MRS	0.182	0.338	0.520
DCE	0.364	0.338	0.702
MRI or MRS	0.523	0.338	0.861
MRI or DCE	0.652	0.338	0.990

a Biopsies taken in men with no detectable prostate cancer.
b Biopsies taken in men with detectable prostate cancer.

TABLE 42 Expected numbers of unnecessary and appropriate biopsies: 70-year-old cohort

Strategy	Expected no. of unnecessary biopsies[a]	Expected no. of appropriate biopsies[b]	Total expected no. of biopsies
TRUS	0.756	0.360	1.116
MRI	0.340	0.320	0.660
MRS	0.181	0.320	0.502
DCE	0.363	0.320	0.683
MRI or MRS	0.522	0.320	0.842
MRI or DCE	0.650	0.320	0.970

a Biopsies taken in men with no detectable prostate cancer.
b Biopsies taken in men with detectable prostate cancer.

TABLE 43 Deterministic sensitivity analysis scenarios using LYs as unit of outcome (men aged 60 years; cancer prevalence 24%)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs	Incremental LYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 1. Biopsy costs inflated to account for additional pathology time associated with > 10 cores; MRS/MRI costs also adjusted to the NHS reference costs						
Syst. TRUS	4018	[b]	14.16796	[b]	[b]	[b]
T2-MRI	4024	7	14.16890	0.000936	7198	7198
MRS	4060	35	14.17081	0.001911	18,565	14,826
DCE	4108	49	14.16669	–0.004120	Dominated	Dominated
MRI or MRS	4169	109	14.17203	0.001221	89,122	37,123
MRI or DCE	4205	37	14.16949	–0.002540	Dominated	122,622
Scenario 2. Sensitivity of MRS adjusted to miss only low-grade cancer						
Syst. TRUS	3895	[b]	14.16796	[b]	[b]	[b]
T2-MRI	3902	7	14.16890	0.000936	7447	7447
MRS	3956	54	14.17243	0.003535	15,214	13,588
DCE	3984	28	14.16669	–0.005750	Dominated	Dominated
MRI or MRS	4031	75	14.17203	–0.00040	Dominated	33,425
MRI or DCE	4056	100	14.16949	–0.00294	Dominated	105,351
Scenario 3. Sensitivity of comparator reduced to 60%						
Syst. TRUS	3882	[b]	14.15943	[b]	[b]	[b]
T2-MRI	3899	16	14.16768	0.008258	1975	1975
MRS	3948	49	14.16959	0.001911	25,861	6463
DCE	3981	32	14.16547	–0.004120	Dominated	16,216
MRI or MRS	4028	80	14.17082	0.001221	65,219	12,761
MRI or DCE	4053	25	14.16828	–0.002540	Dominated	19,269
Scenario 4. Application of sensitivity/specificity estimates obtained from the indirect comparison (T2-MRI sensitivity 0.84/specificity 0.58; MRS sensitivity 0.92/specificity 0.65)						
Syst. TRUS	3895	[b]	14.16796	[b]	[b]	[b]
MRI	3895	0	14.16827	0.000309	174	174
MRS	3970	75	14.17080	0.002529	29,604	26,403
DCE	3986	16	14.16669	–0.004110	Dominated	Dominated
MRI or MRS	4029	59	14.17234	0.001548	37,870	30,451
MRI or DCE	4052	23	14.17139	–0.000960	Dominated	45,713

continued

TABLE 43 Deterministic sensitivity analysis scenarios using LYs as unit of outcome (men aged 60 years; cancer prevalence 24%) (*continued*)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs	Incremental LYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 5. Biopsy costs uplifted for systematic TRUS (assumes 14-core TRUS biopsy is £86 more costly than MRS/MRI-directed biopsy, and £112 more costly than MRS)						
MRI	3907	[b]	14.16890	[b]	[b]	[b]
MRS	3955	48	14.17081	0.001911	25,032	25,032
DCE	3991	36	14.16669	–0.004120	Dominated	Dominated
Syst. TRUS	3991	36	14.16796	–0.002850	Dominated	Dominated
MRI or MRS	4034	79	14.17203	0.001221	64,355	40,363
MRI or DCE	4061	27	14.16949	–0.002540	Dominated	258,868
Scenario 6. MRI reduces the risk of biopsy complications by 50%						
Syst. TRUS	3895	[b]	14.16796	[b]	[b]	[b]
MRI	3899	4	14.16893	0.000968	4284	4284
MRS	3949	50	14.17083	0.001902	26,362	18,917
DCE	3981	32	14.16672	–0.004110	Dominated	Dominated
MRI or MRS	4027	78	14.17207	0.001242	62,656	32,125
MRI or DCE	4052	25	14.16954	–0.002530	Dominated	99,198
Scenario 7. Subsequent repeat biopsy offers have 80% uptake (repeat offer every 12 months for those remaining with undiagnosed cancer)						
Syst. TRUS	3888	[b]	14.16628	[b]	[b]	[b]
MRI	3895	8	14.16737	0.001091	6891	6891
MRS	3946	51	14.16962	0.003334	22,544	17,420
DCE	3976	30	14.16478	–0.001510	Dominated	Dominated
MRI or MRS	4026	80	14.17106	0.004777	55,739	28,990
MRI or DCE	4050	24	14.16808	0.001796	Dominated	90,288
Scenario 8. LYs discounted at 1.5% per annum						
Syst. TRUS	3895	[b]	17.18299	[b]	[b]	[b]
MRI	3902	7	17.18416	0.001172	5953	5953
MRS	3952	49	17.18656	0.002393	20,637	15,811
DCE	3984	32	17.18140	–0.005160	Dominated	Dominated
MRI or MRS	4031	80	17.18809	0.001531	52,000	26,684
MRI or DCE	4056	25	17.18491	–0.003180	Dominated	84,112

TABLE 43 Deterministic sensitivity analysis scenarios using LYs as unit of outcome (men aged 60 years; cancer prevalence 24%) (*continued*)

Strategy	Average cost (£)	Incremental cost (£)[a]	Average LYs	Incremental LYs[a]	ICER[a] (£)	ICER vs common baseline (£)
Scenario 9. Disease progression calibrated to prostate cancer mortality rates observed in the PIVOT trial[149]						
Syst. TRUS	3751	[b]	14.27118	[b]	[b]	[b]
MRI	3758	7	14.27176	0.000580	12,035	12,035
MRS	3808	49	14.27291	0.001145	43,122	32,678
DCE	3840	32	14.27044	–0.002460	Dominated	Dominated
MRI or MRS	3887	80	14.27362	0.000711	112,027	55,830
MRI or DCE	3913	25	14.27210	–0.001520	Dominated	175,577
Scenario 10. Use extended-cores biopsy for all patients negative on MRS/MRI						
Syst. TRUS	3895	[b]	14.16796	[b]	[b]	[b]
MRI	4007	112	14.17252	0.004559	24,525	24,525
MRS	4087	80	14.17284	0.000318	250,318[c]	39,251
DCE	4087	80	14.17305	0.000530	150,695	37,668
MRI or MRS	4090	3	14.17215	–0.000900	Dominated	46,462
MRI or DCE	4090	3	14.17262	–0.000420	Dominated	41,839

Syst. TRUS, systematic TRUS-guided extended-cores (15) biopsy.

a Incremental costs and LYs are estimated in comparison with the next less costly non-dominated strategy.

b Common baseline.

c Strategy dominated by combinations of other strategies.

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