NIHR Reference No. DAR135477

Final amended version, 12th of May 2022

ASSESSMENT GROUP'S PROTOCOL

MRI FUSION BIOPSY IN PEOPLE WITH SUSPECTED PROSTATE CANCER: A SYSTEMATIC REVIEW AND ECONOMIC ANALYSIS

External Assessment Group	CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD
Project Leads	Sofia Dias, Professor of Health Technology Assessment, CRD, University of York, Heslington, York YO10 5DD. Telephone number: [redacted] E-mail address: [redacted] Ana Duarte, Research Fellow, CHE, University of York, Heslington, York YO10 5DD. Telephone number: [redacted] E-mail address: [redacted]

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

PROSPERO registration number: CRD42022329259

PLAIN ENGLISH SUMMARY

Prostate cancer is the most commonly diagnosed cancer in men in the UK. Around one in eight men get prostate cancer at some point in their life. Many procedures and tests can be used to investigate cases of suspected prostate cancer, including blood testing to measure levels of prostate specific antigen (PSA) (increased levels can indicate presence of cancer) and a digital rectal examination (a procedure in which a doctor inserts their finger into the person's rectum so they can feel the prostate gland), to see whether the prostate gland is an abnormal shape or size. Other risk factors may be considered such as whether there is any family history of prostate cancer.

Information from the above tests and procedures can help inform a decision to have a Magnetic resonance imaging (MRI) (a technique that allows you to 'see' soft tissue (flesh) within the body) taken of the prostate to identify areas of concern that may be cancerous. These areas can be seen as a lesion on the MRI image. If a lesion is visible on the MRI, then a targeted prostate biopsy (using a biopsy needle to take of a small number of samples of the prostate tissue in the area where the lesion is visible) will be used to diagnose prostate cancer. Additional samples may also be taken from different regions of the prostate (systematic biopsy). If a lesion is not visible, but prostate cancer is still suspected, a systematic prostate biopsy can be recommended instead.

During the prostate biopsy procedure an ultrasound probe is placed in the rectum (back passage). The ultrasound probe uses sound waves to make an image of the prostate which is shown on a small screen. The ultrasound image helps the doctor move the biopsy needle to the correct location. Currently during a targeted prostate biopsy, the doctor will view the MRI image beforehand to help to guide the biopsy needle to areas of interest within the prostate during the procedure (cognitive fusion biopsy). An alternative approach is available that uses a computer software to combine the MRI and ultrasound image during the procedure, so the area of concern can be visualised in real time (MRI fusion biopsy).

The aim of our research is to investigate whether the use of MRI fusion biopsy gives a more accurate diagnosis of prostate cancer compared to cognitive fusion biopsy, and whether the costs of MRI fusion biopsy, and any cancer treatments then given, produce benefits to patients that are considered an acceptable use of NHS resources (i.e., whether they are effective, safe and provide value for money). We will review all the relevant available research studies, using detailed systematic methods. We will examine how accurate MRI fusion biopsies are at detecting prostate cancer and if there are any harmful effects from the biopsy. We will also look at how much MRI fusion biopsy costs, per patient. To do this we will create a computer-software based economic model to estimate the costs and benefits to patients and the NHS of MRI fusion biopsy.

1 DECISION PROBLEM

Prostate cancer is the most commonly diagnosed cancer in men the UK. The estimated lifetime risk of a prostate cancer diagnosis is one in eight for males born in the UK;[1, 2] over 57,000 new cases were diagnosed in 2018, with an estimated ten-year survival rate of 77.6%. Early stage diagnosis is associated with improved survival outcomes compared with patients diagnosed at the latest stage of the disease.[2] Prostate cancer primarily affects people aged 50 years or more, and the risk of developing prostate cancers increases with age.[2] People of African family background and individuals with a family history of prostate cancer are at higher risk of prostate cancer.[3, 4]

For people presenting to primary care with certain clinical signs and symptoms that may indicate prostate cancer, NICE's guideline for suspected cancer recognition and referral advises[5] to consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with: any lower urinary tract symptoms (such as nocturia, urinary frequency, hesitancy, urgency or retention) or erectile dysfunction or visible haematuria. The guideline recommends men should be referred using a suspected cancer pathway (for an appointment within 2 weeks) for prostate cancer if their prostate-specific antigen levels are above the age-specific reference range or if their prostate feels malignant on digital rectal examination.

NICE's guideline for diagnosis and management of prostate cancer advises that, in patients with suspected clinically localised prostate cancer, multiparametric MRI (mpMRI) should be offered as the first-line investigation except in those patients who would not be able to have radical treatment.[6] Clinical experts highlight that biparametric MRI (bpMRI) is sometimes used in current practice where mpMRI is not available. The results of the MRI are reported using a 5-point Likert scale, that estimates the risk that an area seen on the MRI scan may be a cancer or not. The Prostate Imaging Reporting and Data System (PI-RADS) is an alternative to the Likert scale assessment of MRI results.[7-9] Here, each lesion is assigned a score from 1 to 5, with higher scores, usually PI-RADS 4 and 5, indicating a higher likelihood of clinically significant cancer. The definition of clinically significant cancer is heterogeneous, but it generally means prostate cancer that may cause excess morbidity or death.[10] Although the exact definition of clinically significant prostate cancer varies across studies and clinical guidelines, it usually refers to organ-confined cancer above a specific Gleason score (or grade) and maximum cancer core length.

MRI-influenced prostate biopsy should be offered to people whose Likert score or PI-RADS score is 3 or more. For people whose Likert score is 1 or 2, omitting a prostate biopsy should be considered but only after discussing the risks and benefits with the person and reaching a shared decision. If a person opts to have a biopsy, systematic prostate biopsy is offered. NHS England guidance[11] states that people with a Likert or PI-RADS score of 1 or 2 and people with a Likert or PI-RADS score of 3

who also have a PSA density less than 0.15ng (or 0.12ng in some centres) of PSA per mL of serum per mL of prostate volume may be discharged, taking account of risk factors and patient preferences.

People diagnosed with prostate cancer are assigned a Cambridge Prognostic Group (CPG) risk category (1-5), based on the PSA result, Gleason score determined by histological analysis of the biopsy and clinical stage based on the MRI scan.[12] These risk categories, along with the outcome of discussion with patients regarding the benefits and harms of the treatment options, determine which treatment option is chosen. This ranges from active surveillance, where patients are followed up at regular intervals with PSA testing, for patients with CPG 1 or 2 to radical prostatectomy or radical radiotherapy for people with localised cancer and CPG ≥2. Patients with locally advanced prostate cancer and CPG 4 or 5 may also be offered docetaxel chemotherapy.

1.1 Biopsy

Prostate biopsies may be performed via the transrectal route or the transperineal route. Both routes use a transrectal ultrasound probe inserted into the anus to generate a live image of the prostate. With transrectal ultrasound (TRUS) prostate biopsy, a biopsy needle is inserted through the rectal wall via the anus. TRUS biopsies are usually performed under local anaesthesia, although it can also be carried out under general anaesthesia (for example if the patient is unlikely to tolerate the procedure otherwise). In a transperineal biopsy, the biopsy needle is inserted through the perineum. Historically, transperineal biopsies were always conducted under general anaesthesia. However, recent developments in transperineal biopsy techniques have made the procedure more tolerable, and it is now routinely performed under local anaesthesia.[13]NICE draft guidance has recently recommended that local anaesthetic transperineal (LATP) prostate biopsy, using the freehand needle positioning devices PrecisionPoint, EZU-PA3U device, Trinity Perine Grid, and UA1232 puncture attachment, as options for diagnosing prostate cancer. [14, 15]

Different methods exist for sampling the prostate tissue, and the choice of biopsy approach may depend on the information from the MRI, specific risk factors (such as PSA density, family history and ethnicity) and individual clinician preference. The site (or sites) for biopsy can be *targeted* based on MRI findings. This approach takes only a number of tissue samples or cores, for people who have a suspicious lesion identified by an MRI scan. The biopsies can also be *systematic*, whereby multiple samples are taken in a systematic fashion from different regions of the prostate according to a predefined scheme. A systematic only biopsy approach may be taken for instance where clinical suspicion is high but not reflected in the MRI, although there is regional variation in this practice.

The European Association of Urology (EUA) guidelines on prostate cancer recommends combining targeted and systematic biopsy in people with a PI-RADS score of 3 or more who have not had a prior biopsy.[10] In UK clinical practice, after targeting sites of interest for biopsy in eligible people,

additional biopsy cores may be taken from the area around the target lesion and a systematic biopsy is performed in addition to the targeted biopsy. Although not strictly recommended by NICE, their guideline on the diagnostic and management of prostate cancer (NG131)[12] notes that most often, MRI influenced biopsies will be performed in combination with systematic biopsies. However, there is variation in practice dependent on local protocols in terms of whether off-target cores are sampled or not, the number of samples taken and the sampling pattern for the systemic component of combined biopsies.

Currently, MRI-influenced prostate biopsy may use one of three different approaches:

- Visual estimation (or cognitive fusion), in which the operator interprets the MRI imaging before the biopsy and manually targets the area of interest using TRUS as a guide; additional samples are also taken in a systematic way according to a pre-defined protocol. This is the current standard of care.
- MRI fusion software, which automatically overlays the MRI image onto the real-time TRUS therefore allowing for real-time visualisation of the area of interest; additional samples are also taken in a systematic way according to a pre-defined protocol.
- In-bore biopsy, carried out within the MRI scanner, where the diagnostic MRI is fused with real-time MRI to ensure accurate targeting of the needle.

The assessment will consider whether MRI fusion biopsies are clinically useful and cost-effective as an alternative to targeted cognitive fusion biopsy. In-bore biopsies are outside the scope of this assessment, as they are not used in standard clinical practice.

1.2 MRI fusion prostate biopsy

Use of MRI fusion prostate biopsy systems may potentially improve detection rate of clinically significant prostate cancer compared with cognitive fusion, whilst reducing the number of samples taken, potentially reducing pain and risk of sepsis associated with the procedure. It could improve the accuracy of assignment of prognostic scores such as Gleason, which influences subsequent treatment and associated patient outcomes. The technology could reduce the number of repeat biopsies for those patients with a negative index biopsy, avoiding unnecessary travel and anxiety for the person. Some MRI fusion technologies also allow operators to keep records of previous biopsy sites to allow the urologist to return to those areas with greater precision for follow-up or additional testing.

The mechanism by which MRI fusion techniques may lead to improved accuracy relates notably to a better targeting of suspicious prostate lesions, including in locations that are more challenging to diagnose, such as anterior and posterior lesions.[16, 17] However, systematic review evidence on the accuracy of MRI fusion biopsy systems compared with cognitive fusion methods is mixed. Watts et

al. 2020[18] found a non-statistically significant trend toward improved rates of prostate cancer detection compared to cognitive fusion, whilst Bass et al. 2021[19] found no evidence that MRI fusion was superior to cognitive fusion at detecting clinically significant prostate cancers, and Sathianathen et al. 2019[20] found no difference between the two methods for detecting prostate cancer. An older review (Valerio et al 2015)[21] concluded that MRI fusion biopsies detect more clinically significant cancers, using fewer biopsy cores. Between-study heterogeneity ranged from moderate[18] to high,[19] although review methods and selection criteria varied.

The purpose of this assessment is to investigate different MRI fusion biopsy systems for targeted biopsy in people with suspected prostate cancer, compared to the current standard of care, and to explore the heterogeneity in existing evidence to ensure conclusions are relevant to the UK NHS setting.

1.3 Interventions

This assessment will evaluate MRI fusion technologies matching the following criteria:

- intended for use in people with suspected prostate cancer;
- available in the UK;
- holds a CE-mark;
- compatible with MRI scanners of 1.5 Tesla field strength or above;

This includes; Artemis (InnoMedicus Artemis), Biojet (Healthcare Supply Solutions Ltd), BiopSee (Medcom), bkFusion (BK Medical UK Ltd and MIM Software Inc), Fusion Bx 2.0 (Focal Healthcare), FusionVu (ExactImaging), iSR'obot™ Mona Lisa (Biobot iSR'obot), KOELIS Trinity (KOELIS and Kebomed) UroNav Fusion Biopsy System (Phillips). Table 1 presents a brief summary of the characteristics of these nine technologies. A description of the principal features of the technologies is given below.

1.3.1 Artemis (InnoMedicus Artemis)

The Artemis fusion biopsy system comprises a semi-robotic mechanical arm and a mobile workstation. The system includes the ProFuse radiology software for preparation of MRI data for fusion and reporting findings on the ARTEMIS biopsy system. The system allows both elastic and rigid estimation to account for prostate deformation, and supports both transrectal and transperineal biopsies. The mechanical arm is used to track the prostate in real-time and guide the biopsy needle.

At the time of writing this protocol, the company had not yet provided any information on this technology's compatibility with a picture archiving and communication system (PACS), image measurement capabilities and ability to produce archivable cartograms.

1.3.2 Biojet (Healthcare Supply Solutions Ltd)

The BioJet MR Fusion system comprises MRI fusion software, a mobile workstation, and is compatible with third party ultrasounds. The system uses elastic estimations and is compatible with both transrectal and transperineal biopsies and supports both stabilised and freehand biopsy approaches. For stabilised biopsies patient movement is tracked through the stepper, whereas freehand biopsies done without the stepper require more manual input from the operator.

The software enables image measurements and generates reports displaying the location of sampled areas. BioJet can be connected to a local PACS.

1.3.3 BiopSee (Medcom)

The BiopSee consists of the BiopSee software and the MedSta cart (workstation), and is compatible with third party ultrasounds. The system supports both elastic and rigid estimation to account for prostate deformation, and allows both transrectal and transperineal biopsies. The system can be used for stabilised and freehand biopsy approaches. A stabilising arm is available for transperineal stabilised biopsies. Patient movement is tracked through the stepper during stabilised biopsies, or through a magnetic tracker, which is attached to the probe during freehand biopsies. The system can automatically adjust for patient movement, or the user can manually adjust the contours when a patient moves.

The BiopSee records all positions of the needle and shows the coverage of the prostate. Image measurements such as prostate and lesion volumes are also possible. The data is stored locally and can be connected to a PACS for import and export of images.

1.3.4 bkFusion (BK Medical UK Ltd and MIM Software Inc)

BK Medical UK Ltd offers three versions of bkFusion software: one for transrectal, one for freehand transperineal and one for stabilised transperineal biopsies. The software can be integrated into either the bk3000 or bk5000 ultrasounds. The bkFusion system uses rigid estimation to account for prostate deformation. Predictive Fusion software re-orientates the MRI image before the biopsy. The transrectal and freehand transperineal fusion systems comprises a magnetic field generator and sensor to track the probe position. The stabilised transperineal fusion system uses a stepper to track the probe position.

Image measurements such as prostate volume are possible. A detailed report of the biopsy can be saved locally, or transferred to a PACS.

1.3.5 Fusion Bx 2.0 (Focal Healthcare)

The Fusion Bx 2.0 is a biopsy device that includes a counter-balanced, semi-robotic arm that is mounted to a mobile cart. The Fusion Bx 2.0 comprises Fusion MR software which is compatible with third party ultrasounds. The system uses both elastic and rigid estimation to account for prostate deformation, and supports both transrectal and transperineal biopsies. The semi-robotic arm can be used as a stepper for stabilised biopsies, or can allow complete freedom of movement for use during a freehand biopsy. Patient movements are tracked with sensors inside the semi-robotic arm.

The software allows image measurements such as prostate volume and distances can be calculated. Data on the biopsied samples and the regions of interest are recorded on a 3D image of the prostate. The system can connect to PACS using a wired Ethernet or Wi-Fi connection.

1.3.6 FusionVu (ExactImaging)

The ExactVu micro-ultrasound device includes a FusionVu feature that enables MRI fusion biopsy. A stabiliser arm or stepper is available for stabilised biopsies, and freehand biopsies are also possible. The system uses rigid estimation followed by real-time visualisation of the lesions using micro-ultrasound, and supports both transperineal and transrectal biopsies. The system tracks and adjusts for patient movement using data from a movement sensor together with the live ultrasound images.

The software provides image measurements such as prostate volume and lesion size. Information on the orientation of all images and video frames are recorded so that the same position can be found if a repeat biopsy is performed. The system is PACS compatible, but a separate software (Weasis DICOM viewer) is available where a PACS is not available.

1.3.7 iSR'obot Mona Lisa (Biobot iSR'obot)

The iSR'obot Mona Lisa is a robotic transperineal prostate biopsy system with MRI-ultrasound fusion capability. The system uses UroFusion software to highlight regions of interest on MR images and fuses the MRI model with the ultrasound model. The robotic needle guide allows automated positioning and depth control of the biopsy needle to the targeted biopsy core. The system uses elastic estimation to account for prostate deformation.

Reports are generated with 3D images and coordinates are recorded of each biopsy sample. At the time of writing this protocol, the company had not provided any information on the tracking of patient movement, whether freehand biopsies can be done, PACS compatibility and image measurement capabilities of this system.

1.3.8 KOELIS Trinity (KOELIS and Kebomed)

The KOELIS Trinity is a mobile ultrasound system with mapping fusion software, which comprises PROMAP 3D-Prostate Suite software and the TRINITY ultrasound system (workstation, RECFIRE ultrasound probes, guides specific to transperineal or transrectal biopsies, and a Steady Pro probe holder). The system uses both elastic and rigid estimation to account for prostate deformation, and supports both transrectal and transperineal biopsies. It enables both stabilised and freehand probe biopsies. The Organ Based Tracking Fusion software identifies and compensates for patient movements and prostate deformations to record each core location.

The PROMAP software produces a 3D map of the prostate recording the position of MRI lesion targets and location of biopsy samples. The KOELIS Trinity provides image measurements such as prostate volume, exact measurements of the regions of interest and other quantitative measurements of the image. Data can be transferred to a PACS.

1.3.9 UroNav Fusion Biopsy System (Phillips)

The UroNav Fusion Biopsy System includes an electromagnetic tracking system, a mobile workstation and DynaCAD Prostate fusion software. The system is compatible with third party ultrasounds. It supports both transperineal and transrectal biopsies, with stabilised or freehand approaches. The system can be used with the UroNav mobile stepper system and the two navigation sensors to track patient movement.

The UroNav Fusion Biopsy system provides the core location data, images and videos. At the time of writing this protocol, the company had not provided any information on image estimation methods for prostate deformation, patient movement tracking feasibility for freehand biopsies, PACS compatibility and image measurement capabilities of this system.

Table 1. Summary of technologies features

MRI Fusion system	Manufacturer	Hardware system	Fixation for biopsies	Elastic or rigid estimation
ARTEMIS	InnoMedicus Artemis	ARTEMIS	Stabilised, Freehand unknown, Semi-robotic arm	Both
BioJet	Healthcare Supply Solutions Ltd	Third party ultrasounds	Stabilised, Freehand (without tracking movement)	Both
BiopSee	Medcom	MedSta or third party ultrasounds	Stabilised, Freehand	Both
bkFusion	BK Medical UK Ltd and MIM Software Inc	BK3000 or BK5000	Stabilised, Freehand	Rigid
Fusion Bx 2.0	Focal Healthcare	Third party ultrasounds	Stabilised, Freehand, Robotic arm	Both
Fusion Vu	ExactImaging	ExactVu	Stabilised, Freehand	Rigid
iSR'obot™ Mona Lisa	Biobot iSR'obot	iSR'obot™ Mona Lisa	Stabilised, Freehand unknown, Robotic arm	Elastic
KOELIS Trinity	KOELIS and Kebomed	TRINITY ultrasound system	Stabilised, Freehand	Both
UroNav Fusion Biopsy System	Phillips	Third party ultrasounds	Stabilised, Freehand	Unknown

1.4 Populations and relevant subgroups

People with suspected prostate cancer who have had an MRI scan that indicates a significant lesion. (Likert or PI-RADS score of 3 or more). The subgroups relevant to this appraisal will include people with specific lesion locations (anterior, posterior), patients who have had a previous negative prostate biopsy and are referred for a repeat biopsy within 12 months.

1.5 Place of the intervention in the diagnostic and care pathway

MRI fusion biopsy for people with suspected prostate cancer, takes place at the same point in the treatment pathway as the current standard of care, targeted cognitive fusion biopsy.

Patients having a first targeted biopsy

MRI fusion biopsy (with or without systematic biopsy) would be offered to people referred to secondary care with suspected prostate cancer (those with PSA levels above the age-specific reference range or those whose prostate is suspicious of malignancy based on rectal examination), who have evidence of lesions after undergoing an MRI. Clinical guidance recommends that targeted MRI influenced biopsy is offered to patients whose MRI results suggest a Likert/PI-RADS score of 3[11, 22] or more. NHS England[11] recommend offering targeted biopsy to patients with a Likert/PI-RADS of 3, only when accompanied of high PSA density (≥0.12 or 0.15ng per mL serum per mL of prostate volume depending on local protocols). Patients whose biopsy result is positive will be offered active surveillance or radical treatment (see sections 1.5.1 and 1.5.2).

People with a Likert/PI-RADS score of <3 (i.e. with no targetable lesions based on MRI) may be offered a systematic biopsy conditional on patients' preference (after discussion of risks and benefits of the procedure) and are therefore outside of the scope of this assessment.[11, 22]

Patients having repeat targeted biopsy

For those patients whose MRI influenced biopsy is negative, results will be reviewed by the urological cancer multi-disciplinary team (MDT) and the possibility of significant disease discussed with the patient. The MDT decides on whether to offer a repeat biopsy with MRI fusion based on individual risk factors (including whether the biopsy showed high-grade prostatic intra-epithelial neoplasia, atypical small acinar proliferation or whether the digital rectal examination result was abnormal).[10, 11, 22] Patients whose repeat biopsy result is positive will be offered active surveillance or radical treatment (see sections 1.5.1 and 1.5.2). If a repeat biopsy is not offered, patients could instead undergo active surveillance with PSA testing or may be discharged depending on MRI and histology findings.[11]

1.5.1 Management following positive/negative diagnosis

People with newly diagnosed localised or locally advanced prostate cancer are assigned a Cambridge Prognostic Group (CPG) risk category, either (low (CPG 1), favourable intermediate (CPG 2), unfavourable intermediate (CPG 3), high risk (CPG 4) or very high risk (CPG 5). The CPG score is assigned based on the person's PSA levels, the Gleason score of the lesion(s) (based on histological analysis of the biopsy) and the clinical stage of the disease.[12] These risk categories, along with the outcome of discussion with patients regarding the benefits and harms of the treatment options, determine which treatment option is chosen.

1.5.2 Active surveillance, watchful waiting and radical treatment options

Active surveillance is a potentially 'curative' monitoring strategy for people with localised prostate cancer for whom radical treatments (such as radical prostatectomy or radical radiotherapy) are suitable; it allows avoiding or deferring these treatments when disease progression is likely to be slow. Current NICE guidance suggests a schedule of active surveillance involving regular monitoring of PSA levels and kinetics, and annual digital rectal examinations. Reassessment with mpMRI and/or re-biopsy can be triggered if concerns about clinical or PSA changes emerge at any time during active surveillance; a positive result on re-biopsy would then result in offering radical treatment.

For people with CPG 1, active surveillance is offered (radical treatments can be considered if active surveillance is not suitable or acceptable to the person). For people with CPG 2, a choice between active surveillance, radical prostatectomy or radical radiotherapy is offered. For people with CPG 3,

localised prostate cancer, radical prostatectomy or radical radiotherapy is offered, and active surveillance can be considered for people who choose not to have immediate radical treatment.

People with localised prostate cancer who do not wish to undergo potentially curative treatment with radical prostatectomy or radical radiotherapy (or for whom this is not suitable), can be managed with watchful waiting. This is a monitoring strategy without curative intent. It is less intensive than active surveillance, involving fewer tests (e.g., annual PSA level measurements and not leading to MRI or biopsy). [12]

Radical prostatectomy or radical radiotherapy is offered to people with CPG 4 and 5 localised and locally advanced prostate cancer, when it is likely the person's cancer can be controlled in the long term. Docetaxel chemotherapy may also be considered for these patients.

NICE recommends that people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer should be offered a combination of radical radiotherapy and androgen deprivation (an anti-hormone therapy). Brachytherapy in combination with external beam radiotherapy should also be considered for people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer.[12]

1.6 Relevant comparator

The comparator for this assessment is targeted transperineal or transrectal prostate biopsy using cognitive fusion with or without systematic biopsy, under local or general anaesthesia, in which the operator interprets the MRI imaging before the biopsy and manually targets the area of interest using TRUS as a guide (as described in Section 1.3). Clinical experts highlighted that the expertise of the person performing the biopsy may affect the accuracy and procedure time of cognitive fusion.

1.7 Key factors to be addressed

Throughout this assessment key considerations will include the lack of evidence comparing the technologies of interest to a sufficiently accurate reference standard and the presence of additional factors that may affect the diagnostic accuracy of targeted biopsies, some of which may be difficult to measure and to accurately quantify from the evidence.

1.8 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment

‘In-bore’ biopsy, or ‘in-gantry’ biopsy, is a technique that involves performing the prostate biopsy in the MRI scanner, using the MR images taken immediately after each needle placement to guide the biopsy. MRI fusion software that integrates AI-driven diagnosis of prostate cancer are also used. The use of in bore MRI and AI-driven software, and individuals with relapsing prostate cancer, are beyond the scope of this assessment.

1.9 Objectives

The aim of the project is to assess the clinical and cost-effectiveness of MRI fusion biopsy systems in people with suspected localised and locally advanced prostate cancer.

To achieve this, the following objectives are proposed:

Clinical effectiveness

- To perform a systematic review of the diagnostic accuracy and clinical efficacy of nine MRI fusion systems compared with cognitive fusion targeted biopsy and with each other, in people with suspected prostate cancer who have had an MRI scan that indicates a lesion.
- To compare the diagnostic accuracy of different MRI fusion biopsy systems with each other and with cognitive fusion targeted biopsy in people with suspected prostate cancer who have had an MRI scan that indicates a lesion using meta-analytical methods and, where possible and appropriate, to combine the diagnostic accuracy of different MRI fusion systems. Where possible and applicable, to assess potential sources of heterogeneity in diagnostic accuracy, including operator experience.
- To perform a narrative systematic review of the clinical efficacy, safety and practical implementation of MRI fusion targeted biopsy. This will include assessment of intermediate outcomes, mortality and morbidity, patient-centred outcomes, adverse events, and acceptability to clinicians and patients.

Cost effectiveness

- To conduct a systematic review and critical appraisal of relevant cost-effectiveness evidence of the use of MRI fusion biopsy systems compared to cognitive fusion for targeted biopsy in people with suspected prostate cancer who have had an MRI scan indicating a lesion;
- To develop and validate a decision-analytic model to estimate the cost-effectiveness of MRI fusion targeted biopsy systems in people with suspected prostate cancer who have had an MRI scan indicating a lesion compared to targeted biopsy using cognitive fusion. This will require linking intermediate outcomes, such as the diagnostic accuracy of MRI fusion biopsy systems to subsequent management decisions and to final health outcomes including morbidity and mortality associated with alternative treatment options (e.g., active surveillance and radical treatment). Final health outcomes will be evaluated in terms of quality-adjusted life years (QALYs).
- To populate the model using the most appropriate available evidence. This evidence is likely to be identified from published literature, routine data sources and potentially using data elicited from relevant clinical experts and companies.

- To estimate the incremental cost-effectiveness of the MRI fusion biopsy systems compared to the current standard of care for the population of interest (cognitive fusion biopsy), based on an assessment of long-term National Health Service (NHS) and Personal Social Service (PSS) costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes.
- To characterise the parameter uncertainty in the data used to populate the model and present the resulting uncertainty in the results to decision makers. To this purpose, we will perform comprehensive (probabilistic and deterministic) sensitivity analyses varying parameter inputs, and structural assumptions of the model, as appropriate.
- Where possible and applicable, to assess the impact of potential sources of heterogeneity on cost-effectiveness, including subgroup analyses (e.g., patients with previous negative biopsy results within 12 months) and consideration of other factors that may affect diagnostic accuracy;

2 METHODS FOR SYNTHESISING EVIDENCE OF CLINICAL EFFECTIVENESS

The systematic review will be conducted following the general principles recommended in CRD's guidance and reported in accordance with the PRISMA statement [23,24]

2.1 Search strategy

Comprehensive searches of the literature will be undertaken to identify studies of transperineal or transrectal MRI fusion or cognitive fusion biopsy.

A draft search strategy for Ovid MEDLINE is included in Appendix 1. The search strategy combines terms for prostate cancer with terms relating to prostate biopsy using MRI fusion software or cognitive fusion. Named MRI fusion software and hardware will also be included in the strategy (e.g. Fusion Bx, Biojet, KOELIS Trinity and bkFusion). The MEDLINE strategy will be adapted as appropriate to run on the other databases and resources. Search restrictions will be applied (from 2008 onwards), due to the relatively recent nature of the technologies under assessment, and as informed by scoping searches and previous systematic reviews.[18, 19, 25, 26] No language or study design restrictions will be applied to the searches.

The following databases will be searched: MEDLINE ALL, Embase, CINAHL, Health Management Information Consortium (HMIC), Science Citation Index, LILACS, Cochrane Database of Systematic Reviews (CDSR), CENTRAL, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, International Health Technology Assessment database (INAHTA), NHS Economic Evaluation Database (NHS EED) and EconLit.

Ongoing and unpublished studies will be identified by searches of Conference Proceedings Citation Index: Science, ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform portal, Open Access Theses and Dissertations, Proquest Dissertations & Theses A&I, and PROSPERO.

A search for relevant guidelines will be carried out via the following websites: National Institute for Health and Care Excellence (NICE), ECRI Guidelines Trust, Guidelines International Network (GIN) and the TRIP database.

Additionally, company websites will be searched to identify relevant publications and other materials relating to the technology. Where required and appropriate, the companies will be contacted to provide details of all studies (completed or ongoing) that they have conducted. Reference lists of included studies and relevant systematic reviews will be scanned to identify any further potentially relevant studies.

2.1.1 Additional literature searching

In order to identify and appraise existing evidence on the clinical and cost-effectiveness of MRI fusion systems, and inform the conceptualisation of a decision model, it is anticipated that sources of evidence on the diagnosis, management and treatment of prostate cancer will be required, beyond that reported in the literature on MRI fusion techniques. This is further discussed in section 2.7.

2.2 Study selection

All titles and abstracts will be screened by at least one reviewer. Full text papers of any titles and abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below (section 2.3). Disagreements will be resolved by consensus or, where necessary, by consulting a third reviewer. Conference abstracts will be eligible if they provide sufficient information for inclusion, and attempts will be made to contact authors for further data. The eligibility criteria that will be used to identify relevant studies are listed below.

2.3 Inclusion criteria

Population

People with suspected prostate cancer who have had an MRI scan that indicates a significant lesion (Likert or PI-RADS score of 3 or more). This includes people who have not had a prior biopsy and people who have had a previous negative prostate biopsy and are referred for a repeat biopsy. No time limit since the first negative biopsy will be set for inclusion of studies with repeat biopsies, although

applicability with respect to the scope will be considered as part of the quality assessment (see section 2.5).

Studies primarily focused on the following patient populations will be excluded: people who do not have a lesion visible on their MR image, people on active surveillance care pathway, and people with relapsing prostate cancer. Patients who cannot have an MRI scan will be excluded. Studies including a small subset of individuals with a Likert or PI-RADS score of 2 or less will be included if they provide data primarily for the eligible population; their applicability will be assessed during quality assessment (see section 2.5).

Interventions

Studies evaluating MRI fusion alone or in combination with cognitive fusion or systematic biopsy, under local or general anaesthesia will be eligible. No exclusions will be made by biopsy route. The following MRI fusion technologies will be included.

- Artemis (InnoMedicus Artemis)
- Biojet (Healthcare Supply Solutions Ltd)
- BiopSee (Medcom)
- bkFusion (BK Medical UK Ltd and MIM Software Inc)
- Fusion Bx 2.0 (Focal Healthcare)
- FusionVu (Exact Imaging)
- iSR'obot Mona Lisa™ (Biobot iSR'obot)
- KOELIS Trinity (KOELIS and Kebomed)
- UroNav Fusion Biopsy System (Phillips)

Comparators

Targeted transperineal or transrectal prostate biopsy using cognitive fusion with or without systematic biopsy, under local or general anaesthesia.

Although systematic biopsies and 'in bore' biopsies are outside the scope of this review, studies that evaluate these methods will not be excluded if they provide separate data to compare targeted biopsies using MRI fusion against cognitive fusion.

Reference standard

Total cancer cases in diagnostic accuracy studies are commonly identified using a combination of MRI fusion, cognitive fusion and systematic biopsies as 'reference standard'.[18, 19] In those studies,

diagnostic accuracy estimates of MRI fusion and cognitive fusion are therefore inherently dependent on the accuracy of mpMRI, TRUS and fusion approaches, as well as the accuracy of the biopsy method, which may vary by type and route. Reference standards that use histopathology from biopsy samples rather than whole prostate resection may also miss positive cases, and reference standards that include results from samples identified by MRI fusion and/or cognitive fusion are at risk of incorporation bias. Reference standards that use histopathology from whole prostate resection are usually only reported for those who have been classified as high risk and have had radical prostatectomy. In addition, histopathology, although commonly used as gold standard test for cancer detection and grading, may also misclassify a small proportion (approximately 2%) of negative prostate cancer cases as positive.[27]

Template-guided biopsy, including transperineal template-guided mapping biopsy (TTMB) and template-guided saturation biopsy (TSB), will be a reference standard. TTMB is a transperineal TRUS-guided biopsy of the prostate using a 5-mm brachytherapy grid, with at least one biopsy from each hole. TSB includes 20 or more transperineal or transrectal TRUS-guided biopsies of the prostate performed to comprehensively sample the whole prostate, according to a predefined core distribution pattern. Template-guided biopsies using a uniform grid and taken at 5 mm intervals can technically only miss tumours that are smaller than the distance between the adjacent cores.[26] Although template guided biopsy is imperfect, notably due to the fact that test accuracy depends on the intensity of cores taken and core trajectory,[21, 26] it is an optimal reference standard, as it aims to comprehensively sample all zones of the prostate.

As template-guided biopsies are invasive and may not be used in diagnostic accuracy studies, combinations of reference standards with lower diagnostic accuracy (e.g., cognitive fusion with MRI fusion and systematic biopsies with fewer than 20 cores) will also be eligible for inclusion. The risk of incorporation bias (when results of an index test form part of the reference standard test) in studies that use a combination of methods that include cognitive and/or MRI fusion as a reference standard will be accounted for during quality assessment.

A positive biopsy will be defined as histopathological confirmation of one of the target conditions within the biopsy cores.

Outcomes

The following intermediate outcomes will be eligible:

- Measures of diagnostic accuracy (including sensitivity, specificity, test positive/negative rates)

- Cancer detection rates (number of patients with detected cancer by MRI fusion or cognitive fusion divided by the total number of patients with confirmed cancer)
- Clinically significant cancer detection rates (all definitions)
- Clinically insignificant cancer detection rates (all definitions)
- Cancer detection rates by prognostic score (such as Cambridge Prognostic groups [CPG] 1 to 5 or other similar classification that can be mapped into the CPG classification) and/or Gleason score
- Biopsy positivity rate (ratio of positive biopsies out of total number of biopsy samples)
- Biopsy sample suitability/quality
- Number of biopsy samples taken
- Procedure completion rates
- Software failure rate
- Time to diagnosis
- Length of hospital stay (emergency department and inpatient stay)
- Time taken for MR image preparation
- Time taken for biopsy procedure
- Number of repeat biopsies within 12 months
- Subsequent prostate cancer management (such as no treatment, active surveillance, radical prostatectomy, radical radiotherapy, and hormone therapy)

The following clinical outcomes will be eligible:

- Rates of biopsy related complications and adverse events, including infection, sepsis and haematuria, urinary retention, erectile dysfunction and bowel function
- Hospitalisation events after biopsy
- Survival
- Progression free survival
- Adverse events from treatment

Patient- and carer-reported outcomes will be eligible, including:

- Health-related quality of life
- Other self-reported outcomes including tolerability, embarrassment and loss of dignity

The following implementation endpoints will be eligible:

- Operator preferences
- Barriers and facilitators to implementation

The following cost outcomes will be eligible:

- Costs of MRI fusion software and any proprietary hardware (including the workstation, ultrasound systems, probe holders, replacement parts, consumables such as guides, and maintenance);
- Cost of staff time (including MR image interpretation time and biopsy procedure time) and of any associated training;
- Medical costs arising from the biopsy such as anaesthetic, sedation, hospital admissions and stays;
- Costs related to using intervention (including any time analysing and storing data);
- Costs of histopathology biopsy samples analysis;
- Cost of treatment of cancer (including costs of any adverse events);
- Costs relating to follow-up;
- Costs of subsequent biopsies;
- Costs arising from watchful waiting;
- Costs arising from active surveillance.

Study designs

Prospective studies comparing MRI vs. cognitive fusion biopsy, randomised and non-randomised, that report the results of both MRI fusion and cognitive fusion biopsy separately.

Where no prospective evidence is identified for an eligible MRI fusion technology, retrospective comparative studies will be considered.

No restriction by healthcare setting will be made.

2.4 Data extraction

Information on study details (including study design, sample size), patient characteristics (e.g., age, PSA, PI-RADS/Likert score and version, reason for referral, whether first biopsy, repeat biopsy, lesion location), intervention characteristics (including MRI fusion technology type and version, MRI technology and magnet strength, TRUS/TP, whether the procedure used fixed/free hand; local/general anaesthetic and was based on biparametric or mpMRI, the use and number of targeted and systematic core biopsy samples, operator experience), outcomes data and definitions of outcomes will be extracted by at least one reviewer using a standardised data extraction form and independently checked by a second reviewer.

Discrepancies will be resolved by discussion, with involvement of a third reviewer where necessary. Where required and appropriate, attempts will be made to contact authors and companies for

additional information, including unpublished data, missing data, relevant subgroup data and more granular outcome data (e.g., matrices reporting a breakdown of detection rates by cancer prognostic score). Data from relevant studies with multiple publications will be extracted and reported as a single study. The most recent or most complete publication will be used in situations where the possibility of overlapping populations cannot be excluded. Where not reported, rates of clinically insignificant cancers will be imputed by subtracting the number of clinically significant cancers from the total number of cancers detected (as per Bass et al. 2021[19]).

2.5 Quality assessment

The quality of the diagnostic accuracy studies will be assessed using the QUADAS-2 tool (Quality Assessment tool of Diagnostic Accuracy Studies). QUADAS-2 evaluates both risk of bias and study applicability to the review question. Signalling questions will be modified as necessary to incorporate review-specific issues, such as incorporation bias, and applicability of study populations to the NICE scope. Other types of study (e.g. those reporting intermediate and/or clinical outcomes) will be assessed using standard criteria appropriate to specific study designs such as the Cochrane risk of bias tool (v.2) for RCTs and ROBINS-I for non-randomised studies.[28, 29]

The quality assessments will be performed by one reviewer and independently checked by a second reviewer. Disagreements will be resolved through consensus, and where necessary, by consulting a third reviewer.

2.6 Methods of analysis/synthesis

The characteristics of the included studies will be summarised using a structured narrative synthesis. Numerical and statistical results will be presented in tables and figures as appropriate.

As standard sensitivity and specificity data are not likely to be available for all studies as there is no traditional 'gold standard' that can be measured for all patients, the focus of the synthesis will be on comparative measures with clinical importance and relevant to the economic model, including:

- cancer detection rates (the number of patients with detected cancer by MRI fusion or cognitive fusion divided by the total number of patients with confirmed cancer) for all cancer, for clinically significant and clinically insignificant cancer and for particular stages and grades of cancer, if available.
- Cancer grading using classifications such as CPG, Gleason scores, or equivalent
- Subsequent procedures, including number of repeat biopsies
- Clinical outcomes, including procedure complication rates and adverse events, survival outcomes and HRQoL.

Meta-analysis

If feasible, and where available, data will be meta-analysed using statistical methods as recommended by methodological guidelines in evidence synthesis. The feasibility and appropriateness of meta-analysis will be assessed according to factors including the availability of study data and the level of clinical and statistical heterogeneity across the included studies. Comparisons will be made primarily between MRI fusion and cognitive fusion biopsy methods but a comparison of these fusion methods with systematic biopsy may be considered if it can provide indirect evidence for the comparison of interest, or to strengthen inferences between clinical outcomes of relevance to the economic model. The feasibility of using indirect evidence will be assessed by considering the structure of the available evidence (whether there are studies providing direct or indirect evidence to form a connected network of evidence) and the applicability of each of the studies to the scope.

Analyses will be conducted for the different types of biopsy approaches (targeted only, or combined targeted and systematic) separately, comparing each against each other. Initially, each MRI fusion biopsy system will be considered separately via indirect comparisons or network meta-analysis, if evidence allows. An assessment of the amount of heterogeneity and presence of inconsistency will be carried out, as appropriate.

In addition, an assessment of what evidence may be considered exchangeable between technologies will be carried out by considering additional evidence from the literature (e.g. studies of similar devices in other populations, audits), expert clinical opinion, similarity in device characteristics and potential sources of heterogeneity. Where reasonable, devices will be pooled together to allow estimation of diagnostic accuracy of MRI fusion systems (i.e., with the different systems assumed to have similar effectiveness) compared with cognitive fusion biopsy.

The analyses will be conducted per patient, and where applicable, per sample. Methods of meta-analysis/network meta-analysis, appropriate for the type of outcome, will be used, following guidance from the Cochrane Handbook.[30] Appropriate statistical software will be used to run the analyses. Analyses will be run primarily in R using specialist plug-in packages for diagnostic or network meta-analyses, as appropriate. Sensitivity analyses will be performed to test the robustness of results to changes in assumptions, such as random effects and fixed effect models, assumptions on exchangeable intervention characteristics, and to the risk of bias (including incorporation bias) and applicability of the included studies to the UK NHS setting.

Although we anticipate that much of the available evidence will be from non-randomised within-patient studies, should randomised evidence be available, this will be meta-analysed separately.[30]

2.6.1 Factors that may affect diagnostic accuracy

Clinical experts highlighted that the expertise of the person performing the biopsy may affect the accuracy and duration of the procedure. Where sufficient data are available (or can be obtained from study authors or companies) for intermediate and clinical outcomes, pooled relative effects will be estimated for the subgroups of interest, including the population being biopsied (first biopsy, repeat biopsy) and to assess the impact of operator experience on diagnostic accuracy of MRI fusion and cognitive fusion, using subgroup or regression analyses as appropriate.

Clinical experts noted that route of access for the cognitive and MRI fusion biopsies (transrectal vs. transperineal) may also affect the accuracy of the procedures, as well as the type of probe (fixed vs. freehand vs. double freehand) used during the procedure, and characteristics of the MRI fusion technologies (e.g. elastic vs. rigid). In addition, biopsies may be taken under local or general anaesthetic. According to clinical opinion, there is a preference for undertaking biopsies under local anaesthetic in the NHS, unless contra-indicted. It is unclear whether the accuracy of MRI fusion biopsy depends on the type of anaesthetic used during the procedure. Where possible we will tabulate data and pool relative effects by type of procedure (fixed/free hand; local/general anaesthetic; sampling method), MRI characteristics (biparametric vs. mpMRI; intensity of imaging field) and MRI fusion characteristics (e.g. rigid vs. elastic estimation). Clinical judgment will inform the appropriateness of analyses and interpretation of the results. Synthesis models that consider these characteristics to lead to exchangeable or identical diagnostic accuracy will be explored. Model fit and heterogeneity will be assessed.

2.6.2 Narrative synthesis

Narrative summaries will be used for any outcomes where meta-analyses or other statistical analyses are not feasible. We will extract summary information on the findings of included studies that relate to the clinical and implementation outcomes, and summarise and harmonise these across studies. We will tabulate or plot results reported in studies and narratively describe and compare them. We will also summarise the conclusions of these studies, suggested consequences for MRI fusion biopsy systems, recommendations for practice and suggested needs for further research.

2.7 Additional clinical evidence

Where appropriate, additional pragmatic searches will be conducted to identify evidence for outcomes listed in Section 2.3 including: procedure completion rates, software failure rate, time to diagnosis, length of hospital stay (emergency department and inpatient stay), time taken for biopsy procedure, and repeat biopsy rates. Should we find a large volume and wide variety of non-comparative observational studies, priority will be given to the studies at low risk of bias (as per Cochrane

criteria)[28] and that most closely match the recommendations in the NICE guidance on prostate cancer[5, 22]and the population under the scope of this evaluation.

To support the conceptualisation of the decision model, additional reviews may be required (See section 2.1.1). To inform the economic model, further pragmatic searches will be conducted as required, notably to identify evidence on outcomes from subsequent cancer management strategies following MRI influenced biopsy and on underlying distributions of cancer risk categories/prognostic groups in specific populations (e.g., biopsy naïve vs. repeat biopsy, Likert/PI-RADS scores). As discussed in section 2.1.1, additional searches of key databases may be conducted using appropriate limits (e.g., study design, language, date), references from evidence reviews used to inform recent relevant guidelines will be checked (e.g., NG131[12,22] and EUA guidance[10]) and we will seek clinical advice to identify more recent relevant studies. For comparative evidence, priority will be given to recent, well-conducted systematic reviews and meta-analyses (as per CRD guidance criteria), followed by individual RCTs and observational studies at low risk of bias (as per Cochrane criteria).[28, 29]

3 METHODS FOR SYNTHESISING EVIDENCE OF COST EFFECTIVENESS

Cost-effectiveness evidence relevant to this assessment will be reviewed and synthesised to inform a cost-effectiveness analysis of the MRI fusion biopsy systems.

The cost-effectiveness analysis of MRI fusion biopsy system will be in line with the NICE reference case. The perspective of the analysis will be that of the NHS and PSS. Health benefits will be expressed in terms of QALYs and both costs and QALYs will be discounted at an annual rate of 3.5%.

In the subsequent sections, we describe the individual components of the synthesis of cost-effectiveness, which include:

i. A systematic review and critical appraisal of relevant cost-effectiveness evidence of the use of MRI fusion biopsy systems compared to cognitive fusion for targeted biopsy in people with suspected prostate cancer who have had an MRI scan indicating a lesion;
ii. Further additional pragmatic searches to support model conceptualisation, and/or identify relevant as input sources, with a particular emphasis on UK-based or generalisable models;
iii. The development and analysis of a *de novo* decision-analytic model, including:
    a. A model conceptualisation exercise, where the structures, inputs and assumptions of the models identified in the reviews (i. and ii.) are considered;
    b. Model implementation based on the results of the conceptualisation exercise;

c. The cost-effectiveness analysis of MRI fusion biopsy systems.

3.1 Identifying and systematically reviewing published cost-effectiveness studies

The results of the comprehensive literature searches carried out to identify all studies relating to the use of the MRI fusion biopsy systems in targeted biopsies (Section 2.1) will be used to identify any relevant studies on the cost-effectiveness of the technologies compared to cognitive fusion in people with suspected prostate cancer. A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside clinical trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature. Studies that report only resource use, costs or health-related quality of life will be excluded from the results of the systematic review. However, these studies may be considered separately as potentially relevant sources of evidence to inform parameters in the new decision-analytic model.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison within the text of the report. In particular, information will be extracted on the perspective of analysis, comparators, study population and setting, main analytic approaches (e.g., patient-level analysis/ decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g., deterministic/probabilistic sensitivity analysis).

The appropriateness of existing decision-analytic models to inform the current decision problem will be assessed based on:

i. Consistency with the decision problem being considered in this assessment, including relevance to the UK;
ii. Relevance of outputs for decision making (i.e., to estimate long-term NHS costs and QALYs based on morbidity and mortality associated with prostate cancer tailoring according to patient prognosis and preferences); and
iii. Flexibility within the model structure to reflect different subgroups (e.g., patients with previous negative biopsy results) and potential factors affecting diagnostic accuracy to be considered.

Preliminary scoping searches identified one publication potentially relevant in terms of i) positioning of MRI fusion biopsy systems in the diagnostic pathway and ii) its direct comparison to cognitive fusion biopsy.[31] This study uses a decision tree structure to model the diagnostic pathway, biopsy

complications and cancer treatment allocation. Lifetime costs and QALYs pay-offs, conditional on true disease status and treatment received are attributed to the terminal nodes of the decision tree. The cancer treatment distribution and the pay-offs are sourced from US rather than UK relevant sources, and therefore, this model is anticipated to be of limited appropriateness to inform the decision problem of this assessment.

3.2 Additional pragmatic searches and reviews of cost-effectiveness studies

If the existing cost-effectiveness literature for the MRI fusion biopsy systems in scope is of limited appropriateness to inform the decision problem at hand (as suggested by the preliminary scoping searches), an additional review of other relevant cost-effectiveness models will be conducted to assist in the conceptualisation of a *de novo* decision-analytic model for assessing the cost-effectiveness of MRI fusion technologies. We will review cost-effectiveness modelling studies evaluating diagnostic strategies in the same position(s) in the diagnostic pathway as the one(s) proposed for MRI fusion biopsy systems identified in the searches defined above (Section 2.1), which do not fulfil the inclusion criteria defined by the scope. We will select the studies considered potentially informative for the model conceptualisation and for the identification of relevant input sources of evidence with a particular emphasis on those used in UK based or UK generalisable models. One such model is a recent UK decision-analytic model assessing the cost-effectiveness of transperineal biopsy for diagnosing prostate cancer recently developed to inform NICE guidance.[32] It is anticipated that this model will be relevant to the current assessment. Other cost-effectiveness studies identified in the reviews conducted within this previous assessment will also be considered for inclusion in our pragmatic review of relevant cost-effectiveness studies.

These studies will not be subject to a formal assessment. Instead, this review will examine the relevant decision analytic models to:

i. Identify key components of value, i.e., the features of the technologies vs. comparators that allow establishing and quantifying trade-offs, the balance of which determines the net value of the technologies;
ii. Characterise the modelling/evidence-linkage approaches used to model the key components of value, describing the underlying structural assumptions and identifying relevant data sources in the context of UK decision making;
iii. Identify value drivers, i.e., factors expected to have a considerable impact on cost-effectiveness;
iv. Identify main areas of uncertainty and evidence scarcity, and characterise approaches taken to deal with these issues;

v. Identify sources of heterogeneity that may be of relevance at the point of prostate biopsy in the diagnostic pathway, as well as characterise approaches taken to handle heterogeneity; and
vi. Identify relevant data sources.

Emphasis will be placed on characterising mechanisms of value accrual that may be relevant to the current assessment of MRI fusion biopsy systems.

Linked evidence approaches and data sources from these models considered appropriate, contemporary and relevant for the current decision problem, will be integrated in the overall development of a *de novo* decision-analytic model for the evaluation of the MRI fusion biopsy systems. The appropriateness for the current decision problem of the evidence linkage mechanisms and data sources used in these previously developed models will be assessed as specified in Section 3.1.

3.3 Evaluation of costs and cost effectiveness

3.3.1.1 Evaluation of costs

Costs will be considered from an NHS and PSS perspective. Depending on data availability, the resource utilisation and costs associated with the diagnosis and management of patients with suspected prostate cancer undergoing targeted biopsy with a) MRI fusion systems and b) cognitive fusion, are likely to include:

- Direct costs associated with the technologies, namely the MRI fusion software and any proprietary hardware, as well as associated staff time to undergo training, operate the technologies, perform the biopsy procedures and interpret MR images and results;
- Costs related to using intervention (including any time analysing and storing data).
- Medical costs arising from the biopsy procedure and any procedural complications (e.g., anaesthetic, sedation, hospital admissions and stays); costs of histopathology biopsy analysis; cost of cancer treatment (and related adverse events); costs relating to follow-up; costs of subsequent biopsies; costs of watchful waiting and of active surveillance.

3.3.2 Evaluation of cost-effectiveness

The cost-effectiveness of targeted biopsy with or without a systematic component, under local or general anaesthesia, with MRI fusion systems will be compared to cognitive fusion for the diagnosis of people with suspected prostate cancer who have had an MRI scan indicating a lesion, using a newly developed decision-analytic model.

The decision-analytic model development is described in a subsequent section (See Section 3.4). In brief, the model will link diagnostic and other intermediate outcome measures associated with MRI

fusion biopsy systems to subsequent management decisions and/or disease-status to final health outcomes, where feasible based on the available evidence. Final health outcomes will be evaluated in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to their additional cost, in units which permit comparison with other uses of health service resources. The final specification of the model will be determined during the review and model conceptualisation stage.

The cost-effectiveness of the MRI fusion biopsy systems will be compared to cognitive fusion, with or without a systematic component, under local or general anaesthesia, for people undergoing targeted biopsy for suspected prostate cancer. If evidence allows, the cost-effectiveness of each of the nine MRI fusion biopsy systems will be assessed separately (see Section 3.4.1.2). If it is not feasible to estimate the cost-effectiveness for some of the MRI fusion systems, the range of costs and resource consequences and potential clinical benefits associated with these systems will be described based on available evidence. The cost-effectiveness (efficiency) of the different systems will be considered within a full incremental analysis and supplemented with cost-effectiveness estimates for each system independently.

The cost-effectiveness of the MRI fusion systems will be evaluated based on the NHS and PSS costs and QALYs estimated over the time horizon for the different strategies under comparison. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes.

The set of most plausible and relevant inputs and structural assumptions will be applied in the base-case analysis. The cost-effectiveness of the MRI fusion systems will be expressed in terms of incremental cost per quality-adjusted life year and/or net health (or monetary) benefits at the relevant cost-effectiveness thresholds. Conventional cost-effectiveness rules will be applied to assess whether the use of MRI fusion systems can be considered an appropriate use of NHS resources.

3.3.2.1 Handling of uncertainty

Uncertainty in the data used to populate the model will be characterised and translated into decision uncertainty when presenting results to decision makers. To fulfil this purpose the model will be set up probabilistically. Thus, where possible, uncertainty in inputs will be reflected using appropriate probability distributions, rather than as a fixed parameter input. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. We will estimate the probability of the alternative strategies being cost-effective at a given cost-effectiveness threshold (expressed as cost per QALY). If appropriate and informative we will also illustrate decision uncertainty graphically using cost-effectiveness acceptability curves, which show the probability that an intervention is expected to be cost-effective for a given estimate of health opportunity costs (i.e., cost-effectiveness threshold).

The impact of parameter and structural uncertainty in the cost-effectiveness estimates will also be explored via sensitivity, scenario and/or threshold analyses. These will ascertain how sensitive the cost-effectiveness base-case results to changes in the parameter inputs (e.g., impact of varying disease prevalence), structural assumptions of the model and the time horizon.

3.3.2.2 Handling of heterogeneity

Where possible and applicable, we will assess the impact of potential sources of heterogeneity on cost-effectiveness, in light of the findings of the clinical effectiveness review (see Section 2).

Heterogeneity may arise from the underlying characteristics of the patients. For example, patients with previous negative biopsy results within 12 months are likely to have a different cancer prevalence and prognostic risk distribution compared with those who undergo their first biopsy, which may impact differently on the estimates of cost-effectiveness for these two subgroups of the population.

Heterogeneity may also stem from operator experience, features of the technology (e.g., rigid vs. flexible estimation), of the biopsy (e.g., route of access, type of probe, type of anaesthesia, targeted only or combined with systematic, etc.) and the MRI imaging (e.g., bpMRI vs. mpMRI, intensity of imaging field), which may affect diagnostic accuracy (see Section 2.6.1). The quantity and strength of evidence on the potential factors affecting diagnostic accuracy will guide the approach taken to incorporate these in the model. For example, some of these factors may be included in the definition of the diagnostic strategies by considering the possible combinations of MRI fusion and cognitive fusion biopsy with the different types of biopsy approaches (e.g., transperineal vs. transrectal) and anaesthesia (local vs. general). Alternatively, the impact of additional factors potentially affecting cost-effectiveness estimates may be explored via sensitivity and scenario analyses.

3.4 Development of a health economic model

A *de novo* decision analytic model will be developed to evaluate the cost-effectiveness of the nine MRI fusion targeted biopsy compared to targeted biopsy using cognitive fusion in people with suspected prostate cancer who have had an MRI scan indicating a lesion.

The population, interventions and comparator are as set out in Sections 1.4, 1.3 and 1.6, while the outcomes to be considered are those reported in Section 2.3.

The model will be developed in accordance with the NICE reference case. The perspective will be that of the NHS and PSS, health benefits will be expressed in terms of QALYs and both costs and QALYs will be discounted at an annual rate of 3.5%.

3.4.1 General structure of the model

3.4.1.1 Model conceptualisation

The model conceptualisation will draw on the outputs of the economic evidence reviews (Sections 3.1 and 3.2) to assist in the development of a new decision-analytic model. For this purpose, the proposed model structure should:

i. Account for the direct impacts on costs and health outcomes of MRI fusion biopsy systems (e.g., consequences of adverse events and direct costs of the technology);
ii. Link the diagnostic accuracy of MRI fusion biopsy systems to short-term costs and consequences (e.g., via its impact on rates of subsequent biopsies, and changes to the distribution of patients classified according to CPG or other relevant classification [which determines the range of cancer treatment options] and treatment allocation compared to cognitive fusion biopsy);
iii. Link the short-term consequences to potential longer-term costs and consequences (e.g., impact of treatment on prostate cancer progression and associated mortality) using the best available evidence.

We anticipate the general model structure will comprise a decision tree and a Markov model. The decision tree will estimate diagnostic outcomes, and cancer treatment allocation for each strategy, and quantify associated short-term costs and HRQoL outcomes, i.e., direct costs of the technologies, and the diagnostic pathway related costs and consequences. The costs and consequences of the diagnostic pathway include those associated with the index biopsy, repeat biopsies and their related complications, as well as with cancer staging. The Markov model will link the diagnostic outcomes and treatment to longer-term costs and HRQoL outcomes.

The model conceptualisation will explicitly draw on the previously developed models identified in Sections 3.1 and 3.2. We will ascertain if any of the existing models can be adapted based on the following aspects:

i. Appropriateness to inform the decision problem being considered in this assessment (as detailed in Section 3.1; and
ii. Ability to reproduce the model or to collaborate with the model developers.

One potential candidate for adaptation is the abovementioned decision-analytic model developed by the Southampton Health Technology Assessments Centre assessing the cost-effectiveness of transperineal biopsy for diagnosing prostate cancer,[32] henceforth referred to as the Southampton model. The decision problem in this previous assessment has some elements of overlap with the current assessment in terms of:

i. Population of interest – people with suspected prostate cancer (which includes those with a Likert/Pi-RADS score ≥3 and who are of interest to the assessment at hand);
ii. Underlying diagnostic technique – biopsy with access via transrectal or transperineal route;
iii. Alternative biopsy methods (e.g., with fixed vs. free-hand probes; general vs. local anaesthesia);
iv. Short-term and longer-term outcomes considered.

The model is described in brief below to illustrate the type of model adaptations that may be required if this model is found to be appropriate for adaptation.

The Southampton model evaluated the cost-effectiveness of using transperineal compared to TRUS biopsy in people with suspected prostate cancer, so it includes the position of the diagnostic pathway at which MRI fusion biopsy systems are used. Its structure combines a decision tree and Markov model. The decision tree stratifies according to true cancer status and diagnostic outcomes for each diagnostic strategy, and captures morbidity and mortality associated with the diagnostic procedures. Patients diagnosed as having no cancer are discharged to routine follow-up, while those diagnosed with cancer are offered treatment conditional on their diagnosed disease risk according to the 2019 update of the relevant NICE guideline (NG131).[22]

The Markov model component of the Southampton model is an adaptation of the health economic model in the 2019 update of NG131 (henceforth referred to as the NG131 model).[33] The Markov model component comprises 11 health states stratified by a) true and diagnosed cancer status and b) risk category and disease spread: 'true negatives' (no prostate cancer or undiagnosed low-risk disease); 'false negatives' (undiagnosed intermediate, high-risk or metastatic disease); 'true positives' (diagnosed disease from low-risk to metastatic); and death related to prostate cancer or from other causes. The risk categories and cancer treatment considered are based on the clinical guidance at the time (i.e., 2019 version of NG131).[22] In the Southampton model and for each diagnostic strategy, the patient cohort(s) enter the longer-term model according to their diagnostic outcomes at the terminal nodes of the decision tree component. Transitions across health states include subsequent diagnosis, disease progression and death due to metastatic prostate cancer or other causes. Transition probabilities of disease progression and death due to metastatic cancer are based on calibrated data assumed to reflect the outcomes of patients in UK clinical practice.

If it is feasible and appropriate to adapt the Southampton model, or another similarly relevant model, for the purpose of the current assessment, anticipated modifications to the model(s) will include adaptions to more closely reflect the decision problem, such as:

- Restricting the modelled population to patients who are eligible for an MRI influenced/targeted biopsy, and update parameters accordingly (e.g., baseline disease prevalence);
- Updating parameters to reflect the technologies under comparison (e.g., diagnostic accuracy, probability of repeat biopsies, and biopsy complications);
- Inclusion of additional outcomes (e.g., software failure rates).

Evidence permitting, modifications will also include extensions in line with the recently updated NG131,[12] including the update to recommend a five CPG classification system from biopsy instead of the previously used three risk categories.[22] This has implications for diagnostic accuracy and the linkage mechanism to determine subsequent treatment of patients and the longer-term outcomes of correctly classified and misclassified patients.

3.4.1.2 Data sources

The decision-analytic model will be populated using the most appropriate available evidence, as identified in the clinical and cost-effectiveness reviews (Sections 2, 3.1 and 3.2). Other potential sources of evidence include routine data sources and using data elicited from relevant clinical experts and companies.

The findings of the reviews of diagnostic accuracy and other clinical effectiveness and safety evidence on the MRI fusion biopsy systems compared to cognitive fusion (see Sections 2) will be used to inform the related parameters for each of the nine MRI fusion biopsy systems (if evidence allows). We will consider the exchangeability of evidence across technologies as appropriate and in accordance with the differences identified in the evidence reviews, and take an approach to handle data consistent with what is detailed in Section 2.6.

Data provided by the companies on the direct resource use (e.g., training requirements) and costs of the MRI fusion systems (e.g., software licence and hardware costs) will be used to inform these parameters as appropriate.

UK relevant evidence identified in the economic reviews (Sections 3.1 and 3.2) will also be considered for the model parameterisation (and to support necessary structural assumptions).

Clinical opinion will be sought to assess the appropriateness of the data sources and of the structural assumptions and to identify additional data sources (e.g., local trust audits). Clinical judgement may be formally elicited in the absence of empirical evidence on model parameters.

3.4.1.3 Model implementation and validation

It is anticipated that the model will be developed in Microsoft Excel and/or the statistical programming language R; the choice of software will have to await the final conceptualisation of the model.

The validation of the implemented model will comprise:

- The review of individual components of the model by members of the project team with modelling experience and not directly involved in the implementation of these components against the model description on the report;
- Testing the internal validity of the model by varying parameters to extreme value and checking whether the model outputs behave accordingly;
- Cross-validating results against those from cost-effectiveness models from published literature if appropriate.

4 HANDLING INFORMATION FROM THE COMPANIES

All data submitted by the company(s) will be considered if received by the EAG no later than 15th of June 2022. Data arriving after this date may not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any 'commercial in confidence' data provided by a company and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data provided by the manufacturers or study analysts will be highlighted in yellow and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Confidential data will be stored securely, and will only be accessible to members of the project team.

If confidential information is included in the decision-analytic model developed for this assessment then a version using dummy data or publicly available data in place of confidential data will be provided.

5 COMPETING INTERESTS OF AUTHORS

The authors have no competing interests.

6 TIMETABLE/MILESTONES

Milestone	Date to be completed
Submission of final protocol	10/05/2022
Submission of progress report	09/08/2022
Submission of draft Diagnostic Assessment Report	03/10/2022
Submission of final Diagnostic Assessment Report	31/10/2022

7 REFERENCES

1. Public Health England. *Cancer registration statistics, England: final release, 2018*. Public Health England; 2020. Available from: https://www.gov.uk/government/statistics/cancer-registration-statistics-england-2018-final-release/cancer-registration-statistics-england-final-release-2018 [accessed 2nd April 2022].

2. Cancer Research UK. *Prostate cancer statistics - Prostate cancer incidence*. 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero [accessed 23rd March 2022].

3. Jones AL, Chinegwundoh F. Update on prostate cancer in black men within the UK. *Ecancermedicalscience* 2014;**8**:455.

4. Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. *PLoS One* 2011;**6**:e27130.

5. National Institute for Health and Care Excellence. *Suspected cancer: recognition and referral [NG12]*. London: NICE; 2015.

6. National Institute for Health and Care Excellence. *Prostate cancer: diagnosis and management. [D] Evidence review for diagnosing and identifying clinically significant prostate cancer*. London: NICE; 2019.

7. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;**22**:746-57.

8. Turkbey B, Rosenkrantz AB, Haider MA, Padhani AR, Villeirs G, Macura KJ, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. *Eur Urol* 2019;**76**:340-51.

9. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol* 2016;**69**:16-40.

10. European Association of Urology. *EAU guidelines on prostate cancer*. Arnhem, The Netherlands: EAU Guidelines Office 2022.

11. NHS England. *Implementing a timed prostate cancer diagnostic pathway. A handbook for local health and care systems*. London: NHS England; 2018.

12. National Institute for Health and Care Excellence. *Prostate cancer: diagnosis and management [NG131] (Last updated: 15 December 2021)*. NICE; 2021. Available from: https://www.nice.org.uk/guidance/ng131 [accessed 11th April 2022].

13. Lopez JF, Campbell A, Omer A, Stroman L, Bondad J, Austin T, et al. Local anaesthetic transperineal (LATP) prostate biopsy using a probe-mounted transperineal access system: a multicentre prospective outcome analysis. *BJU Int* 2021;**128**:311-8.

14. National Institute for Health and Care Excellence. *NICE recommends new diagnostic devices for men with suspected prostate cancer in draft guidance*. NICE; 2022. Available from: https://www.nice.org.uk/news/article/nice-recommends-new-diagnostic-devices-for-men-with-suspected-prostate-cancer-in-draft-guidance [accessed 9th May 2022].

15. National Institute for Health and Care Excellence. *Transperineal biopsy for diagnosing prostate cancer. In development [GID-DG10043]*. NICE; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-dg10043 [accessed 9th May 2022].

16. Al-Ahmadie HA, Tickoo SK, Olgac S, Gopalan A, Scardino PT, Reuter VE, et al. Anterior-predominant prostatic tumors: zone of origin and pathologic outcomes at radical prostatectomy. *Am J Surg Pathol* 2008;**32**:229-35.

17. Bott SRJ, Young MPA, Kellett MJ, Parkinson MC. Anterior prostate cancer: is it more difficult to diagnose? *BJU Int* 2002;**89**:886-9.

18. Watts KL, Frechette L, Muller B, Ilinksy D, Kovac E, Sankin A, et al. Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer. *Urol Oncol* 2020;**38**:734 e19- e25.

19. Bass EJ, Pantovic A, Connor MJ, Loeb S, Rastinehad AR, Winkler M, et al. Diagnostic accuracy of magnetic resonance imaging targeted biopsy techniques compared to transrectal ultrasound guided biopsy of the prostate: a systematic review and meta-analysis [published online ahead of print September 21 2021]. *Prostate Cancer Prostatic Dis* 2021:10.1038/s41391-021-00449-7.

20. Sathianathen NJ, Butaney M, Bongiorno C, Konety BR, Bolton DM, Lawrentschuk N. Accuracy of the magnetic resonance imaging pathway in the detection of prostate cancer: a systematic review and meta-analysis. *Prostate cancer and prostatic diseases* 2019;**22**:39-48.

21. Valerio M, Donaldson I, Emberton M, Ehdaie B, Hadaschik BA, Marks LS, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. *Eur Urol* 2015;**68**:8-19.

22. National Institute of Health and Care Excellence. *Prostate cancer: diagnosis and management. NICE guideline [NG131]*. London: NICE; 2019.

23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021;**10**:89.

24. Centre for Reviews and Dissemination. *Systematic Reviews: CRD's guidance for undertaking reviews in healthcare*. York: CRD, University of York; 2009.

25. Wegelin O, van Melick HHE, Hooft L, Bosch J, Reitsma HB, Barentsz JO, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: a systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? *Eur Urol* 2017;**71**:517-31.

26. Drost FJH, Osses DF, Nieboer D, Steyerberg EW, Bangma CH, Roobol MJ, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochrane Database of Systematic Reviews* 2019:Issue 4, Art. No.: CD012663. DOI: 10.1002/14651858.CD012663.pub2.

27. Beltran L, Ahmad AS, Sandu H, Kudahetti S, Soosay G, Møller H, et al. Histopathologic false-positive diagnoses of prostate cancer in the age of immunohistochemistry. *Am J Surg Pathol* 2019;**43**:361-8.

28. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

29. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

30. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*: Cochrane; 2022. Available from: www.training.cochrane.org/handbook

31. Pahwa S, Schiltz NK, Ponsky LE, Lu Z, Griswold MA, Gulani V. Cost-effectiveness of MR imaging-guided strategies for detection of prostate cancer in biopsy-naive men. *Radiology* 2017;**285**:157-66.

32. Souto-Ribeiro I, Woods L, Maund E, Scott DA, Lord J, Picot J, et al. *Transperineal biopsy in people with suspected prostate cancer - a systematic review and economic evaluation*. Southampton: Southampton Health Technology Assessments Centre (SHTAC); 2022.

33. Nationl Institute for Health and Care Excellence. *Prostate cancer update health economic model report*. NICE; 2019. Available from: https://www.nice.org.uk/guidance/ng131/evidence/health-economic-model-report-pdf-6784206157 [accessed 11th April 2022].

APPENDICES

Appendix 1: MEDLINE search strategy

Database: Ovid MEDLINE(R) ALL <1946 to May 05, 2022>
Search Strategy:
---
1 exp Prostatic Neoplasms/ (142330)
2 Prostatic Intraepithelial Neoplasia/ (1399)
3 ((prostate$ or prostatic or intraprostatic) adj4 (cancer$ or neoplas$ or tumour$ or tumor$ or malignan$ or metasta$ or carcinoma$ or adenocarcinoma$ or lesion$ or nodul$ or sarcoma$ or lymphoma$)).ti,ab. (165476)
4 (PCa or sPCa or csPCa or PrCa).ti,ab. (52495)
5 (((atypical adj3 proliferation) or ASAP) and prostate$).mp. (287)
6 1 or 2 or 3 or 4 or 5 (224592)
7 Magnetic Resonance Imaging/ (453040)
8 Multiparametric Magnetic Resonance Imaging/ (978)
9 (magnetic resonance or MRI or MR imag$ or MR scan$).ti,ab. (559839)
10 (mpMRI or mp-MRI or mpMR imag$ or mpMR scan$ or mp-MR imag$ or mp-MR scan$ or bpMRI or bp-MRI or bpMR imag$ or bpMR scan$ or bp-MR imag$ or bp-MR scan$).ti,ab. (2070)
11 7 or 8 or 9 or 10 (720921)
12 Image Interpretation, Computer-Assisted/ (47633)
13 (fusion$ or fuse$ or fusing$).ti,ab. (298797)
14 cognitive$.ti,ab. (424219)
15 (visual$ adj3 (estimat$ or direct$ or align$ or guid$ or influenc$)).ti,ab. (28390)
16 registration$.ti,ab. (161025)
17 (elastic or rigid or nonrigid).ti,ab. (137895)
18 Software/ (120282)
19 (software or hardware).ti,ab. (224052)
20 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (1353078)
21 Prostate/ (39199)
22 (prostate$ or prostatic).ti,ab. (234060)
23 21 or 22 (238077)
24 Biopsy/ (185138)
25 Image-Guided Biopsy/ (5034)
26 Endoscopic Ultrasound-Guided Fine Needle Aspiration/ (3247)
27 Biopsy, Fine-Needle/ (14947)
28 Biopsy, Large-Core Needle/ (2302)
29 Biopsy, Needle/ (49648)
30 (biopsy or biopsie$ or rebiopsy or rebiopsie$).ti,ab. (426886)
31 24 or 25 or 26 or 27 or 28 or 29 or 30 (548555)
32 23 and 31 (26191)
33 6 and 11 and 20 and 32 (1630)
34 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (biopsy or biopsie$)).ti,ab. (865)
35 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops$).ti,ab. (157)
36 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (ultrasound$ or ultrasonic$ or ultrasonograph$ or TRUS or transperineal$ or transrectal$)).ti,ab. (772)
37 34 or 35 or 36 (1627)
38 6 and 37 (664)
39 (target$ adj4 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (3808)
40 (focal adj2 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (635)
41 39 or 40 (4412)
42 6 and 41 (1852)

43 (target$ adj4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).ti,ab. (3996)
44 (focal adj2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).ti,ab. (546)
45 43 or 44 (4527)
46 6 and 32 and 45 (1130)
47 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj3 (guid$ or influenc$ or direct$ or align$)).ti,ab. (11926)
48 6 and 32 and 47 (956)
49 ((MRI stratified or magnetic resonance imaging stratified) adj3 pathway$).ti,ab. (3)
50 33 or 38 or 42 or 46 or 48 or 49 (3282)
51 (MRGB or MR-GB or MRIGB or MRI-GB).ti,ab. (75)
52 (MRIFB or MRI-FB).ti,ab. (3)
53 (MRFTB or MRF-TB).ti,ab. (9)
54 (MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx).ti,ab. (98)
55 FBx.ti,ab. (94)
56 (FUSTB or FUS-TB or TB-FUS).ti,ab. (9)
57 Fusion TB.ti,ab. (21)
58 (MRI-TRUS or MRI-TRUSB or MRI-TPB).ti,ab. (192)
59 (COG-TB or TB-COG or CBx).ti,ab. (531)
60 TRUS-TB.ti,ab. (3)
61 ("MRI/TRUS" or "mpMRI/TRUS" or "MR/US" or "MRI/TRUS-TB").ti,ab. (308)
62 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (1110)
63 6 and 62 (440)
64 50 or 63 (3309)
65 (fusion$ adj3 (software or hardware or computer$ or device$ or system$ or technolog$ or machine$ or platform$)).ti,ab. (5677)
66 6 and 65 (294)
67 64 or 66 (3348)
68 KOELIS.ti,ab. (23)
69 Fusion Bx.ti,ab. (1)
70 Biojet.ti,ab. (28)
71 (Trinity or PROMAP).ti,ab. (1327)
72 Fusion MR.ti,ab. (9)
73 (bkFusion or bk Fusion or BK3000 or BK 3000 or BK5000 or BK 5000 or Predictive Fusion).ti,ab. (7)
74 70 or 71 or 72 or 73 (1370)
75 6 and 74 (21)
76 68 or 69 or 75 (39)
77 Biopsee.ti,ab. (6)
78 UroNav.ti,ab. (17)
79 ("iSR'obot" or iSRobot or iSR obot or UroFusion or UroBiopsy).ti,ab. (2)
80 (FusionVu$ or ExactVu$).ti,ab. (11)
81 DynaCAD.ti,ab. (9)
82 (ARTEMIS or ProFuse).ti,ab. (4762)
83 Mona Lisa.ti,ab. (106)
84 81 or 82 or 83 (4876)
85 6 and 84 (55)
86 77 or 78 or 79 or 80 (33)
87 85 or 86 (81)
88 67 or 76 or 87 (3379)
89 exp animals/ not humans.sh. (5004297)
90 88 not 89 (3374)
91 limit 90 to yr="2008 -Current" (3146)