NIHR | National Institute for Health and Care Research

Journals Library

Check for updates

Health Technology Assessment

Volume 28 • Issue 61 • October 2024

ISSN 2046-4924

MRI software and cognitive fusion biopsies in people with suspected prostate cancer: a systematic review, network meta-analysis and cost-effectiveness analysis

Alexis Llewellyn, Thai Han Phung, Marta O Soares, Lucy Shepherd, David Glynn, Melissa Harden, Ruth Walker, Ana Duarte and Sofia Dias

DOI 10.3310/PLFG4210

MRI software and cognitive fusion biopsies in people with suspected prostate cancer: a systematic review, network meta-analysis and cost-effectiveness analysis

Alexis Llewellyn,[1] Thai Han Phung,[2] Marta O Soares,[2] Lucy Shepherd,[1] David Glynn,[2] Melissa Harden,[1] Ruth Walker,[1] Ana Duarte[2] and Sofia Dias[1*]

[1]Centre for Reviews and Dissemination, University of York, York, UK
[2]Centre for Health Economics, University of York, York, UK

[*]Corresponding author

Published October 2024
DOI: 10.3310/PLFG4210

This report should be referenced as follows:

Llewellyn A, Phung TH, Soares MO, Shepherd L, Glynn D, Harden M, *et al.* MRI software and cognitive fusion biopsies in people with suspected prostate cancer: a systematic review, network meta-analysis and cost-effectiveness analysis. *Health Technol Assess* 2024;**28**(61). https://doi.org/10.3310/PLFG4210

Health Technology Assessment

NICE TAR and DAR

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

Launched in 1997, *Health Technology Assessment* (HTA) has an impact factor of 3.6 and is ranked 32nd (out of 105 titles) in the 'Health Care Sciences & Services' category of the Clarivate 2022 Journal Citation Reports (Science Edition). It is also indexed by MEDLINE, CINAHL (EBSCO Information Services, Ipswich, MA, USA), EMBASE (Elsevier, Amsterdam, the Netherlands), NCBI Bookshelf, DOAJ, Europe PMC, the Cochrane Library (John Wiley & Sons, Inc., Hoboken, NJ, USA), INAHTA, the British Nursing Index (ProQuest LLC, Ann Arbor, MI, USA), Ulrichsweb™ (ProQuest LLC, Ann Arbor, MI, USA) and the Science Citation Index Expanded™ (Clarivate™, Philadelphia, PA, USA).

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta.

Criteria for inclusion in the *Health Technology Assessment* journal
Manuscripts are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This article

The research reported in this issue of the journal was commissioned and funded by the Evidence Synthesis Programme on behalf of NICE as award number NIHR135477. The protocol was agreed in May 2022. The draft manuscript began editorial review in December 2022 and was accepted for publication in June 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

This article presents independent research funded by the National Institute for Health and Care Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, the HTA programme or the Department of Health and Social Care.

This article was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Newgen Digitalworks Pvt Ltd, Chennai, India (www.newgen.co).

Abstract

MRI software and cognitive fusion biopsies in people with suspected prostate cancer: a systematic review, network meta-analysis and cost-effectiveness analysis

Alexis Llewellyn,[1] Thai Han Phung,[2] Marta O Soares,[2] Lucy Shepherd,[1] David Glynn,[2] Melissa Harden,[1] Ruth Walker,[1] Ana Duarte[2] and Sofia Dias[1*]

[1]Centre for Reviews and Dissemination, University of York, York, UK
[2]Centre for Health Economics, University of York, York, UK

[*]Corresponding author sofia.dias@york.ac.uk

Background: Magnetic resonance imaging localises cancer in the prostate, allowing for a targeted biopsy with or without transrectal ultrasound-guided systematic biopsy. Targeted biopsy methods include cognitive fusion, where prostate lesions suspicious on magnetic resonance imaging are targeted visually during live ultrasound, and software fusion, where computer software overlays the magnetic resonance imaging image onto the ultrasound in real time. The effectiveness and cost-effectiveness of software fusion technologies compared with cognitive fusion biopsy are uncertain.

Objectives: To assess the clinical and cost-effectiveness of software fusion biopsy technologies in people with suspected localised and locally advanced prostate cancer.

A systematic review was conducted to evaluate the diagnostic accuracy, clinical efficacy and practical implementation of nine software fusion devices compared to cognitive fusion biopsies, and with each other, in people with suspected prostate cancer. Comprehensive searches including MEDLINE, and Embase were conducted up to August 2022 to identify studies which compared software fusion and cognitive fusion biopsies in people with suspected prostate cancer. Risk of bias was assessed with quality assessment of diagnostic accuracy studies-comparative tool.

A network meta-analysis comparing software and cognitive fusion with or without concomitant systematic biopsy, and systematic biopsy alone was conducted. Additional outcomes, including safety and usability, were synthesised narratively.

A de novo decision model was developed to estimate the cost-effectiveness of targeted software fusion biopsy relative to cognitive fusion biopsy with or without concomitant systematic biopsy for prostate cancer identification in biopsy-naive people. Scenario analyses were undertaken to explore the robustness of the results to variation in the model data sources and alternative assumptions.

Results: Twenty-three studies (3773 patients with software fusion, 2154 cognitive fusion) were included, of which 13 informed the main meta-analyses. Evidence was available for seven of the nine fusion devices specified in the protocol and at high risk of bias.

The meta-analyses show that patients undergoing software fusion biopsy may have: (1) a lower probability of being classified as not having cancer, (2) similar probability of being classified as having non-clinically significant cancer (International Society of Urological Pathology grade 1) and (3) higher probability of being classified at higher International Society of Urological Pathology grades, particularly International Society of Urological Pathology 2. Similar results were obtained when comparing between

same biopsy methods where both were combined with systematic biopsy. Evidence was insufficient to conclude whether any individual devices were superior to cognitive fusion, or whether some software fusion technologies were superior to others.

Uncertainty in the relative diagnostic accuracy of software fusion versus cognitive fusion reduce the strength of any statements on its cost-effectiveness. The economic analysis suggests incremental cost-effectiveness ratios for software fusion biopsy versus cognitive fusion are within the bounds of cost-effectiveness (£1826 and £5623 per additional quality-adjusted life-year with or with concomitant systematic biopsy, respectively), but this finding needs cautious interpretation.

Limitations: There was insufficient evidence to explore the impact of effect modifiers.

Conclusions: Software fusion biopsies may be associated with increased cancer detection in relation to cognitive fusion biopsies, but the evidence is at high risk of bias. Sufficiently powered, high-quality studies are required. Cost-effectiveness results should be interpreted with caution given the limitations of the diagnostic accuracy evidence.

Study registration: This trial is registered as PROSPERO CRD42022329259.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: 135477) and is published in full in *Health Technology Assessment*; Vol. 28, No. 61. See the NIHR Funding and Awards website for further information.

Contents

List of tables

List of figures

List of supplementary material

Report Supplementary Material 1 Studies excluded from the systematic review of clinical evidence

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/PLFG4210).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ADT	androgen deprivation therapy
AE	adverse event
bpMRI	bi-parametric magnetic resonance imaging
CF	cognitive fusion
CNS	clinically non-significant
CPG	Cambridge Prognostic Group
CrI	credible interval
CS	clinically significant
CSPCa	clinically significant prostate cancer
DCD	diagnostics consultation document
DRE	digital rectal examination
DTX	docetaxel
EAG	External Assessment Group
EAU	European Association of Urology
FN	false negative
GATP	general anaesthesia transperineal
GG	grade group
GIN	Guidelines International Network
GP	general practitioner
GS	Gleason score
HR	hazard ratio
HRG	healthcare resource group
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
INHB	incremental net health benefit
IQR	interquartile range
ISUP	International Society of Urological Pathology
LATP	local anaesthetic transperineal
LATRUS	local anaesthesia transrectal ultrasound
mpMRI	multiparametric magnetic resonance imaging
MRI	magnetic resonance imaging
NA	not applicable
NC	no cancer
NG131	NICE Guideline 131
NHB	net health benefit
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	network meta-analysis
NPCA	National Prostate Cancer Audit
NPV	negative predictive value
NR	not reported
NRFT	no recurrence following treatment
OS	overall survival
PACS	picture archiving and communication system
PCa	prostate cancer
PFS	progression-free survival
PI-RADS	prostate imaging – reporting and data system
PRFT	possible recurrence following treatment
PSA	prostate-specific antigen
PSS	Personal Social Service
QALE	quality-adjusted life expectancy
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFI	response to information request
RR	Relative risk/risk ratio
SF	software fusion

SOC	standard of care	TSB	template-guided saturation biopsy
TA	technology appraisal	TTMB	template-guided mapping biopsy
TN	true negative	UTI	urinary tract infection
TP	transperineal biopsy		
TRUS	transrectal ultrasound		

Glossary

Active surveillance Monitoring of a person following a diagnosis of prostate cancer, with a view to switching to radical treatment if the cancer progresses. Aims to prevent the risk of overtreatment by avoiding immediate radical intervention. Active surveillance typically includes regular monitoring of prostate-specific antigen (PSA) levels and digital rectal examination.

Cognitive fusion biopsy When the operator views both sets of MRI and ultrasound images and mentally translates the MRI target lesions onto the real-time ultrasound images during the biopsy procedure, to guide the placement of biopsy needles. Also referred to as visual estimation or visual registration.

Double freehand A transperineal biopsy technique whereby the ultrasound probe is held in the hand, rather than being supported by a stepping device. Unlike the freehand technique, the introducer needle is not attached to the ultrasound probe and is held in the other hand.

Elastic registration During software fusion with elastic registration, the MRI image is altered to match the ultrasound image, to adjust for potential deformation to the prostate during the biopsy. Also referred to as non-rigid registration.

Freehand A biopsy in which the ultrasound probe is held in the hand, rather than being supported by a stepping device. This allows the probe to be moved in all directions. A needle attached to the ultrasound probe is then used to puncture the perineum before the biopsy needle is passed through. The biopsy needle can be pivoted to take the samples, reducing the number of puncture sites on the perineum.

Gleason system A system used to grade prostate cancer cells to estimate how quickly they are likely to grow (Gleason grade). Grade Group 1 is the least aggressive, indicating that the cancer is likely to grow very slowly, if at all. Grade Group 5 is the most aggressive, indicating the cells look very abnormal and the cancer is likely to grow quickly. Since prostate tumours are often made up of cancerous cells that have different grades, two grades are assigned for each patient. A primary grade is given to describe the cells that make up the largest area of the tumour and a secondary grade is given to describe the cells of the next largest area. For example, a Gleason score written as 3 + 4 = 7 indicates that most of the tumour is grade 3 and the next largest section of the tumour is grade 4. To help with outcome prediction and patient communication, Gleason scores ≤ 6, 3 + 4, 4 + 3, 8 and 9–10, respectively, can be reported as five risk groups defined by the International Society of Urological Pathology (ISUP), that is, ISUP grades 1–5.

Grid and stepping device A stepping device used in prostate biopsy to cradle the ultrasound probe. On this device, a grid can be attached. A grid (or template) is used in transperineal biopsies. The grid, which is placed in front of the perineum, includes a number of holes in which the biopsy needle can be inserted. Each hole is correlated to numbers and letters which allow for precise sampling of prostate. Also referred to as a template (the grid) and a stepper (stepping device).

In-bore biopsy Technique that involves performing the prostate biopsy in the MRI scanner, where the needle is inserted within the MRI machine, and placement is guided by the MRI images in real time. Also referred to as in-gantry biopsy.

ISUP Gleason grades Grouping of Gleason scores into risk groups defined by the International Society of Urological Pathology (ISUP) to help with outcome prediction and patient communication.

Likert score A Likert score is reported using a 5-point Likert scale. The Likert scale, when used in the diagnosis of prostate cancer, accounts for clinical factors and lesion size on the MRI. A score of 1 indicates prostate cancer is very unlikely and a score of 5 indicates prostate cancer is very likely. Likert scores are used to help decide whether or not to have a prostate biopsy at the current time. The Likert score differs from the PI-RADS score in that it accounts for clinical factors and does not require the MRI to be conducted in a particular sequence.

PI-RADS score prostate imaging – reporting and data system (PI-RADS) score is a system whereby each lesion, identified by MRI, is assigned a score from 1 to 5 to indicate the likelihood of clinically significant cancer (where 1 is very unlikely and 5 is very likely). PI-RADS v2 is the current validated version. It differs from the Likert score in that it does not account for clinical factors and it requires the MRI to be conducted in a particular order.

Rigid registration During software fusion with rigid registration, the MRI image is fixed, and is not adjusted to match the ultrasound image when potential deformation to the prostate may occur during the biopsy.

Route of access A route employed to reach the prostate with a biopsy needle. Can be either via the rectum (transrectal) or the perineum (transperineal). Also referred to as biopsy route.

Semi-robotic arm Used in prostate biopsies, the semi-robotic arm is attached to the ultrasound probe. It allows the operator to manoeuvre the probe into the position of interest while ensuring a consistent level of pressure on the prostate to reduce prostate deformation.

Software fusion biopsy Software fusion is software-based technology used to fuse pre-biopsy MRI image and real-time ultrasound images to create a detailed 3D image. Software fusion biopsy refers to biopsies where software fusion is used to guide and record the placement of biopsy needles. Also referred to as MRI fusion.

Systematic biopsy Biopsy method where samples are taken in a systematic fashion from different regions of the prostate according to a predefined scheme. The number of cores sampled can range from 6 to 14, and is most commonly 12. Also referred to as random biopsy or 12-core biopsy.

Targeted biopsy Biopsy where the site (or sites) for sampling is (or are) targeted based on the location of one or more potentially cancerous lesions identified by a MRI scan. Includes software fusion biopsy, cognitive fusion biopsy, and in-bore biopsy. Also referred to as MRI-targeted.

Template biopsy Biopsy method where samples are taken in a systematic fashion from different regions of the prostate using a grid template. The minimum number of cores is typically 20. Also referred to as template prostate mapping.

Transrectal ultrasound (TRUS) biopsy Where a biopsy needle is inserted through the rectal wall via the anus, and positioning is informed by ultrasound imaging.

Watchful waiting Monitoring of a person, diagnosed with prostate cancer, where any potential treatment offered aims to control rather than cure the prostate cancer (palliative rather than curative intent).

Plain language summary

Men with an magnetic resonance imaging scan that shows possible prostate cancer (PCa) are offered prostate biopsies, where samples of the prostate tissue are collected with a needle, to confirm the presence and severity of cancer. Different biopsy methods exist. In a cognitive fusion biopsy, clinicians will target abnormal looking parts of the prostate by looking at the magnetic resonance imaging scan alongside 'live' ultrasound images. During a software fusion (SF) biopsy, a computer software is used to overlay the magnetic resonance imaging scan onto the ultrasound image. This study evaluated whether SF is better at detecting cancer compared with cognitive fusion biopsy, and whether it represents value for money for the National Health Service.

We did a comprehensive review of the literature. We combined and re-analysed the evidence, and assessed its quality. We investigated whether SF biopsies are sufficient value for money.

Compared with cognitive fusion, patients receiving a SF biopsy may have: (1) a lower probability of having a 'no cancer' result, (2) similar probability of having a benign, non-clinically significant (CS) cancer result and (3) higher probability of detecting CS cancer. However, it is uncertain to what extent SF is more accurate than cognitive fusion, because of concerns about the quality of the evidence. We found no evidence that any SF devices were superior to others. Using additional, random biopsies alongside software or cognitive fusion would increase the detection of PCa.

We also looked for evidence on the value for money of the SF biopsies to detect PCa and found no relevant studies. We weighed the costs and the benefits of SF biopsy compared to cognitive fusion to determine whether it could be a good use of National Health Service money. The poor quality of information makes the value of the technologies largely unknown.

Scientific summary

Background

Prostate cancer (PCa) is the most commonly diagnosed cancer in men in the UK. In the NHS people with suspected PCa are offered multiparametric magnetic resonance imaging (mpMRI). People with suspected PCa, according to MRI, are offered a biopsy procedure to confirm the presence and severity of cancer. Traditionally patients were offered a systematic transrectal, ultrasound-guided prostate biopsy (or systematic biopsy). Since the introduction of mpMRI, specific areas of abnormal tissue can be targeted, by combining (or fusing) the results of mpMRI and ultrasound imaging. Several methods for fusing MRI and ultrasound images exist, including cognitive fusion (CF), in which a region of interest is identified prior to biopsy and the biopsy operator estimates where it might be on an ultrasound image, and software fusion (SF), where regions of interest on magnetic resonace images are identified and contoured before biopsy and overlayed with the prostate contours on ultrasound images during the biopsy. Systematic biopsy may be used in addition to targeted biopsy. A number of SF technologies are available. However, the effectiveness and cost-effectiveness of SF compared with CF is uncertain.

Objectives

This study aimed to assess the clinical and cost-effectiveness of SF biopsy systems in people with suspected localised and locally advanced PCa.

Methods

Systematic review

A systematic review of the diagnostic accuracy, clinical effectiveness, safety and practical implementation of nine SF systems compared with CF and with each other, in people suspected PCa according to MRI was conducted.

Comprehensive bibliographic searches, including MEDLINE and EMBASE and supplementary sources, were conducted up to 2 August 2022 for published and unpublished literature.

Studies of people with suspected PCa who have had a MRI scan that indicates a significant lesion [Likert or prostate imaging – reporting and data system (PI-RADS) score of 3 or more], including biopsy-naive and repeat biopsy patients with a previous negative prostate biopsy, and comparing SF with CF or with another SF device, were included. The following SF technologies were 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 LisaTM (Biobot iSR'obot), KOELIS Trinity (KOELIS and Kebomed) and UroNav Fusion Biopsy System (Phillips). Previous versions were also eligible. In-bore (or in-gantry) biopsies were excluded. Prospective, randomised and non-randomised comparative studies were included, and retrospective evidence where no prospective evidence could be found for an eligible SF device. To provide sufficient evidence for a network meta-analysis (NMA), within-patient comparisons or randomised controlled trials (RCTs) between SF and systematic biopsy, and between CF and systematic biopsy, were also eligible to inform indirect comparisons of diagnostic accuracy.

Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and of all full-text papers subsequently obtained. Data extraction and quality

assessment were conducted by at least one researcher and checked by a second. Risk of bias of diagnostic accuracy studies was assessed using quality assessment of diagnostic accuracy studies-comparative (QUADAS-C).

For diagnostic accuracy outcomes, studies reporting sufficient data were included in network meta-analyses comparing SF and CF with or without concomitant systematic biopsy, and systematic biopsy alone, where odds of being categorised in each of different cancer grades were allowed to vary by biopsy type. Results were reported as odds ratios with 95% credible intervals (CrIs). Additional diagnostic accuracy results that could not be pooled in a meta-analysis and clinical effectiveness, safety and implementation outcomes were synthesised narratively.

Economic analysis

Cost-effectiveness evidence comparing SF biopsy systems with CF for targeted prostate biopsy in men with suspected PCa was identified by the previously mentioned searches, with evidence narratively summarised and tabulated. Studies were appraised for their quality, generalisability and appropriateness to inform the decision problem as defined by the National Institute for Health and Care Excellence Diagnostics Assessment Report (NICE DAR) scope. A targeted search was conducted to identify evidence to support the development of a de novo decision model. The searches aimed to identify cost-effectiveness evidence of diagnostic strategies at the point of biopsy to support the model conceptualisation. Evidence was reviewed to (1) identify value components of the biopsy approaches, (2) characterise alternative mechanisms of evidence linkage from disease prevalence, diagnostic accuracy, choice of treatment to final outcomes, and (3) identify any UK-relevant sources of evidence. A de novo decision analytic model was developed to estimate the cost-effectiveness of SF compared to CF. The model evaluated two strategies for two alternative comparisons: (1) targeted SF biopsy versus targeted cognitive biopsy and (2) combined (targeted and systematic) SF biopsy versus combined cognitive biopsy. The four strategies could not be incrementally compared due to the mechanism of evidence generation for the diagnostic accuracy, which relied on separate evidence networks.

The de novo model consisted of two components: (1) a decision tree, which captured biopsy adverse events (AEs), repeated biopsies and classified individuals according to their biopsy results and underlying true disease status, and (2) long-term model to link classification to clinical management decisions and this to longer-term costs and consequences (e.g. disease progression and PCa mortality) so that differences in costs, life-year gains and quality-adjusted life-years (QALYs) were quantified over a lifetime horizon.

The model required the development of (1) an extension to the evidence synthesis to allow quantifying the extension of test misclassification in the diagnostic model with SF biopsy and CF biopsy, and (2) an inference model to derive unobservable transition probabilities for the long-term model.

Results

The systematic review of clinical evidence included a total of 3733 patients who received SF and 2154 individuals with CF from 23 studies. Evidence was included for all devices specified in the protocol, except for Fusion Bx 2.0 and FusionVu. Overall, the evidence for all devices was at high risk of bias. Overall, biopsy-naive patients were under-represented. Fourteen studies were included in the meta-analyses.

Diagnostic accuracy

Across all analyses results must be interpreted with caution due to the high risk of bias in the evidence base and wide uncertainty over the results. The meta-analyses show that patients undergoing SF biopsy may have: (1) a lower probability of being classified as not having cancer, (2) similar probability of being classified as having non-clinically significant cancer [International Society of Urological Pathology (ISUP)

grade 1], and (3) higher probability of being classified at higher ISUP grades, particularly ISUP 2. Similar results were obtained where both biopsy methods were combined with systematic biopsy.

Additional meta-analyses of cancer detection rates suggest that, compared with CF biopsy, SF may identify more PCa (any grade) (OR 1.30; 95% CrI 1.06, 1.61). Adding systematic biopsy to cognitive or SF may increase the detection of all PCa and of clinically significant (CS) cancer, and from this evidence there is no suggestion that SF with concomitant systematic biopsy is superior to CF with systematic biopsy.

Meta-analyses of cancer detection rates, by individual device, showed that compared with CF biopsy, BioJet and Urostation are associated with a higher detection of PCa overall. There was no evidence that any of the SF devices increased detection of CS cancer (except for BioJet, although this is based on one low-quality study), and overall, the evidence was insufficient to conclude whether any individual devices were superior to CF, or whether some SF technologies are more accurate than others.

Clinical effectiveness

There is no evidence that biopsy positivity rates and safety outcomes differ significantly between SF and CF, or between SF devices. There was some evidence that systems with rigid registration (BioJet or UroNav) are easier and faster to use than elastic registration (KOELIS Trinity), although this is informed by a single, small study and is not conclusive.

Cost-effectiveness

One full cost-effectiveness study of SF compared targeted SF to targeted CF. However, the findings of the study were not considered generalisable to the decision problem under assessment. Sixteen studies were identified of which nine were selected to inform the conceptualisation and parameterisation of the de novo decision model.

The base-case cost-effectiveness analysis suggests for the targeted biopsy and the combined biopsy comparisons, that SF strategy is on average costlier and yields greater QALYs than the CF strategy, resulting in a probabilistic incremental cost-effectiveness ratio (ICER) of £6197 and £2199 per additional QALY for each comparison, respectively. These ICERs are below the lower bound of the cost-effectiveness threshold range recommended by NICE, suggesting that SF may be cost-effective compared to CFs in both the targeted and the combined comparisons. However, these results should be interpreted cautiously given the uncertainties in the relative diagnostic accuracy evidence which informs the model. The probabilistic analysis suggests a higher probability of cost-effectiveness for SF versus CF at the range of cost-effectiveness thresholds recommended by NICE (0.64 and 0.68 at £20,000 and £30,000 per additional QALY for targeted SF biopsy).

Discussion

This assessment includes a broad, comprehensive literature search for software and CF technologies and has been conducted following recognised guidelines to ensure high quality. The review identified evidence on the diagnostic accuracy of nine SF technologies, and is the first systematic review to formally compare the relative accuracy of SF and CF, with and without systematic biopsy, as well as different SF devices, using both direct and indirect evidence in a NMA. Unlike recent systematic review evidence, our review found that SF increased detection of clinically insignificant cancer compared with CF.

Our review has a number of limitations. The evidence included in the systematic review is at high risk of bias overall. There was variation in patient and study characteristics. Biopsy-naive patients, who form the large majority of patients eligible for targeted biopsy, were under-represented, although there was insufficient evidence to evaluate whether the relative accuracy of software and CF differed between

biopsy-naive and repeat biopsy patients. There was insufficient evidence to explore the impact of a number of other potential effect modifiers, including lesion location, operator experience, biopsy routes and anaesthesia methods. There were few studies per comparison, not all studies reported outcomes by all cancer grades, and most estimates from the meta-analyses were imprecise, particularly at higher cancer grades where data were most sparse. The network meta-analyses relied on the assumption that CF was equivalent across different centres, which is uncertain.

No evidence was found for most of this assessment's prespecified outcomes: biopsy sample suitability/quality, number of repeat biopsies performed, procedure completion rates, software failure rate, time to diagnosis, length of hospital stay, time taken for MR image preparation, subsequent PCa management, re-biopsy rate, hospitalisation, overall survival, progression-free survival (PFS), patient- and carer-reported outcomes [including tolerability and health-related quality of life (HRQoL)], barriers and facilitators to implementations.

The cost-effectiveness results are driven by the modelled differences in diagnostic accuracy between software and CF, particularly the increased correct detection of Cambridge Prognostic Group 1 (CPG 1) (resulting in net losses for SF) and CPG 2 (resulting in net gains for SF). The External Assessment Group (EAG)'s NMA and its extension underpinned the economic model, so its limitations apply to the cost-effectiveness estimates. The magnitude of value realised for SF, compared with CF, depends on the balance between different degrees of misclassification and correct classification with the two technologies and on the prevalence of disease at each cancer grade. The value of SF is thus driven by comparative diagnostic accuracy (compared to 'gold standard') derived where evidence is particularly sparse (cancer grades above 2), and by prevalence, which is also affected by evidence sparsity. Therefore, the estimates of cost-effectiveness are affected by unquantified uncertainty and should be interpreted with caution.

Conclusions

Compared to CF biopsy, patients undergoing SF biopsy may show a lower probability of being classified as not having cancer, similar probability of being classified as having non-CS cancer, and a higher probability of being classified at higher ISUPs, particularly ISUP 2. Both SF and CF biopsy can miss CS cancer lesions, and the addition of standard-systematic biopsy increases the detection of all PCa and CS cancer for both fusion methods. There is insufficient evidence to conclude on the relative accuracy and clinical effectiveness of different software devices.

Cost-effectiveness estimates comparing software to CF were generally favourable to SF, except where the technologies were assumed to have the same diagnostic accuracy. The drivers of economic value of SF, comparative diagnostic accuracy and prevalence, are affected by unquantified uncertainty. Judgements on the economic value of SF require integration of the uncertainties over the clinical evidence with the overall cost-effectiveness.

Recommendations for further research

High-quality, sufficiently powered RCT evidence comparing SF biopsy with CF biopsy is required to address limitations from the existing evidence. Improved reporting of diagnostic accuracy outcomes would enable future syntheses to make use of a larger body of evidence.

Study registration

This trial is registered as PROSPERO CRD42022329259.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Evidence Synthesis programme (NIHR award ref: 135477) and is published in full in *Health Technology Assessment*; Vol. 28, No. 61. See the NIHR Funding and Awards website for further information.

Chapter 1 Background and definition of the decision problem

Description of health problem

Prostate cancer (PCa) is the most commonly diagnosed cancer in men in the UK; it accounts for more than a quarter (27%) of all male cancer diagnoses in 2016–8.[1] It is the second most common cause of cancer death in males in the UK, accounting for 14% of all cancer deaths. The estimated lifetime risk of a PCa diagnosis is one in eight for males born in the UK.[2,3] Over 57,000 new cases were diagnosed in 2018, with an estimated 10-year survival rate of 77.6%. Since the early 1990s, estimates of PCa incidence rates have increased by nearly half (48%) in males in the UK (2016–8) and are projected to rise by 12% between 2014 and 2035, resulting in 233 cases per 100,000 males by 2035.[3]

Early-stage diagnosis is associated with improved survival outcomes compared with patients diagnosed at the latest stage of the disease. PCa primarily affects people aged 50 years or more, and the risk of developing PCa increases with age.[3] In England and Wales, 87% of people diagnosed with PCa are aged 60 years or older,[4] and on average each year around a third of new cases (34%) were in males aged 75 and older.[2] People from an African family background and individuals with a family history of PCa are at higher risk of PCa.[5,6]

Prostate cancer might be suspected if any of the following symptoms cannot be attributed to other health conditions: lower urinary tract symptoms, such as frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder; erectile dysfunction; haematuria; lower back or bone pain; lethargy and weight loss.

The descriptor 'clinically significant' (CS) is widely used to differentiate PCa that may lead to morbidity or death from types of PCa that do not. This distinction is important as insignificant PCa that does not cause harm is common.[7] Autopsy studies, in men who died of causes other than PCa, indicate that there is a significant prevalence of non-CS prostate in the general male population, which increases with age.[7] PCa screening may therefore lead to overdiagnosis, by identifying cancers that are not destined to cause morbidity or mortality. Men with these cancers are at risk of being harmed by early detection and unnecessary treatment,[8,9] such as radical prostatectomy or radiotherapy with no additional mortality benefit compared to an active surveillance approach, which includes regular monitoring of prostate-specific antigen (PSA) levels and digital rectal examination (DRE). On the other hand, individuals with undetected cancer or with lesions incorrectly classed as benign may miss out on relevant treatment. Clinical guidelines have focused efforts to address the risk of overtreatment and undertreatment of PCa, notably with recent updates to diagnosis pathways and refinements to risk stratification of cancer lesions.[10–12]

Care pathways for the diagnosis and management of prostate cancer

Referral to suspected cancer pathway

There is no screening programme in the UK for PCa, although PSA testing is available for asymptomatic individuals above 50 years of age requesting this test.[13] For people presenting to primary care with certain clinical signs and symptoms that may indicate PCa, National Institute for Health and Care Excellence (NICE)'s guideline for suspected cancer recognition and referral advises to consider a PSA test and DRE to assess for PCa in men with: any lower urinary tract symptoms (such as nocturia, urinary frequency, hesitancy, urgency or retention) or erectile dysfunction or visible haematuria.[14] The

guideline recommends men should be referred using a suspected cancer pathway (for an appointment within 2 weeks) for PCa if their PSA levels are above the age-specific reference range or if their prostate feels malignant (hard, or lumpy) on DRE. The NHS Faster Diagnosis Standard requires that patients are diagnosed or have cancer ruled out within 28 days of being referred urgently by their general practitioner (GP) for suspected cancer,[15] and NICE requires that GPs should have direct access to appropriate imaging tests.[16]

Figure 1 summarises the EAG's interpretation of the pathway for the diagnosis and care of individuals with suspected PCa according to NICE guidance (NG) 131 and the NHS timed PCa pathway, which was validated by clinical advisers to the EAG.[12,17]

Magnetic resonance imaging for suspected cancer

National Institute for Health and Care Excellence's guideline for diagnosis and management of PCa advises that, in patients with suspected clinically localised PCa, multiparametric magnetic resonance imaging (mpMRI) should be offered as the first-line investigation, but not to those patients who would not be able to have radical treatment.[12] This guidance superseded prior guidance which recommended transrectal ultrasound (TRUS)-guided systematic biopsy as first-line test. Introduced in the 2019 review of the guidelines, the recommendation to offer first-line mpMRI followed the results of PROMIS and PRECISION studies which found a greater negative predictive value (NPV) with mpMRI as first-line diagnostic test compared with the traditional standard-of-care use of TRUS-guided systematic biopsy.[18,19]

The results of the MRI can be reported using a 5-point Likert scale as recommended in NICE Guideline 131 (NG131), which 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.[20–22] 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 CS cancer.

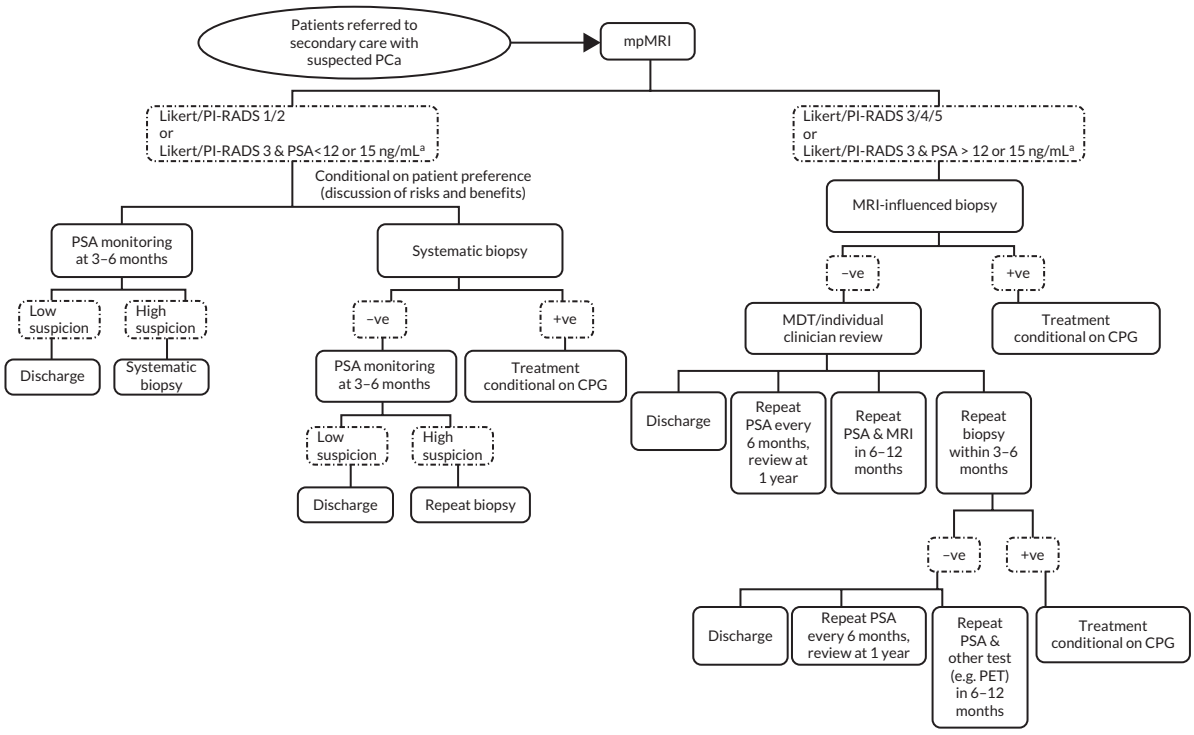


FIGURE 1 Diagnostic and care pathway for individuals with suspected prostate cancer. a, per mL of prostate volume. MDT, multidisciplinary team.

Multiparametric magnetic resonance imaging and compliance with National Institute for Health and Care Excellence guidance

Uptake of MRI, prior to biopsy in England and Wales, has significantly increased in recent years, from 37% in 2017 to 87% in 2019. Data from 10 of 14 trusts in Scotland also indicate that uptake of a pre-biopsy bi-parametric MRI (bpMRI) or mpMRI as first-line diagnostic ranged from 75% to 100% across centres, although most trusts have not yet met the new NHS Scotland target of 95%.[23,24] TRUS biopsy is still offered as first-line investigation for some patients, although the practice is becoming increasingly rare.[4] Clinical advice to the EAG noted that in some hospitals, patient presenting with an overtly malignant feeling prostate gland (T4) and high PSA may proceed directly to TRUS and biopsy before having MRI to speed up diagnosis. Reasons for deviating from the recent NICE guidance include challenges in meeting waiting targets and the limited availability of mpMRI slots. The COVID-19 pandemic has also disrupted the implementation of the guidance.[23,24]

Clinical advisers to the EAG highlighted that bpMRI is sometimes used in current practice where mpMRI is not available. Although the 2019 National Prostate Cancer Audit (NPCA) indicated that 98% of NHS organisations were able to offer mpMRI on site, challenges in meeting the 28-day diagnostic waiting target have been reported.[25] However, there is no evidence that the accuracy of mpMRI and bpMRI differ in treatment-naive patients.[26]

Although uptake of mpMRI as first-line diagnostic test has increased in recent years, it is unclear to what extent this is implemented in the NHS, and whether and to what extent other alternative pathways may be followed.

Biopsy

The decision to collect biopsy samples is informed by the MRI, as well as specific risk factors (such as PSA density, family history and ethnicity) and individual clinician preference. One or more prostate biopsies may be performed to rule out or confirm the presence of PCa. Different methods exist for sampling the prostate tissue. The site(s) for biopsy can be *targeted* for people who have a suspicious lesion identified by the MRI scan. Tissue samples or cores are only collected from the areas identified in the MRI scan as suspicious. The biopsies can also be *systematic*, where multiple samples are taken in a systematic fashion from different regions of the prostate according to a predefined scheme rather than guided by the MRI results. A systematic only biopsy approach may be taken for instance where clinical suspicion is high but not reflected in the MRI (typically with a LikApplicability of Urostation to KOELISTrinity is unknown. ert/PI-RADS score of 2 or less), although there is regional variation in this practice.

Prostate biopsies may be performed via the transrectal route or the transperineal route. Both routes use a TRUS probe inserted into the anus to generate a live image of the prostate. With 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 (e.g. if the patient is unlikely to tolerate the procedure otherwise). In a transperineal biopsy (TP), the biopsy needle is inserted through the perineum. Historically, TPs were always conducted under general anaesthesia. However, recent developments in TP techniques have made the procedure more tolerable, and it is now routinely performed under local anaesthesia.[27] NICE draft guidance has recently recommended 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 PCa.[28,29] Furthermore, patients may receive a spinal block prior to the biopsy being taken, although practice will vary between centres. Spinal anaesthesia may be conducted in an outpatient office[30] or operating theatre.[31]

When a prostate biopsy is performed, tissue cores from the prostate are obtained for histological examination. The number of cores sampled primarily depends on the biopsy technique, but may also vary based on whether the patient has a previous negative biopsy. In a systematic biopsy, the number of cores sampled can range from 6 to 12 or 14. When more samples are obtained, a greater volume

of the prostate gland is sampled, potentially increasing the detection rate. Obtaining any further cores is associated with a limited increase in diagnostic yield,[32] but an increased risk in the incidence of complications, such as bleeding (haematuria, haematospermia, haemoejaculate, haematochezia or rectal bleeding), infections [e.g. urinary tract infection (UTI)], pain, urinary retention and erectile dysfunction.[33] In MRI-guided biopsies, fewer cores can be obtained, as sampling can be targeted at the areas where there is a high suspicion of cancer. The NICE guidelines do not specify the number of cores that should be obtained from each suspicious area; European guidelines state that multiple (three to five) biopsy cores per lesions should be taken to reduce the chance of missing or under sampling lesions,[34] whereas guidance from the American Urological Association and the Society of Abdominal Radiology's Prostate Cancer Disease-Focused Panel[35] notes that at least two target cores per region of interest should be obtained. Clinical advisers to the EAG indicated that a minimum of two cores per targeted lesion were typically taken in NHS practice, and that for most patients, only one lesion (typically the largest) was targeted.

National Institute for Health and Care Excellence NG131 recommend that a targeted, MRI-influenced prostate biopsy should be offered to people whose Likert score is 3 or more.[10] Currently, MRI-influenced prostate biopsy may use one of three different approaches:

- cognitive fusion (CF or visual estimation), 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
- software fusion (SF), which automatically overlays the MRI image onto the real-time TRUS therefore allowing for real-time visualisation of the area of interest where targeted samples are taken additional samples are also taken in a systematic way according to a pre-defined protocol
- in-bore biopsy, or 'in-gantry' biopsy, a technique that involves performing the prostate biopsy in the MRI scanner, where the diagnostic MRI is fused with real-time MRI using the MR images taken immediately after each needle placement to guide the biopsy.

Cognitive fusion is the current standard of care (SOC). Clinical advisers to the EAG noted that different versions of SF are currently used in a number of NHS centres. In-bore biopsies, and MRI-fusion software that integrates AI-driven diagnosis of PCa, are not used in standard clinical practice.

Software fusion and CF prostate biopsy can be performed with or without the addition of systematic biopsy. The European Association of Urology (EAU) guidelines on PCa recommends combining targeted and systematic biopsy in people with a PI-RADS score of 3 or more who have not had a prior biopsy.[34] 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 PCa (NG131) notes that most often, MRI-influenced biopsies will be performed in combination with systematic biopsies.[10] 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. 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 (whereby multiple samples are taken in a systematic fashion from different regions of the prostate according to a predefined scheme) is offered. NHS England guidance[17] 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 < 0.15 ng (or 0.12 ng 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.

For those patients whose MRI-influenced biopsy is negative, results will be reviewed by a urological cancer multi disciplinary team (MDT), typically including a urologist and a radiologist, and the possibility of significant disease discussed with the patient. However, clinical advice to the EAG noted that in

practice, not all hospitals are able to perform a MDT review of all negative MRI-influenced biopsies, in which case results may be sent for individual clinician review. A decision to offer a repeat biopsy is based on individual risk factors, including whether the biopsy showed high-grade prostatic intra-epithelial neoplasia, atypical small acinar proliferation or whether the DRE result was abnormal.[12,17,34] Clinical advice to the EAG noted that factors determining eligibility for, and timing of, repeat biopsy may vary across centres and will depend on individual risk factors, although patients with a negative biopsy and PI-RADS/Likert scores of 4 or 5, larger suspicious lesions on MRI and fitter patients are more likely to undergo repeat biopsy within 12 months. If a repeat biopsy is not offered, patients could instead undergo active surveillance with PSA testing or may be discharged depending on the MRI and histology findings.[17] Patients whose repeat biopsy result is positive may be offered active surveillance or radical treatment, depending on individual patient characteristics and preferences (see *Software fusion prostate biopsy*). Patients with a negative repeat biopsy may be discharged, or have their PSA levels monitored if cancer is still suspected. Antibiotics, combined with PSA monitoring, may be administered to rule out prostatitis, which may show as false positive on MRI. In some rare cases, further tests such as an additional repeat biopsy, template biopsy, or a positron emission tomography (PET) scan may be conducted to definitely rule out cancer.

Following the biopsy, a pathologist will look at the biopsy samples and assign a Gleason score (GS). The GS is a grading system which estimates the aggressiveness of the PCa, based on the pattern of the cancer cells and the extent of cell differentiation. Gleason grade 1 cells look like normal prostate tissue, and Gleason grade 5 cells have mutated to such an extent that they do not resemble typical prostate cells. A primary grade is given to describe the cells that make up the largest area of the tumour and a secondary grade is given to describe the cells of the next largest area. For example, a GS written as 3 + 4 = 7 indicates that most of the tumour is grade 3 and the next largest section of the tumour is grade 4. The two most common patterns of cells (e.g. Gleason grades 3 and 4) are added together to determine a GS. GSs can range from 2 to 10, with a score of 6 being the lowest grade cancer. To help with outcome prediction and patient communication, GSs ≤ 6, 3 + 4, 4 + 3, 8 and 9–10, respectively, can be reported as five risk groups defined by the International Society of Urological Pathology (ISUP), that is, ISUP grades 1–5, respectively.[36]

Although the exact definition of CSPCa varies across studies, it commonly refers to organ-confined cancer above a specific GS (or grade) and maximum cancer core length, indicating PCa that may cause excess morbidity or death.[34] European guidelines state that lesions with a GS between 2 and 6 can be considered clinically insignificant. Recent studies have commonly defined CSPCa as above a GS of 7 (3 + 4), some have used a narrower definition, including above 7 (4 + 3).[19,37–39] Some publications provide more than one definition within a single study, reflecting the lack of consensus and difficulty in defining clinical significance.[40,41]

People diagnosed with PCa are assigned a Cambridge Prognostic Group (CPG) risk category. The CPG score is assigned based on the person's PSA levels, the GS of the lesion(s) (based on histological analysis of the biopsy) and the clinical stage of the disease.[10] The EAU guidance states that further tests, such as abdominopelvic imaging and bone scans, may be required to determine clinical stage of the disease when there is suspicion that the cancer has spread to the lymph nodes or the bone marrow.[34] The CPG risk category and definition is described in *Table 1*.

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, 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 PCa and CPG 4 or 5 may also be offered docetaxel (DTX) chemotherapy. The recommendation to use the CPG five-tier risk prediction model was included in the NICE NG131 2021 update[10] and superseded a three-tier risk classification model including low-, intermediate- and high-risk/locally advanced groups, which did not differentiate between favourable intermediate risk (CPG 2) and unfavourable intermediate risk (CPG 3). Another

TABLE 1 Cambridge Prognostic Group risk categories and the respective definition based on GS, PSA level and clinical stage

CPG	Risk category	Definition
CPG 1	Low risk	GS 6 (GG 1) *AND* PSA < 10 ng/ml *AND* stages T1–T2
CPG 2	Favourable intermediate risk	GS 3 + 4 = 7 (GG 2) **OR** PSA 10–20 ng/ml *AND* stages T1–T2
CPG 3	Unfavourable intermediate risk	GS 3 + 4 = 7 (GG 2) *AND* PSA 10–20 ng/ml *AND* stages T1–T2 **OR** GS 4 + 3 = 7 (GG 3) *AND* stages T1–2
CPG 4	High risk	**One of:** GS 8 (GG 4) **OR** PSA > 20 ng/ml **OR** Stage T3
CPG 5	Very high risk	**Any combination of:** GS 8 (GG 4), PSA > 20ng/ml or Stage T3. **OR** GS 9–10 (GG 5) **OR** Stage T4

GG, grade group.

important difference between the two classifications is that CPG 1 includes more men than the low-risk group in the previously recommended risk classification; some men who previously would have been in the intermediate-risk group are now classified as CPG 1. This change in risk prediction model aims to reduce under- and over-treatment in people who are at either end of the tiers, following evidence from the NICE's surveillance programme that indicated that active surveillance may not be appropriate in patients with unfavourable intermediate PCa, and that patients with favourable intermediate risk and lower risk may be over-treated.[10,12,42,43]

Software fusion prostate biopsy

Using a digital overlay, SF biopsies allow operators to view a real-time ultrasound image alongside the patient's MRI. This requires a period of preparation, to obtain and annotate the MRI images prior to biopsy.[44] MRI images are first downloaded onto a dedicated processing software before they are annotated by contouring the edge of the prostate and the regions of interest. Clinical advice to the EAG suggests that, for an experienced practitioner, this contouring can take around 5–7 minutes. The annotated MRI scans are then uploaded onto a fusion software platform and are fused with the real-time ultrasound image. Updates to the fusion software are possible, and, depending on the fusion device, are covered by a service contract or can be purchased with a one-off payment.

Use of SF prostate biopsy systems may potentially improve detection rate of CSPCa compared with CF, while 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 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.

However, the accuracy of a prostate biopsy may be impacted by a number of factors. Movement during the procedure (which could stem from patient pain),[45] operator experience,[46] difference in bladder size or prostate deformation may impact the accuracy of the biopsy, as the MRI image may not accurately reflect the prostate shape at the point of biopsy. Mechanisms using 'elastic' prostate registration, where the MRI image alters to fit the ultrasound image, have been designed to account for prostate deformation and allow for more accurate targeting of the lesions of interest.[47] Errors during the fusion of images, specifically incorrect image registration or discordance between the MRI and ultrasound image planes, especially around the base of the prostate, can lead to biopsy failure.[48]

The mechanism by which SF 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.[49,50] However, evidence for the accuracy of SF biopsy systems compared with CF methods is limited. Watts et al.[51] and Sathianathen et al.[52] found no statistically significant difference between SF and CF in PCa detection, while Bass et al.[53] found no evidence that SF was superior to CF at detecting CSPCas. An older review found that SF biopsies detect more CS cancers, using fewer biopsy cores.[54] Between-study heterogeneity ranged from moderate[51] to high,[53] although review methods and selection criteria varied.

Prostate cancer management: active surveillance, watchful waiting and radical treatment options

Active surveillance is a monitoring strategy for people with localised PCa 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, while maintaining the possibility to initiate timely curative treatment. Current NICE guidance suggests a schedule of active surveillance involving regular monitoring of PSA levels and kinetics, and annual DREs. 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 (GS 3 + 4 or above) 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 radical radiotherapy with androgen deprivation (anti-hormone therapy), radical prostatectomy or active surveillance is given. For people with CPG 3, localised PCa, radical prostatectomy or radical radiotherapy with androgen deprivation is offered, and active surveillance can be considered for people who choose not to have immediate radical treatment. This recommendation is informed by a randomised trial that found that PCa-specific mortality is low (approximately 1%) at 10 years follow-up and does not differ significantly between active surveillance, prostatectomy or radical radiotherapy in individuals with localised PCa, although surgery and radiotherapy resulted in lower incidences of disease progression and metastatic disease compared with active monitoring. Radical prostatectomy may also be associated with worse urinary and erectile dysfunction outcomes compared with active surveillance and radical radiotherapy at up to 6 years follow-up.[55] People with CPG 4 and 5, localised or locally advanced PCa, should be offered a combination of radical radiotherapy and androgen deprivation. Evidence from an individual patient data (IPD) meta-analysis shows that the addition of androgen deprivation therapy (ADT) to radiotherapy significantly improves metastasis-free survival.[56] Brachytherapy (a form of radiotherapy where radiation is directly targeted on the tumour by inserting radioactive pellets into the prostate) in combination with external beam radiotherapy should also be considered for people with CPG 2, 3, 4 and 5 localised or locally advanced PCa.[57] Randomised controlled trial (RCT) evidence shows a reduction in biochemical failure (such as local recurrence or distant metastases) associated with the

use of low-dose-rate brachytherapy plus external beam radiotherapy at 6.5 years follow-up for people with high-risk (CPG 4 and 5) localised PCa.[58]

Radical prostatectomy or radical radiotherapy is offered to people with CPG 4 and 5 localised and locally advanced PCa, when it is likely that the person's cancer can be controlled in the long term. DTX chemotherapy may also be considered for these patients. This recommendation follows RCT evidence indicating that clinical progression-free survival (PFS) was prolonged in individuals with hormone-sensitive high-risk PCa receiving DTX compared to standard care alone.[59–61]

Finally, some patients with metastatic disease, where the cancer has spread outside the prostate may still undergo targeted biopsy to aid decision-making for localised treatment where the patient may receive some symptomatic benefit.

People with localised PCa, 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 that aims to achieve disease control rather than cure. It is less formal and intensive than active surveillance and involves fewer tests (e.g. typically an annual PSA level measurements not leading to a MRI or biopsy[10]) and is more likely to be offered to older, frailer populations. With watchful waiting, treatment is generally only considered in response to symptoms. Since MRI as first-line test is only recommended for patients fit for radical treatment, only a small subset of patients who received a MRI for suspected prostate lesions, such as those with worsening health since initial investigation and a PCa diagnosis, are expected to undergo watchful waiting in practice. Some patients who are not fit enough or eligible for curative treatment may also be offered a MRI because their lack of eligibility for radical treatment is not identified prior to undergoing imaging.

Description of technologies under assessment

This assessment will evaluate SF technologies matching the following criteria:

- intended for use in people with suspected PCa
- 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 (Exact Imaging), iSR'obot™ Mona Lisa (Biobot iSR'obot), KOELIS Trinity (KOELIS and Kebomed) and UroNav Fusion Biopsy System (Phillips). *Table 23*, *Appendix 1*, presents a brief summary of the characteristics of these nine technologies.

Software fusion devices can have a variety of different features, which means they vary in the way in which they operate.

- **Positioning of the ultrasound probe:** An ultrasound probe can be cradled and held stationary using a device called a stepper which is attached to a workstation (also known as a stabilised approach). It can be supported by a semi-robotic arm, which allows for the ultrasound probe to be manoeuvred, while maintaining a stable pressure on the prostate. 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. Finally, the ultrasound probe can be held by hand (using a freehand technique).
- **Core sampling technique:** Different techniques can be used to take the cores, especially in the case of transperineal biopsies. First, a grid or template can be used, which is attached to a stepper and placed in front of the perineum. The grid is marked with a number of holes, which correspond to

a letter and a number to allow for multiple cores to be taken in a systematic way. Alternatively, a coaxial needle can be used. In this technique, a larger introductory needle is used to puncture the perineum before the biopsy needles is passed through. This biopsy needle can be angled to take multiple biopsies without creating multiple puncture wounds to the perineum. The coaxial needle is used with the freehand technique, where it is attached to the ultrasound probe, or in a double freehand technique, where the needle is held by hand.

- **Image registration:** During SF, the mpMRI images are fused with the ultrasound images during the biopsy procedure. The mpMRI image can be fixed (known as rigid registration) and will not move when the prostate is deformed, either by patient movement or by the insertion of a needle; or elastic, which means the mpMRI image adjusts to match the ultrasound image to account for prostate deformation.

A description of the principal features of the technologies is given in *Appendix 1*.

Other interventions

'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. The use of in bore MRI and artificial intelligence (AI)-driven software are beyond the scope of this assessment.

Place of the intervention in the diagnostic and care pathway

Software fusion targeted biopsy, for people with suspected PCa, takes place at the same two points in the diagnostic pathway as targeted CF biopsy, the current SOC.

Patients having a first targeted biopsy

Software fusion biopsy (with or without systematic biopsy) would be offered as an alternative to targeted CF biopsy to people with a Likert/PI-RADS score of 3 or more following a MRI, after having been referred to secondary care with suspected PCa (with PSA levels above the age-specific reference range or those whose prostate is suspicious of malignancy based on rectal examination). Clinical advisers to the EAG indicated that biopsy-naive patients represented the large majority (more than 90%) of patients with suspected PCa undergoing targeted biopsy.

Patients having a repeat targeted biopsy

Patients offered a repeat biopsy, following a prior negative biopsy, could also be offered a SF biopsy as an alternative to targeted CF. As discussed in *Care pathways for the diagnosis and management of prostate cancer*, NG131 recommends that an MDT decides on whether to offer a repeat biopsy based on individual risk factors, although not all centres may be able to perform a MDT review of all negative MRI-influence biopsies, and eligibility and timing of repeat biopsy may vary in practice. In clinical practice, repeat biopsies are likely to be offered to patients whose mpMRI results were not consistent with the biopsy (i.e. mpMRI of 4–5 and no PCa detected on biopsy). NG131 does not recommend repeat MRI for patients requiring a repeat biopsy; instead a repeat targeted biopsy can be conducted based on the initial MRI report. EAG clinical advisers suggested this subgroup would make up <10% of patients with suspected PCa.

Potential pathway positions out of scope for the current assessment

Although SF may also be used to monitor patients and inform treatment for individuals with a PCa diagnosis in active surveillance, this population is beyond the scope of this assessment.

Relevant comparator

The comparator for this assessment is targeted transperineal or transrectal prostate biopsy using CF 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. Clinical advisers to the EAG highlighted that the expertise of the person performing the biopsy may affect the accuracy and procedure time of CF.

Chapter 2 Aims and objectives

The aim of the study was to assess the clinical and cost-effectiveness of SF biopsy systems in people with suspected localised and locally advanced PCa, by addressing the following protocol-specified objectives:

Clinical effectiveness

- To perform a systematic review of the diagnostic accuracy and clinical efficacy of nine SF systems compared with CF targeted biopsy and with each other, in people with suspected PCa who have had a MRI scan that indicates a lesion.
- To compare the diagnostic accuracy of different SF biopsy systems with each other and with CF targeted biopsy in people with suspected PCa who have had a MRI scan that indicates a lesion using meta-analytical methods and to combine the diagnostic accuracy of different SF systems where appropriate.
- To perform a narrative systematic review of the clinical efficacy, safety and practical implementation of SF targeted biopsy. This includes assessment of intermediate outcomes, mortality and morbidity, patient-centred outcomes, adverse events (AEs), 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 SF biopsy systems compared to CF for targeted biopsy in people with suspected PCa who have had a MRI scan indicating a lesion.
- To develop and validate a decision-analytic model to estimate the cost-effectiveness of SF targeted biopsy systems in people with suspected PCa who have had an MRI scan indicating a lesion compared to targeted biopsy using CF. This will require linking intermediate outcomes, such as the diagnostic accuracy of SF biopsy systems to subsequent management decisions and to final health outcomes including morbidity and mortality associated with alternative treatment options. The analysis will take the perspective of the NHS and Personal Social Services (PSS), consistent with the current manual for health technology evaluations by the NICE. 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 SF biopsy systems compared to the current SOC for the population of interest (CF biopsy), based on an assessment of long-term NHS and 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.

Chapter 3 Assessment of diagnostic accuracy and clinical effectiveness

This section presents the methods and results of the systematic review of diagnostic accuracy and clinical effectiveness. *Systematic review methods (study selection, data extraction, quality assessment)* details the systematic review methods, and *Data synthesis methods* presents the data synthesis methods. *Quantity and quality of evidence* summarises the quantity and quality of evidence included in the systematic review, *Diagnostic accuracy results* presents the diagnostic accuracy results of the systematic review and meta-analysis; results for all other outcomes included in the systematic review are presented in *Clinical effectiveness results*. *Diagnostic accuracy and clinical effectiveness: summary and conclusions* summarises the key findings from the systematic review, and *Additional evidence to inform model structure and parameterisation* presents a summary of additional evidence identified to inform the economic model.

Systematic review methods (study selection, data extraction, quality assessment)

Searches

The aim of the literature search was to systematically identify published and unpublished studies of prostate biopsies utilising either SF or CF.

An information specialist (MH) developed a search strategy in Ovid MEDLINE using textword searches of the title and abstracts of database records along with relevant subject heading searches. The search strategy consisted of: (1) terms for PCa AND, (2) terms for MRI AND, (3) terms relating to fusion techniques AND, (4) terms for prostate biopsy. The terms used to describe fusion techniques were found to vary in the literature with some articles lacking any terms for fusion techniques in the title, abstract or subject headings of the database record. Therefore, related terms such as targeted biopsy, focal biopsy or MRI-guided biopsy were added to the strategy along with some proximity searching to capture phrases in the title and abstracts of records around the use of MRI prior to a prostate biopsy. Named SF software and hardware were also included in the strategy (e.g. Fusion Bx, BioJet, KOELIS Trinity, bkFusion).

A date limit was applied (from 2008 onwards), due to the relatively recent nature of the technologies under assessment, and as informed by results of scoping searches and previous systematic reviews.[51,53,62,63] No language or study design restrictions were applied to the searches. The MEDLINE strategy was agreed with the review team and checked by a second information specialist using aspects of the PRESS checklist.[64] The final MEDLINE strategy was adapted for use in all resources searched.

The following databases were searched in May 2022: MEDLINE ALL (Ovid), Cochrane Controlled Register of Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Cumulative Index to Nursing and Allied Health (Ebsco), Database of Abstracts of Reviews of Effects (CRD databases), EconLit (Ovid), EMBASE (Ovid), Health Technology Assessment (HTA) database (CRD databases), Health Management Information Consortium (Ovid), International Health Technology Assessment (INAHTA) database, Latin American and Caribbean Health Sciences Literature (LILACS) database, NHS Economic Evaluation Database (CRD databases), and Science Citation Index (Web of Science).

Further ongoing and unpublished studies were identified through searches of: ClinicalTrials.gov, Conference Proceedings Citation Index: Science (Web of Science), European Union Clinical Trials Register, Open Access Theses and Dissertations, Proquest Dissertations and Theses A&I, PROSPERO, and World Health Organization (WHO) International Clinical Trials Registry Platform portal.

A search for relevant guidelines was carried out via the following websites: NICE, ECRI Guidelines Trust, Guidelines International Network (GIN) international guideline library and the Trip database. Full search strategies for all resources can be found in *Appendix 2*.

Additionally, company websites were searched to identify relevant publications and other materials relating to the technology, and companies registered with NICE at the time of the protocol submission were contacted for further details about their respective technologies. Reference lists of included studies and relevant systematic reviews were scanned to identify any further potentially relevant studies.

An update search was carried out on 2 August 2022 to capture any recently published studies. The update search was undertaken on the following four databases: MEDLINE ALL (Ovid), Cochrane Controlled Register of Trials (Wiley), Embase (Ovid) and the Science Citation Index (Web of Science). Search results were downloaded from each database and added to the EndNote library of original search results for deduplication.

Selection criteria

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

Population

People with suspected PCa who have had a MRI scan that indicates a significant lesion (Likert or PI-RADS score of 3 or more). This included people who were biopsy naive and those who are referred for a repeat biopsy following a previous negative prostate biopsy. No time limit since the first negative biopsy was set for inclusion of studies including patients with repeat biopsies, although applicability with respect to the scope was considered as part of the quality assessment.

Studies primarily focused on people who do not have a lesion visible on their magnetic resonance image, people on an active surveillance care pathway, and people with relapsing PCa were excluded. Patients who could not have a MRI scan were also excluded. Studies including a small subset of individuals with a Likert or PI-RADS score of 2 or less were included if they provided data primarily for the eligible population; their applicability was assessed during quality assessment.

Interventions

Studies evaluating SF alone or in combination with CF or systematic biopsy, under local or general anaesthesia were eligible. No exclusions were made based on the biopsy route. The included SF technologies are described in *Appendix 1*. Where applicable, earlier versions of these technologies were also included, and their applicability was accounted for during quality assessment.

Comparators

Eligible comparators were targeted transperineal or transrectal prostate biopsy using CF 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 were included if they provide separate data to compare targeted biopsies using SF against CF. Studies evaluating several SF technologies against one another were also eligible for inclusion.

Reference standard

Total cancer cases in diagnostic accuracy studies are commonly identified using a combination of SF, CF and systematic biopsies as 'reference standard'.[51,53]

In those studies, diagnostic accuracy estimates of SF and CF 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 radical prostatectomy, may also miss positive cases. Reference standards that include results from samples identified by SF and/or CF are at risk of incorporation bias (when results of an index test are used to establish the final diagnosis). Reference standards that use histopathology from radical prostatectomy 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 the gold standard test for cancer detection and grading, may also misclassify a small proportion (approximately 2%) of negative PCa cases as positive.[65]

Template-guided biopsy, including transperineal template-guided mapping biopsy (TTMB), also called template-guided saturation biopsy (TSB), is seen as a more optimal reference standard, compared with standard 12-core systematic biopsy. 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.[66] Although template-guided biopsy is imperfect, notably due to the fact that test accuracy depends on the intensity of cores taken and core trajectory,[66] it is superior to standard systematic biopsy as a reference standard as it aims to comprehensively sample all zones of the prostate. However, template-guided biopsies are invasive and may not be used in diagnostic accuracy studies, therefore combinations of reference standards with lower diagnostic accuracy (e.g. CF with SF and systematic biopsies with fewer than 20 cores) were also eligible for inclusion.

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

Outcomes

The following intermediate outcomes were eligible:

- measures of diagnostic accuracy (including sensitivity, specificity, test positive/negative rates)
- cancer detection rates (number of patients with detected cancer by SF or CF divided by the total number of patients with confirmed cancer)
- CS cancer detection rates (all definitions)
- clinically insignificant cancer detection rates (all definitions)
- cancer detection rates by prognostic score (such as CPG 1 to 5 or other similar classification that can be mapped into the CPG classification) and/or GS
- 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 PCa management (such as no treatment, active surveillance, radical prostatectomy, radical radiotherapy and hormone therapy).

The following clinical outcomes were eligible:

- rates of biopsy-related complications and AEs, including infection, sepsis and haematuria, urinary retention, erectile dysfunction, and bowel function
- hospitalisation events after biopsy
- survival
- PFS
- AEs from treatment.

Patient- and carer-reported outcomes were eligible, including:

- health-related quality of life (HRQoL)
- other self-reported outcomes including tolerability, embarrassment and loss of dignity.

The following implementation end points were eligible:

- operator preferences
- barriers and facilitators to implementation.

The following cost outcomes were 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 AEs)
- costs relating to follow-up
- costs of subsequent biopsies
- costs arising from watchful waiting
- costs arising from active surveillance.

Study designs

Prospective studies comparing SF against CF biopsy that report the results of both SF and CF biopsy separately were considered. Studies including within-patient comparisons (where SF and CF biopsy are compared within the same patient) and between-patient comparisons (where participants receive either SF or CF biopsy) were included.

Where no prospective evidence could be found to inform the diagnostic accuracy of an eligible SF technology, retrospective studies that met all other selection criteria were included.

No restriction by healthcare setting was made.

Indirect evidence

Where the interventions of interests did not form a connected network to allow comparison of each intervention against every other, prospective, within-patient comparisons or RCTs between SF

and systematic biopsy, and between CF and systematic biopsy, were also eligible to inform indirect comparisons, provided they reported numbers or rates of patients with no cancer (NC), all PCa and CS cancers for either SF or CF against systematic biopsy or template biopsy, and the combination of software or CF with systematic biopsy or template biopsy.

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 and lesion location), intervention characteristics (including SF technology type and version, MRI technology and magnet strength, biopsy route (transrectal or transperineal) 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 were extracted by at least one reviewer (AL or LB) using a standardised data extraction form and independently checked by a second reviewer (AL or LB). Discrepancies were resolved by discussion, with involvement of a third reviewer (SD) where necessary.

Where required and appropriate, attempts were made to contact 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, were extracted and reported as a single study. The most recent or most complete publication were used in situations where the possibility of overlapping populations could not be excluded. Where not reported (NR), rates of clinically insignificant cancers were imputed by subtracting the number of CS cancers from the total number of cancers detected (as per Bass, et al.).[53]

Critical appraisal

The quality of the diagnostic accuracy studies was assessed using the tools Quality Assessment tool of Diagnostic Accuracy Studies (QUADAS)-2 and QUADAS-C tools.[67,68] The QUADAS-2 tool evaluates both risk of bias (associated with the population selection, index test, reference standard and patient flow) and study applicability (population selection, index test and reference standard) of individual studies to the review question. The QUADAS-C tool is designed to assess risk of bias in test comparisons undertaken in studies that evaluate two or more index tests. QUADAS-C is an extension of QUADAS-2 and includes all domains covered by QUADAS-2. Each QUADAS-C domain is informed by each QUADAS-2 judgement for each test and additional signalling questions that are specific for comparisons to produce a risk of bias judgement for the comparison. The quality assessment focused on the risk of bias and applicability of cancer detection outcomes only. Since the review focused on the relative accuracy of two index tests, QUADAS-2 risk of bias assessments were not presented. All studies were quality assessed and checked by a second reviewer. Disagreements were resolved through discussion. Decisions with rationale for judgements were presented in tables.

Data synthesis methods

Meta-analysis

The meta-analyses aimed to compare four types of prostate biopsy approaches: CF, SF, CF with concomitant systematic biopsies, and SF with systematic biopsies. When relative effects comparing more than one intervention are of interest, a network meta-analysis (NMA) should be conducted to allow comparison of all interventions to each other.[69] NMA is an extension of pairwise (two-treatment) meta-analysis to allow comparisons across more than two treatments by producing relative effects for every pair of treatments in a connected network. Direct evidence from studies comparing two interventions directly is pooled with indirect evidence from studies that have a common comparator thus allowing consistent estimates of relative effects to be produced that account for all relevant evidence and are typically more precise. Common- (fixed-) or random-effects models can be used.[70]

Since many studies compared one or more of the four biopsy types of interest to systematic biopsy alone, this biopsy type was also included in the network of interventions in order to allow more comparisons to be made and to increase precision in the estimated relative effects.[69]

Network meta-analyses were conducted using a Bayesian framework estimated through Markov chain Monte Carlo methods. In an attempt to minimise bias, only prospective studies reporting within-patient comparisons, or RCTs reporting comparative results for two or more of the interventions of interest (SF, CF, systematic biopsy or a combination of software/CF with systematic biopsy), were included in the synthesis.

Model convergence was assessed by running two independent chains with different starting values looking at history plot and through inspection of Gelman–Rubin diagnostic plots. Due to data sparseness (few studies per comparison and not all studies reporting all outcomes) only fixed-effects models were fit to the data. Model fit was assessed by comparing the mean total residual deviance to the number of independent data points contributing to the analysis.[71]

Network plots were drawn in R[72] using the *netmeta* package.[73]

Multinomial synthesis model

To adequately distinguish between the different biopsy methods and SF devices, it is necessary not only to describe how they differ in classifying patients as having PCa or not, but also how they differ in classifying patients as having PCa at different Gleason grades, as that determines further treatment strategies. To inform post-biopsy patient management in the economic model, data are modelled by ISUP grade, where reported.

In order to best describe the differences between biopsy methods for each diagnostic category, a multinomial logistic regression model was fitted where the odds of being categorised in each of the different categories in *Table 2* compared to the reference category (no PCa) are allowed to vary by biopsy type. This model is conceptually equivalent to four binomial logistic regressions comparing category $r > 1$ with category 1 (no PCa), for each different biopsy type compared to the reference, cognitive biopsy.

The multinomial logistic regression model accounts for the ordered nature of the categories, which is important since a higher or lower detection of higher-grade cancers may have an impact on the cost-effectiveness of each device. However, the model does not take into account that some of the included studies reported results from different biopsies techniques performed on the same patients.[74] The study arms are treated as independent. This is a limitation of this model, which may inflate the uncertainty in the estimates. Models and code that can incorporate non-independent data (measured on the same patients) with ordered categories are not readily available.

Studies that only report the number of individuals in collapsed categories, for example the number of individuals with NC, non-CS cancer (Gleason 3 + 3) and CS cancer (Gleason > 3 + 3) provide information

TABLE 2 Cancer detection categories used to inform the economic model

Categories	Gleason	ISUP grade
1	-	NC[a]
2	3 + 3	1
3	3 + 4	2
4	4 + 3	3
5	8 – 10	4–5

a Although not formally part of the ISUP grade definition, it is distinguished in the model.

only on the odds ratio of being classified in the first two categories (NC, non-CS cancer). The model has been adapted to allow these studies to be included. However, they provide only limited information to the network compared to studies that report a finer breakdown of GSs.

Models were fitted in WinBUGS 1.4.3.[75] CF prostate biopsy was chosen as the reference intervention, and 'no cancer' as the reference category. Full details of the model and WinBUGS code are given in *Appendix 3*.

The relative effects produced by the model are the odds ratios for being classified in category *r*, instead of category 1 ('no cancer'), using intervention X (SF, systematic biopsy or a combination of software/CF with systematic biopsy), compared to cognitive fusion biopsy. Interpretation of these relative effects is complex since it relates to both a reference treatment and reference category. To aid interpretation, absolute probabilities of being classified in each category, using each intervention, are also reported. Details of how these are calculated are given in *Appendix 3*.

Analyses are presented assuming all SF devices share a common effect, that is they all have the same odds ratio compared to CF biopsy (Model 1a) and assuming individual device effects (Model 1b).

Cancer detection network meta-analysis models

The odds ratios of cancer detection, for different biopsy methods compared to each other, were also pooled. The number of cancers detected were modelled using the NMA model for binomial data with a logit link described in NICE technical support document 2,[71] fitted in R[72] using the package *gemtc*.[76]

Model convergence was assessed through inspection of Gelman–Rubin diagnostic plots. Both fixed-effect and random-effect models were fitted to the data. Non-informative prior distributions were used for all effect parameters and a Uniform (0,5) prior distribution was selected for the between-study standard deviation (SD) in random-effects models.[71] Model fit was assessed through mean total residual deviance and inspection of residual deviance contribution for each study arm. Heterogeneity was assessed by inspecting the size of the between-study SD and its 95% credible interval (CrI), and by comparing the Deviance Information Criteria (DIC) for fixed-effect and random-effects models. Where DIC differed by < 3 points the simplest model (fixed effect) was chosen. Consistency between direct and indirect evidence was assessed by fitting an unrelated mean effects model and where that suggested potential inconsistency, further investigation of the location of inconsistency was carried out by fitting node-split models.[77]

Any cancer detection network meta-analysis

The odds ratios of detecting any PCa (both CS and non-CS, i.e. Gleason ≥ 3 + 3) for different biopsy methods compared to each other were pooled. Analyses are presented assuming all SF devices share a common effect (Model 2a) and for individual device effects (Model 2b).

Clinically significant cancer detection NMA model

The odds ratios of detecting CSPCa (Gleason > 3 + 3), as opposed to NC or Gleason 3 + 3, for different biopsy methods compared to each other were also pooled, for studies that reported it. Analyses are presented assuming all SF devices share a common effect (Model 3a) and for individual device effects (Model 3b).

Narrative synthesis

Results of studies that were not eligible for inclusion in the NMAs, and results of all studies reporting protocol-specified outcomes other than diagnostic accuracy, were synthesised narratively following published guidelines.[78]

Outcomes were presented following the order listed in the protocol, then by comparison. Effect estimates, including metrics, measures of variance, statistical significance (at conventional threshold of

p = 0.05), and direction of effect were presented narratively and/or in tables at patient-level, unless only data per lesion could be extracted. Studies were grouped based on direction of effect and statistical significance. Where NR, outcomes including detection rates, test positive rates and biopsy positivity rates were imputed. No formal statistical methods were used to assess heterogeneity. Results were narratively compared with the meta-analyses, and limitations of the evidence (e.g. inconsistency, risk of bias) informed findings summaries and conclusions.

Quantity and quality of evidence

Figure 2 presents an overview of the study selection process in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The literature searches identified a total of 6289 unique records. After title and abstract screening, 247 references were retrieved and a total of

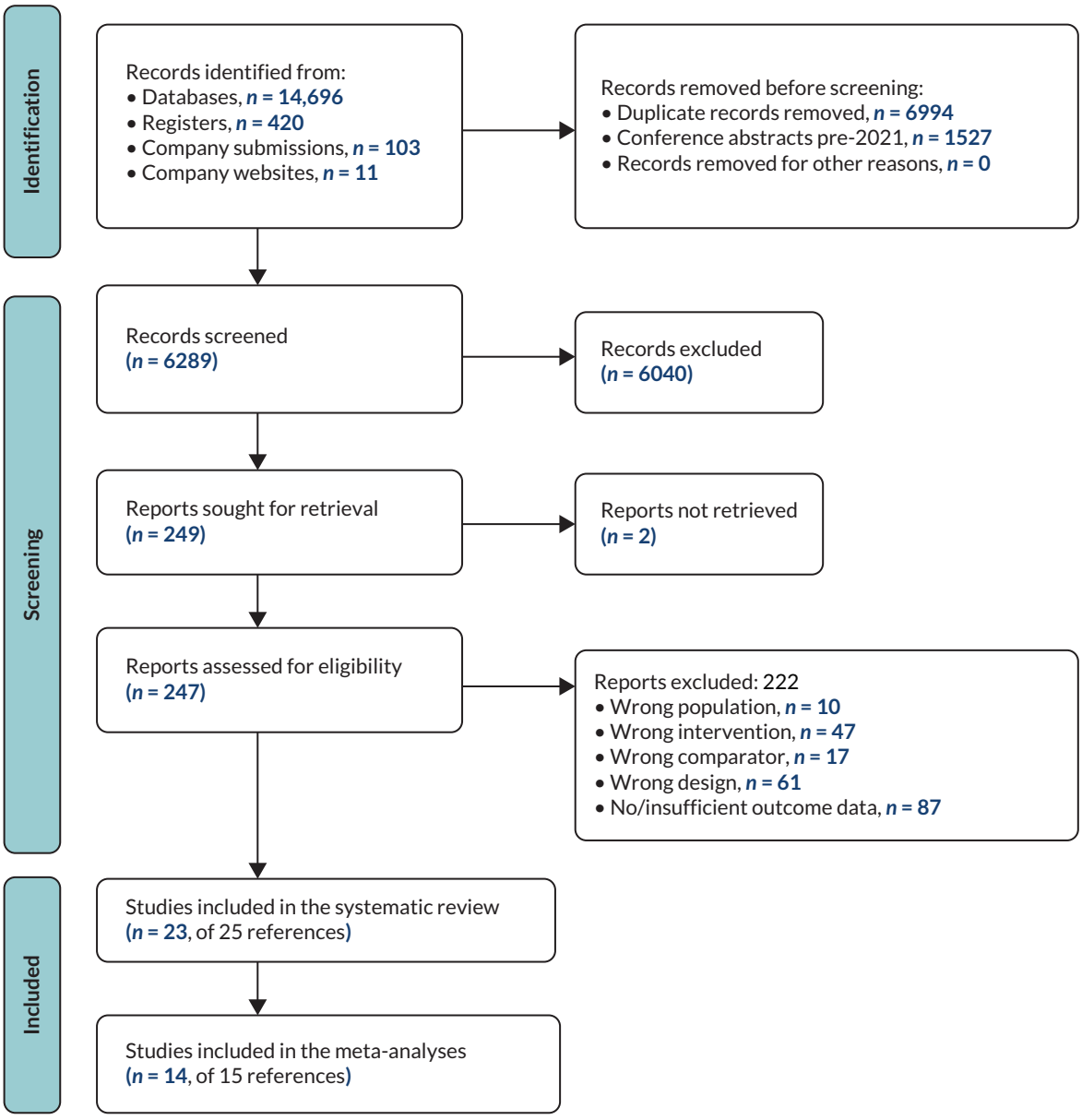


FIGURE 2 Study selection process (PRISMA flow diagram).

23 unique studies were included in the systematic review.[31,79–101] Fourteen studies were included in the quantitative synthesis,[31,79,80,82,84,86–88,92–94,96,97,99] while nine studies were included in the narrative synthesis only.[81,83,85,89–91,95,98,100,101]

Evidence was included for all SF technologies specified in the scope and protocol (all versions) except for Fusion Bx (Focal Healthcare) and ExactVu (Exact Imaging). *Report Supplementary Material 1* presents a summary of the evidence for Fusion Bx and ExactVu that was considered for inclusion and ultimately excluded, and a list of studies excluded from the systematic review, grouped by reason for exclusion.

Description of studies included in the systematic review of diagnostic accuracy and clinical effectiveness

Table 25, *Appendix 4*, presents the characteristics of the 23 studies included in the systematic review. The majority of studies were conducted in Europe,[31,80,81,83,86,89,92–95,98,101] and five studies were conducted in the USA.[87,88,90,96,97]

Twelve studies compared SF against CF; of those, three used a within-patient comparison design (where participants underwent biopsy with both SF and CF within the same session),[88,93,97] and nine compared separate cohorts who received either SF or CF biopsy (between-patient design).[31,82,85,89,90,95,98,100,101] Three studies compared two or more SF software against one another.[79,86,99] Five studies compared SF against systematic biopsy,[80,87,92,94,96] and three studies compared CF with systematic biopsy.[79,86,99]

Three RCTs were included; of those, two compared SF against CF,[31,82] and one compared three SF devices.[83] All other studies were non-randomised trials or observational; of those, four studies used a retrospective design.[85,90,100,101]

The following SF technologies were evaluated: ARTEMIS (five studies),[82,84,88,96,97] BioJet (four studies),[81,83,84,89] BiopSee (two studies),[31,95] BK (two studies, referred to as Predictive Fusion Software in one study[85] and MIM fusion software in another),[100] iSR'obot Mona Lisa (one study)[101] and UroNav (one study).[90] One study evaluated KOELIS Trinity,[83] and six studies evaluated, KOELIS Urostation, an earlier version of the software which used a third-party ultrasound.[80,81,92–94,98]

Table 26, *Appendix 4*, maps the evidence by SF technology, biopsy route, anaesthesia method and registration method, and highlights a number of limitations in reporting and gaps in the evidence. Of the 20 studies that evaluated a SF technology, 7 studies used SF for a TP,[31,84,85,89,95,100,101] and there was no evidence for ARTEMIS, KOELIS and UroNav used in the context of a TP. BiopSee was only evaluated under general anaesthesia,[31,95] and 10 studies did not report their method of anaesthesia.[80,81,89,91–94,96,98,100] Image registration methods (rigid vs. elastic) were NR or could not be inferred in five studies.[84,88,89,95,96]

Table 27, *Appendix 4* , summarises the characteristics of the patients in the included studies. Across all included studies, a total of 3733 patients who received SF and 2154 individuals who underwent CF were analysed and informed estimates of PCa detection. Where reported, the median age ranged from 62 to 73.1 years, median PSA levels ranged from 4.2 ng/mL to 10.7 ng/mL, and all patients had a PI-RADS or Likert score of 3 or more. Seven studies only included biopsy-naive patients,[79,81,82,85,88,95,98] four studies only included patients who received a repeat biopsy following one or more prior negative biopsies[31,86,94,99] and eight studies included a mix of patients with no prior biopsy and individuals undergoing a repeat biopsy following a prior negative biopsy.[80,83,84,87,89–93,101] Three studies included a subset of patients under active surveillance and reported separate results biopsy naive and/or repeat biopsy with prior negative result.[96,97,100] Where reported, all operators were experienced in biopsy procedures, although levels of expertise varied across the studies. *Table 28*, *Appendix 4*, summarises information from the studies on operator experience.

Quality of included studies

Results of the quality and applicability assessment are reported in *Figure 3*, and further details on the rationale for decisions are reported in *Appendix 5*. All studies were at high risk of bias for at least one of the following domains: patient selection, index test, reference standard and flow and timing. Eight studies were at high risk of patient selection bias; all were non-randomised comparisons.[81,83,89,90,95,98,100,101] Three studies were at unclear risk of selection bias;[31,84,85] including the two RCTs,[31,84] and all other studies were at low risk of selection bias. Eight studies had a high risk of bias related to the comparison of index tests,[31,81,84,88,89,93,97,101] and all other 15 studies were at low risk of bias for this domain.

Twenty studies were at high risk of bias associated with the reference standard.[31,79–87,89,90,92,94–96,98–101] For between-patient comparisons, this was primarily due to the fact that total cancer positive cases in each study arm or cohort were derived from different biopsy methods; in within-patient comparisons, as all biopsy methods were performed within the same examination, it was not feasible for studies to truly blind operators from tracks of preceding biopsy methods (true blinding would several biopsy sessions per patient, which would be unethical). Participants in all within-patient comparison studies received SF, CF and/or systematic biopsy within the same examination; the order in which the different biopsy methods were implemented varied where reported, therefore the overall direction of bias due to the lack of operator blinding could not be determined.

Of the 15 studies that compared SF with CF or with another SF device,[31,81–85,88–90,93,95,97,98,100,101] 7 did not use systematic biopsy or include systematic biopsy results as part of a reference standard test.[31,81,83–85,97,101] Of the studies that included systematic biopsy as part of a reference standard test, only one reported blinding the systematic biopsy operator to the MRI report.[88] This is an important design limitation, since knowledge of the MRI report may have influenced the placing of systematic biopsy cores. Clinical advisers to the EAG confirmed that lack of blinding to MRI reports may have improved the accuracy of systematic biopsies relative to targeted biopsies. Therefore, for most of the evidence for systematic biopsy included in this review, there is a risk that the detection of PCa from systematic biopsy may have been overestimated compared with true random, standard systematic biopsy. This said, the lack of blinding to MRI report when using systematic biopsy concomitant with targeted biopsy is reflective of current practice. Blinding of the histopathologists, who analysed the biopsy samples, was generally NR, and none of studies used TTMB. Two studies were at high risk of bias due to missing outcomes data (flow and timing domain),[93,95] and all other studies were at low risk of bias for this domain.

Three studies raised no concerns about their applicability to the review question.[79,82,88] Five studies included a population that was deemed not applicable (NA) to the review question (high concern),[31,86,90,94,99] and five included a significant proportion (approximately half) of patients undergoing repeat biopsy following a prior negative biopsy.[87,89,92,93,101] Although patients with a prior negative biopsy were eligible in this systematic review, clinical advisers to the EAG noted that they made up only a minority (approximately under 10%) of the total population undergoing targeted biopsy who are not under active surveillance. All other studies included mostly biopsy-naive patients and had a

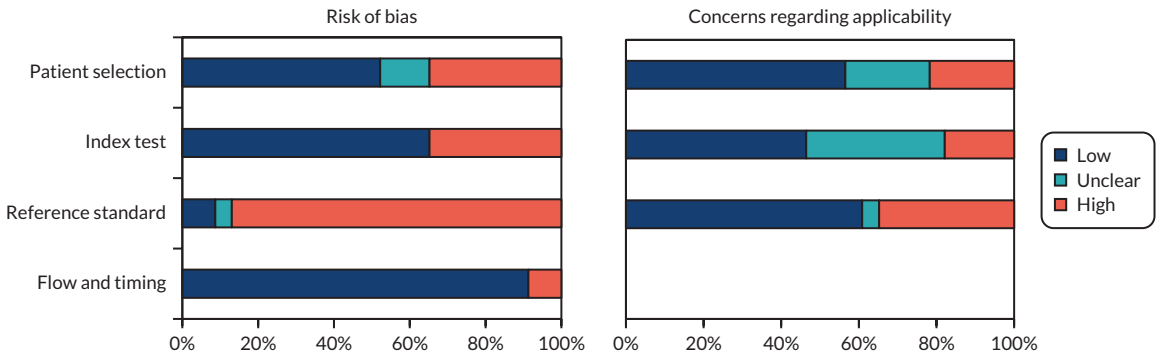


FIGURE 3 Risk of bias and applicability assessment summary of studies included in the systematic review.

population that was considered broadly representative. Five studies used an intervention that was not considered applicable to the review question,[31,84,89,95,101] primarily due to the use of general anaesthesia in all procedures. Clinical advisers to the EAG noted that general anaesthesia is normally only used in a minority of patients, although it may facilitate biopsy targeting due to the lack of patient movement. The applicability of SF was uncertain in 10 studies.[80,81,90,92–94,96,98–100] In four cases, this was due to insufficient reporting about biopsy routes and anaesthesia methods,[90,96,99,100] and in six studies, a KOELIS device with no integrated ultrasound was evaluated, and the applicability of their results to KOELIS Trinity was uncertain.[80,81,92–94,98] Following request for further information from the EAG, the company did not clarify or provide evidence that the diagnostic accuracy of older versions of KOELIS was equivalent to KOELIS Trinity. Eight studies raised concerns about the applicability of the reference standard test.[31,81,83–85,95,97,101]

Diagnostic accuracy results

This section presents the evidence included in the meta-analyses and structure of the networks of evidence (see *Studies included in the meta-analysis and network structure*), the results of the NMAs (see *Meta-analysis results*), and results of studies not included in the meta-analyses (see *Narrative synthesis results*).

Studies included in the meta-analysis and network structure

Model 1a: multinomial synthesis model (base case)

Thirteen studies, identified by the systematic review, with data suitable for inclusion in the NMA are presented in *Table 24*, *Appendix 3* and form the network in *Figure 4*. Rabah *et al.* [84] is excluded as it compared two SF devices, assumed to have identical effects, and therefore does not contribute to the analysis. The multinomial synthesis model was used to synthesise comparative information on the probabilities of being classified at the various ISUP grades of PCa (see *Meta-analysis results*). Resulting estimates are then used in the base-case economic model.

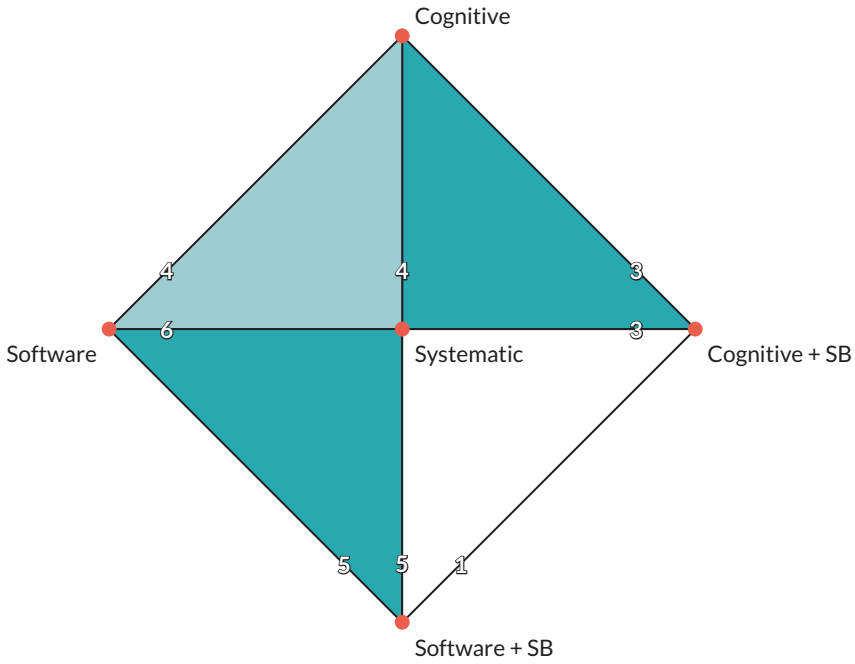


FIGURE 4 Network of biopsy types compared, under the assumption of a common effect for different SF devices. Lines represent comparisons made in studies, numbers on the lines show how many studies included that comparison and shaded areas represent multiarm studies. SB, systematic biopsy.

Due to data sparseness, we assumed that there is no difference in relative effects of the various SF biopsy devices compared to cognitive biopsy and only fixed-effect models could be fitted. This assumption is supported by the limited direct evidence comparing different fusion devices and clinical advice to the EAG. However, the different costs of each device will still be taken into account in the economic model. This assumption will be relaxed in an additional analysis (*Model 1b: Multinomial synthesis model, individual device effects*).

Although the network in *Figure 4* is fully connected (there is a path connecting every intervention to every other), not all studies reported the breakdown of cancers detected by ISUP grade (see *Appendix 3*, *Table 24*). This resulted in a de facto disconnect in the network for comparisons of CF + SB and SF + SB for ISUP grades > 2. Relative effects comparing disconnected components of the network cannot be estimated and are reported separately.

Calculating absolute probabilities

As noted in *Meta-analysis results*, odds ratios estimated from this model are hard to interpret. We will therefore also present results on the absolute probability scale to aid interpretation. To calculate the absolute probabilities of being classified in each category using each intervention, we need to assume a set of underlying baseline probabilities of being classified in each category on one of the included interventions. For ease of interpretation, in this section these underlying baseline probabilities will be assumed to be fixed, that is, to have no uncertainty. All other probabilities are then obtained by applying the estimated odds ratios to these probabilities, as described in *Appendix 2*. These baseline probabilities should be as representative as possible of the population of interest. A targeted review was carried out to determine a good source of evidence on these probabilities (see *Review of additional prevalence, test results and diagnostic accuracy evidence* and *Appendix 8 Distribution of test results obtained with cognitive fusion or software fusion biopsy*).

The two studies with the largest sample size that were identified and deemed most representative of NHS practice were considered as a source of evidence for the baseline probabilities: Filson *et al.*[96] and PAIREDCAP (2019).[88] Two subgroups of patients are of interest: biopsy-naive patients and those undergoing a repeat biopsy after a negative result. Filson (2016)[96] reported probabilities for these two subgroups separately and for two interventions of interest, SF using ARTEMIS and combined SF (ARTEMIS) with systematic biopsy, allowing the same source of baseline probabilities to be used for both disconnected components of the network.

However, Filson *et al.*[96] does not report separate data for ISUP grades 3 and 4–5, as required by the model. We approximated the probabilities of patients being in grade 3 and 4–5 by splitting the combined patients according to the proportions in each category reported in PAIREDCAP (2019)[88] (approximately 60/40).

In a sensitivity analysis for the subgroup of biopsy-naive patients, the distribution of test results from PAIREDCAP (2019)[88] (which only include biopsy-naive patients) was used to inform the baseline probabilities in the first part of the network. In the absence of other suitable sources of evidence, data on biopsy-naive patients from Filson *et al.*[96] will continue to inform the baseline probabilities in the combined biopsy (software/CF plus systematic biopsy) network.

Absolute probabilities were therefore reported for:

- subgroup of biopsy-naive patients (based on Filson *et al.*[96] biopsy-naive data)
- subgroup of previous negative biopsy patients (based on Filson *et al.*[96] previous negative biopsy data)
- a sensitivity analysis using alternative baseline probabilities for the biopsy-naive subgroup (based on biopsy-naive data from PAIREDCAP (2019)[88] and Filson *et al.*[96]).

Results will be reported separately for comparisons of CF, SF and systematic biopsy, and comparisons of combined cognitive/SF with systematic biopsy.

Model 1b: multinomial synthesis model, individual device effects

Fourteen studies identified by the systematic review with data suitable for inclusion in the NMA are presented in *Table 24*, *Appendix 3* and form the network in *Figure 5*. The multinomial synthesis model was used to synthesise comparative information on the probabilities of being classified at the various ISUP grades of PCa (see *Meta-analysis results*).

Although the network in *Figure 5* is fully connected (there is a path connecting every intervention to every other), not all studies reported the breakdown of cancers detected by ISUP grades. This resulted in a de facto disconnect in the network for comparisons of some devices for higher ISUP grades (see *Table 24*, *Appendix 3*). Relative effects comparing disconnected components of the network cannot be estimated and are reported separately, where possible.

Calculating absolute probabilities

Absolute probabilities will be reported for:

- subgroup of biopsy-naive patients (based on Filson *et al.*[96] biopsy-naive data);
- subgroup of previous negative biopsy patients (based on Filson *et al.*[96] previous negative biopsy data).

As many network components are disconnected for high ISUP grades in this analysis, absolute probabilities are only reported where they can be reliably obtained, which limits the interpretation of results.

Model 2a: cancer detection

Data from the studies identified by the systematic review (see *Figure 4*) were pooled in a NMA to compare the proportion of PCas (CS and non-CS, i.e. Gleason ≥ 3 + 3) detected by the different biopsy

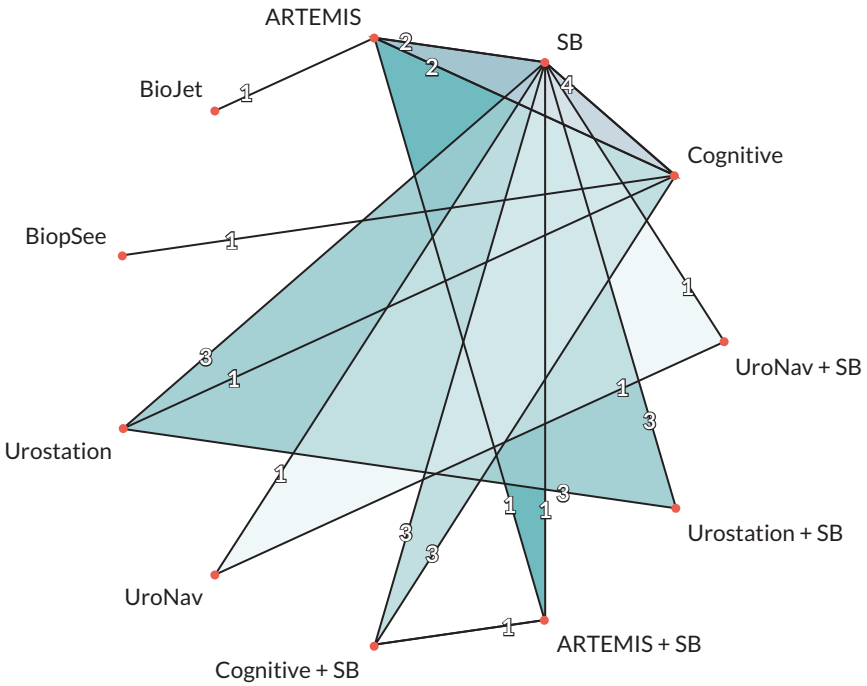


FIGURE 5 Network of biopsy types and devices compared. Lines represent comparisons made in studies, numbers on the lines show how many studies included that comparison and shaded areas represent multiarm studies. SB, systematic biopsy.

strategies. Data were obtained by adding the relevant ISUP grades in *Table 24*, *Appendix 3*, and are presented in *Table 30*, *Appendix 6*.

In Model 2a we assumed that there is no difference in relative effects of the various SF biopsy devices compared to cognitive biopsy. This assumption relaxed in Model 2b where the individual device effects are estimated. Both fixed- and random-effects models were considered.

Model 2b: cancer detection, individual device effects

Data from the studies, identified by the systematic review (see *Figure 5* and *Table 30*, *Appendix 6*), were pooled in a NMA to compare the proportion of PCas (CS and non-CS) detected by the different biopsy strategies. Both fixed- and random-effects models were considered.

Model 3a: clinically significant cancer detection

Data from the studies identified by the systematic review were pooled in aNMA to compare the proportion of CSPCas (Gleason > 3 + 3) detected by the different biopsy strategies. Only 10 studies reported the number of CS cancers detected, obtained by adding the relevant ISUP grades in *Table 24* (see *Appendix 3*), and are presented in *Table 31*, *Appendix 6*. In addition, Rabah *et al.*[84] is excluded as it compared two SF devices, assumed to have identical effects in Model 3a, and therefore does not contribute to this analysis. Nine studies were included in the network (see *Figure 13*, *Appendix 6*). Both fixed- and random-effects models were considered.

Model 3b: clinically significant cancer detection, individual device effects

Data from 10 studies reporting the number of CSPCas detected by the different biopsy strategies (see *Table 31* and *Figure 14*, *Appendix 6*) were pooled in a NMA. Both fixed- and random-effects models were considered.

Meta-analysis results

Model 1a: multinomial synthesis model (base-case)

Models were sampled for 100,000 iterations from 2 independent chains (50,000 iterations on each chain) after checking that convergence was achieved after a burn-in of 50,000 iterations.

Results from fitting Model 1a to the data in *Table 24*, *Appendix 3* (network in *Figure 4*) are presented in *Table 3*. One study (Gomez-Ortiz *et al.*[99]) had a higher than expected contribution to the mean residual deviance (15 compared to its expected contribution of 6) but overall the model fitted the data well with a posterior mean of the residual deviance of 77.4, which is close to the 75 data points included.

TABLE 3 Odds ratios (median and 95% credible interval) of being classified as ISUP grades 1 to 4–5 compared to being categorised as having NC, for systematic biopsy and SF biopsy, compared to categorisations using CF biopsy; and for SF plus systematic biopsy, compared to CF plus systematic biopsy

	Compared to CF biopsy				Compared to cognitive fusion + systematic biopsy	
ISUP grade	SB		SF		SF + SB	
No cancer	Reference					
1	1.57	(1.09 to 2.26)	1.98	(1.28 to 3.06)	1.20	(0.72 to 1.99)
2	2.24	(1.45 to 3.47)	1.34	(0.80 to 2.25)	2.57	(0.95 to 7.97)
3	1.40	(0.82 to 2.38)	1.25	(0.66 to 2.33)	0.66	(0.12 to 2.92)
4–5	1.54	(0.83 to 2.84)	1.58	(0.90 to 2.77)	4.33	(0.45 to 158.38)

SB, systematic biopsy.

Compared to CF biopsy, there is evidence of higher odds of being categorised in ISUP grade 1 instead of NC when using SF (OR 1.98 95% CrI 1.28 to 3.06, *Table 3*). There is no evidence of more patients being categorised as ISUP 2, 3 or 4–5 instead of NC for SF biopsy compared to CF biopsy (see *Table 3*). More patients are categorised as having non-CS cancer (ISUP grade 1) (OR 1.57 95% CrI 1.09 to 2.26) and as having a CS cancer with ISUP grade 2 (OR 2.24 95% CrI 1.45 to 3.47), instead of having NC when using systematic biopsy compared to CF biopsy. There is no clear evidence of more patients being categorised as ISUP 3 or 4–5 instead of NC for systematic biopsy compared to CF biopsy (see *Table 3*). However, we note the large uncertainty in all results, particularly for higher ISUP grades, due to limited data broken down by higher ISUP grades. As discussed in *Quality of included studies*, most of the evidence for systematic biopsy was not blinded to MRI reports. This may have inflated the accuracy of systematic biopsy compared with SF and CF.

Compared to CF plus systematic biopsy, there is no clear evidence of more patients being categorised as having cancer (ISUP grades 1 to 4–5) instead of NC for SF plus systematic biopsy. However, we note the large uncertainty in all results, particularly for the highest category. This is due to few studies reporting data broken down by higher ISUP grades and the small number of patients categorised as ISUP 4–5 using any of the two biopsy types (see *Table 24*, *Appendix 3*).

Absolute probabilities of being classified as having NC or at different ISUP grades for the two subgroups of interest: biopsy-naive patients and patients with a previous negative biopsy based on data from Filson *et al.*[96] are presented for ease of interpretation. A sensitivity analysis for the biopsy-naive subgroup is presented in *Table 32*, *Appendix 6*.

Absolute probabilities: biopsy-naive patients

Using baseline probabilities for SF biopsy and SF plus systematic biopsy from the biopsy-naive subgroup in Filson *et al.*,[96] and applying the odds ratios in *Table 3* the probabilities of being classified as having NC or at different ISUP grades are given in *Table 4*.

For biopsy-naive patients, Model 1a suggests that compared to SF biopsy, patients undergoing CF biopsy may have (see *Table 4*):

1. a higher probability of being classified as not having cancer (55% vs. 47%)
2. similar probability of being classified as having non-CS cancer (ISUP 1, 17% vs. 16%)
3. lower probability of being classified at higher ISUPs, particularly ISUP 2.

Probabilities for systematic biopsy are similar to those for SF biopsy for NC and all ISUP grades. However, results are uncertain.

Results were similar when systematic biopsy was added to software and CF, although there may be a higher probability of patients being classified at ISUP grade 2 with software plus systematic biopsy compared to cognitive plus systematic biopsy, and versus lower probability for ISUP grade 3 (see *Table 4*), although results are imprecise due to the small number of observed events. The proportion of patients classified at ISUP grades 4–5 are similar. However, these results are very uncertain.

Absolute probabilities: previous negative biopsy patients

Using baseline probabilities for SF biopsy and SF plus systematic biopsy from the subgroup of patients with a previous negative biopsy in Filson *et al.*,[96] and applying the odds ratios in *Table 3* the probabilities of being classified as having NC or at different ISUP grades are given in *Table 5*.

For patients with a previous negative biopsy, given a 69% probability of being classified as not having cancer with SF biopsy,[96] the probability of being classified as not having cancer is higher for patients undergoing cognitive biopsy (75% 95% CrI 69% to 80%) but lower for patients undergoing systematic biopsy (64% 95% CrI 59% to 69%). As there is high probability that patients with a prior negative biopsy

TABLE 4 Probabilities (median and 95% CrI) of being classified at different ISUP grades for biopsy-naive patients

	ARTEMIS probabilities from Filson *et al.*[96] biopsy-naive data					ARTEMIS + SB probabilities from Filson *et al.*[96] biopsy-naive data		
ISUP	Cognitive		Systematic		Software[a]	Cognitive + SB		Software + SB[a]
No cancer	0.55	(0.48 to 0.62)	0.42	(0.37 to 0.47)	0.47	0.41	(0.21 to 0.56)	0.36
1	0.17	(0.13 to 0.22)	0.21	(0.17 to 0.25)	0.16	0.21	(0.10 to 0.33)	0.22
2	0.12	(0.08 to 0.16)	0.20	(0.16 to 0.24)	0.20	0.10	(0.03 to 0.23)	0.22
3	0.09	(0.06 to 0.14)	0.10	(0.06 to 0.15)	0.11	0.21	(0.06 to 0.59)	0.12
4–5	0.06	(0.03 to 0.10)	0.07	(0.04 to 0.12)	0.06	0.02	(0.00 to 0.18)	0.08

a Assumed underlying baseline probabilities.

TABLE 5 Probabilities (median and 95% CrI) of being classified at different ISUP grades for patients with a previous negative biopsy

	ARTEMIS probabilities from Filson *et al.*[96] previous negative biopsy data					ARTEMIS + SB probabilities from Filson *et al.*[96] previous negative biopsy data		
ISUP	Cognitive		Systematic		Software[a]	Cognitive + SB	Software + SB[a]	
NC	0.75	(0.69 to 0.80)	0.64	(0.59 to 0.69)	0.69	0.63	(0.38 to 0.76)	0.58
1	0.08	(0.06 to 0.11)	0.11	(0.09 to 0.14)	0.09	0.13	(0.07 to 0.21)	0.15
2	0.06	(0.04 to 0.08)	0.11	(0.09 to 0.13)	0.10	0.05	(0.02 to 0.12)	0.12
3	0.06	(0.04 to 0.10)	0.08	(0.05 to 0.12)	0.08	0.14	(0.04 to 0.47)	0.09
4–5	0.04	(0.02 to 0.07)	0.05	(0.03 to 0.09)	0.05	0.01	(0.00 to 0.13)	0.06

a Assumed underlying baseline probabilities.

will again be classified as having NC with SF, CF or systematic biopsy, the probabilities of being classified at different ISUP grades are small and similar across these biopsy strategies (see *Table 5*).

Similar results were obtained when adding a systematic biopsy to software and CF.

Model 1b: multinomial synthesis model, individual device effects

Models were sampled for 100,000 iterations from 2 independent chains (50,000 iterations on each chain) after checking that convergence was achieved after a burn-in of 50,000 iterations.

Results from fitting Model 1b to the data in *Table 24*, *Appendix 3* (network in *Figure 5*) are presented in *Table 33*, *Appendix 6*. One study (Gomez-Ortiz *et al.*[99]) had a higher than expected contribution to the mean residual deviance (16 compared to its expected contribution of six). Other studies had deviances in the range expected, although the posterior mean of the residual deviance was 89.2, which is higher than the number points included (79). Often a model fit can be poor when data are sparse as many parameters cannot be reliably estimated. However, more complex models, such as random-effects models, cannot be considered due to data sparseness. We would advise caution when interpreting the results from this model.

No odds ratios can be estimated for SF biopsy using UroNav or UroNav plus systematic biopsy since the only study comparing this device does not report details of classifications broken down by category (see *Table 24*, *Appendix 3*).

Compared to CF biopsy, there is only evidence of higher odds of being categorised in ISUP grade 1 instead of NC when using systematic biopsy (OR 1.54 95% CrI 1.06 to 2.24, *Table 33*, *Appendix 6*). There is some evidence that more patients are categorised as ISUP grade 2 instead of having NC when using systematic biopsy, ARTEMIS or Urostation, compared to CF biopsy. There is no clear evidence of more patients being categorised as ISUP 3 or 4–5 instead of NC for systematic biopsy or ARTEMIS compared to CF biopsy. No relative effects are estimable for the other devices and there is large uncertainty in all results.

Compared to CF plus systematic biopsy, there is no clear evidence of more patients being categorised as having cancer (ISUP grades 1 to 4–5) instead of NC for ARTEMIS or Urostation plus systematic biopsy. However, we note the large uncertainty in all results which led to some relative effects not being estimable (see *Table 33*, *Appendix 6*).

Absolute probabilities of being classified as having NC or at different ISUP grades for the two subgroups of interest can only be reported where the odds ratios are estimable for all ISUP grades. Therefore, these are only presented for CF, systematic biopsy and SF using ARTEMIS (assumed underlying baseline probabilities), and when adding systematic biopsy, for biopsy-naive patients and patients with a previous negative biopsy based on data from Filson *et al.*[96] (see *Tables 34* and *35*, *Appendix 6*).

Model 2a: cancer detection

Fixed- and random-effects models were fitted. Based on the model fit statistics (see *Table 36*, *Appendix 6*) both the fixed- and random-effects models fitted the data well and differences in DIC were small. Therefore, the fixed-effect model was selected. The fixed-effect unrelated mean effects model suggested no evidence of inconsistency between direct and indirect evidence based on both the model fit statistics and deviance plots (see *Table 36* and *Figure 15*, *Appendix 6*).

Results from fitting Model 2a to the data in *Table 30*, *Appendix 6* (network in *Figure 4*) are presented in *Figure 6* and all pairwise comparisons are reported in *Table 37*, *Appendix 6*.

Model 2a suggests SF biopsy may classify more patients as having cancer (any ISUP), than CF biopsy (OR 1.30 95% CrI 1.06 to 1.61; *Figure 6*). However, note that this cannot be directly compared to the

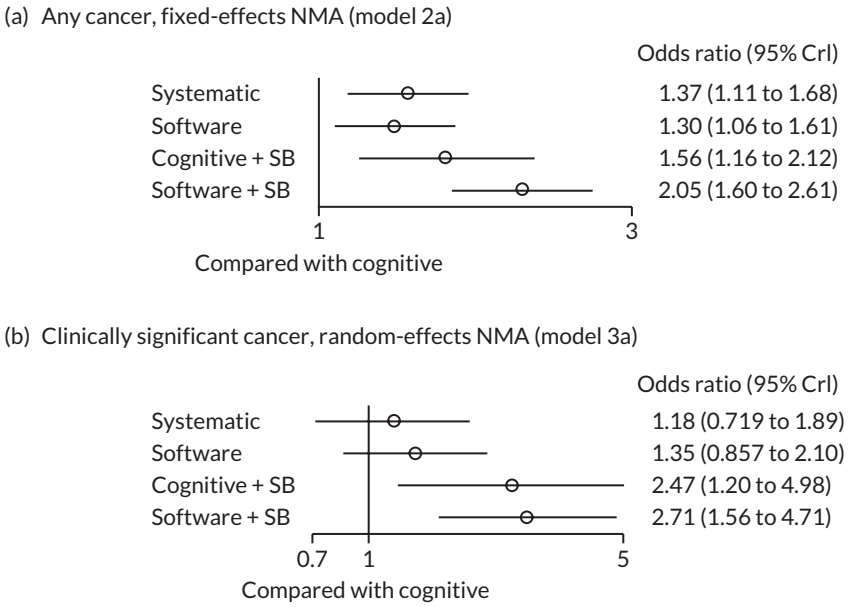


FIGURE 6 Odds ratio of detection (median and 95% CrI) of cancer. OR, odds ratio; SB, systematic biopsy.

results from ISUP 1 for Model 1a, since Model 2a is comparing detection of any cancer, that is, all ISUP 1 to 5 combined, and not only the detection of non-CS cancer. The increase in the ORs for detection of any cancer is driven by the increase in the probability of categorisation at ISUP>1, which in this case is driven by increases at ISUP 2 [see *Model 1a: multinomial synthesis model (base-case)*]. Results for the random-effects model are presented as a sensitivity analysis in *Table 37* and *Figure 16*, *Appendix 6*. As discussed in *Quality of included studies*, the accuracy of systematic biopsy may have been inflated due to study design limitations.

Model 2b: cancer detection, individual device effects

Fixed- and random-effects models were fitted. Based on the model fit statistics (see *Table 36*, *Appendix 6*) both the fixed- and random-effects models fitted the data well and differences in DIC were small. Therefore, the fixed-effects model was selected. The fixed-effects unrelated mean effects model suggested no evidence of inconsistency between direct and indirect evidence based on both the model fit statistics and deviance plots (see *Table 36* and *Figure 15*, *Appendix 6*).

Results from fitting Model 2b to the data in *Table 30*, *Appendix 6* (network in *Figure 4*) are presented in *Figure 7* and all pairwise comparisons are reported in *Table 38*, *Appendix 6*.

Compared to CF biopsy, there is evidence that SF biopsy with BioJet, Urostation and ARTEMIS, and Urostation, UroNav or cognitive biopsy combined with systematic biopsy may detect more cancers. Results for the random-effects model are presented as a sensitivity analysis in *Table 38* and *Figure 16*, *Appendix 6*.

Model 3a: clinically significant cancer detection

Fixed- and random-effects models were fitted. Based on the model fit statistics (see *Table 36*, *Appendix 6*) the random-effects model had a better fit to the data and the difference in DIC was > 3. Therefore, the random-effects model was selected. The random-effects unrelated mean effects model suggested no evidence of inconsistency between direct and indirect evidence based on both the model fit statistics and deviance plots (see *Table 36* and *Figure 15*, *Appendix 6*).

Results from fitting Model 3a to the data in *Table 31*, *Appendix 6* (network in *Figure 13*) are presented in *Figure 6* and all pairwise comparisons are reported in *Table 37*, *Appendix 6*. The posterior median of the

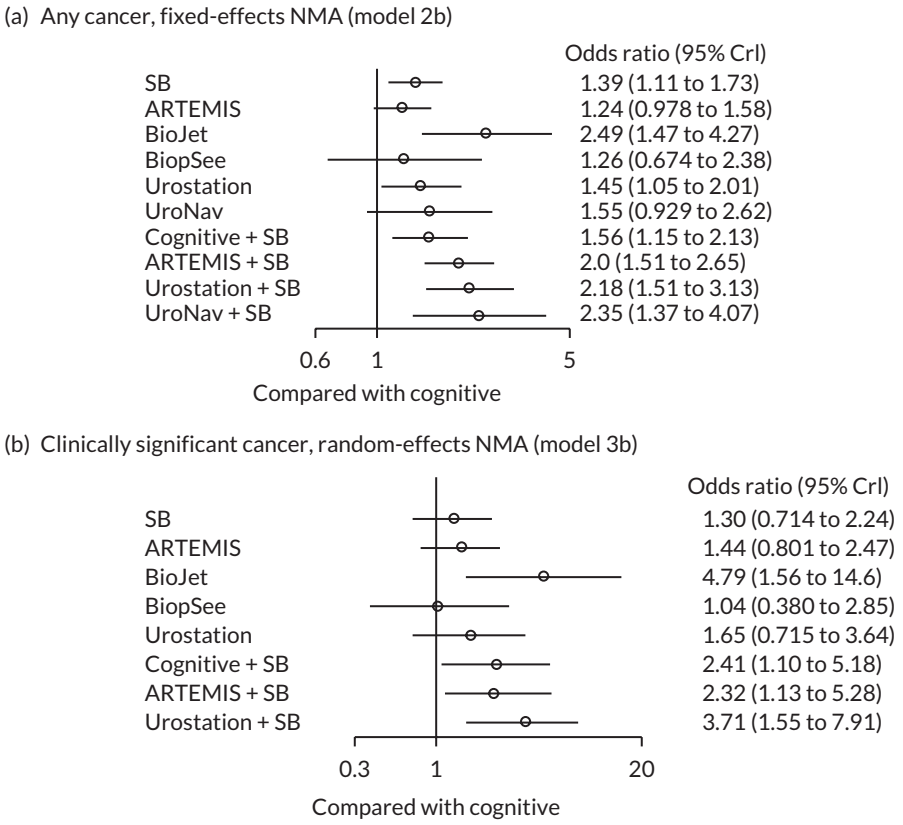


FIGURE 7 Odds ratio of detection (median and 95% CrI) of cancer, individual device effects. OR, odds ratio; SB, systematic biopsy.

between-study heterogeneity SD was 0.313 (95% CrI 0.132 to 0.634), which is moderate on the log odds ratio scale. The full posterior distribution of the between-study SD is presented in *Figure 16*, *Appendix 6*.

While Model 2a suggested SF biopsy may classify more patients as having cancer (ISUP 1 to 5) than CF biopsy (see *Figure 5*), Model 3a also suggests SF biopsy may classify more patients as having CS cancer (ISUP 2, 3, 4–5), as opposed to NC or ISUP 1, than CF biopsy, but with a wider confidence interval (CI) that includes the null effect (OR 1.35 95% CrI 0.86, 2.10; *Figure 6*). By using odds and collapsing ISUP grades, the statistical model has higher power to detect statistically significant differences against NC than against non-CS cancer (which pools NC with ISUP 1). These results are consistent with the findings from Models 1a and 2a. There is some evidence that adding systematic biopsy to cognitive or SF increases CS cancer detection.

Model 3b: clinically significant cancer detection, individual device effects

Fixed- and random-effects models were fitted. Based on the model fit statistics (see *Table 36*, *Appendix 6*) the random-effects model had a better fit to the data and the difference in DIC was > 3. Therefore, the random-effects model was selected. The random-effects unrelated mean effects model suggested no evidence of inconsistency between direct and indirect evidence based on both the model fit statistics and deviance plots (see *Table 36* and *Figure 15*, *Appendix 6*).

Results from fitting Model 3b to the data in *Table 31*, *Appendix 6* (network in *Figure 13*) are presented in *Figure 7* and all pairwise comparisons are reported in *Table 39*, *Appendix 6*. The posterior median of the between-study heterogeneity SD was 0.304 (95% CrI 0.048 to 0.769), which is similar to the posterior heterogeneity from Model 3a. This suggests there is moderate heterogeneity (log odds ratio scale) and that splitting the device effects did not explain the between-study variability. The full posterior distribution of the between-study SD is presented in *Figure 16*, *Appendix 6*.

Compared to CF biopsy, there is no evidence that SF with ARTEMIS, BiopSee, Urostation, or systematic biopsy detect more CS cancers. However, there is evidence that SF with BioJet or adding systematic biopsy to cognitive or SF with ARTEMIS or Urostation may increase CS cancer detection.

Narrative synthesis results

Nine studies reported data on PCa detection but were not included in a meta-analysis, due to reasons specified in *Meta-analysis*.[81,83,85,89–91,95,98,100] None of these studies had a within-patient comparison, and none used a randomised comparison between SF and CF or between two or more eligible SF technologies. Therefore, these studies were considered at higher risk of confounding compared with studies included in the NMA. This section presents a narrative summary of their results.

All nine studies reported a comparison between separate cohorts. Five used a prospective design,[81,83,89,95,98] and four were retrospective.[85,90,91,100] Only one study used propensity score matching to adjust for differences in participant characteristics,[81] and one study performed a comparison between software and CF using conditional logistic regression.[98] All other studies reported naive, unadjusted comparisons.

Six studies compared SF alone with CF alone[85,89–91,95,98] and two studies reported a comparison between SF with concomitant systematic biopsy against CF with systematic biopsy.[89,100] Two studies compared different SF technologies against one another; one compared two technologies (BioJet with Urostation),[81] and another compared three (BioJet, KOELIS Trinity and UroNav).[83] The following SF technologies were evaluated: BioJet (three studies),[81,83,89] BiopSee (one study),[95] bkFusion (two studies)[85,100] and iSR'obot Mono Lisa (one study).[91] Three studies included a SF technology manufactured by KOELIS, including Trinity (one study),[83] Urostation (two studies)[81,98]

The diagnostic accuracy results of studies not included in the meta-analyses are summarised by comparisons in *Narrative synthesis results*. 1 (SF vs. CF), 4.4.3.2 (SF vs. SB) and *Software fusion versus software fusion* (SF vs. SF) with further details presented in *Tables 40–44*, *Appendix 7*. *Subgroups* presents a narrative synthesis of diagnostic accuracy results by lesion location, patient type (biopsy naive and experienced), impact of operator experience and PI-RADS scores of all studies included in the systematic review.

Software fusion versus cognitive fusion

Prostate cancer

Five studies compared SF with CF and reported PCa rates.[85,90,91,95,98] All three studies that reported a definition of PCa used the same threshold (GS of 6). Their results are presented in *Table 40*, *Appendix 7*.

Three studies reported higher test-positive rates of PCa for subjects receiving SF compared with CF; two of those reported that the difference was statistically significant,[91,98] and one did not report measures of statistical significance.[95] One study found no statistically significant difference between CF and SF,[85] and one study reported higher test-positive rates for CF but no measures of statistical significance.[90]

Overall, these five studies broadly agree with the findings of the NMA which showed SF was associated with more PCa detection than CF. However, the evidence from these five studies is inconsistent and also at high risk of confounding, notably due to the lack of paired or randomised comparison.

Clinically significant prostate cancer

Five studies compared SF with CF and reported data on CSPCa test-positive rates.[85,90,91,95,98] All studies defined CS cancer as GS of 7 (3 + 4) or higher. Their results are presented in *Table 41*, *Appendix 7*.

Two studies reported no statistically significant difference in test-positive rates of CSPCa between SF and CF,[85,91] whereas one study reported a statistically significant difference in test positive rates

favouring SF.[98] One study reported a higher rate of CSPCa for CF compared with SF, although it did not report whether this difference was statistically significant.[91] One study reported similar rates of CS cancers between SF and CF,[90] and comparable rates of missed, upstaged and equivalent CS biopsy results identified by each targeted biopsy method against concurrent 14-core, systematic biopsy (SF, $p = 0.172$).

Although outcomes between these studies are inconsistent and are at high risk of bias overall, they do not show evidence of a significant difference in rates of CSPCa detection between SF and CF. This evidence is broadly reflective of the meta-analysis findings.

Software fusion and systematic biopsy versus cognitive fusion and systematic biopsy

Two studies that were excluded from the meta-analyses compared PCa testpositive rates between SF with concomitant systematic biopsy, against CF with systematic biopsy.[89,100] Results are summarised in *Table 42*, *Appendix 7*. There was no statistically significant difference in rates of overall PCa and CS cancer detection between the two methods.

Software fusion versus software fusion

Two studies that were not included in the meta-analyses compared biopsy test-positive rates between SF technologies.[81,83] One study compared BioJet with KOELIS Urostation, and one study evaluated three devices: BioJet, KOELIS Trinity and UroNav. Results are summarised in *Table 43*, *Appendix 7*. Both studies found no statistically significant difference in test-positive rates of PCa and CSPCa between SF devices. Overall, this evidence is consistent with the findings of the meta-analyses.

Subgroups

Three subgroups were prespecified in the NICE scope and review protocol: patients with anterior lesions, patients with posterior lesions, and individuals who have had a previous negative prostate biopsy and are referred for a repeat biopsy within 12 months. The review protocol also specified that the following potential factors affecting diagnostic accuracy would be investigated in subgroup analyses: biopsy-naive patients, and operator experience. Test-positive rates by PI-RADS groups (3, 4 and 5) were also summarised, although this subgroup was no pre-specified.

Network meta-analyses for biopsy-naive or prior negative-biopsy subgroups were not conducted due to the limited number of studies included. Absolute probabilities of being classified as having NC or being at different ISUP grades are presented for biopsy-naive or patients with a previous negative biopsy in the meta-analysis results *Model 1a: multinomial synthesis model (base case)*.

Due to the limited evidence, results for the other subgroups (lesion location, operator experience and PI-RADS) are summarised narratively only.

Lesion location

One study[31] reported test-positive estimates by lesion location (anterior, posterior), and found no significant differences in test-positive rates of PCa and CSPCa between SF (BiopSee) and CF for posterior and anterior located lesions. The results are summarised in *Table 45*, *Appendix 7*. Test-positive rates were also stratified by other locations (peripheral and transition zones, NR here) and showed no statistically significant differences between the two methods.

Repeat biopsy and biopsy-naive patients

Test-positive rates for patients receiving a repeat biopsy following a prior negative biopsy and for biopsy-naive patients are presented in *Appendix 7*, *Tables 46* and *47* respectively. Overall, there was no evidence that SF had higher test-positive rates compared with CF in either subgroup. While it is expected that these characteristics may influence the number of positive cancers detected (due to a

different underlying prevalence of cancer in the different populations), there is no evidence that they may affect the relative diagnostic accuracy across biopsy types.

Impact of operator experience

One study evaluated how operator experience impacts the cancer biopsy positivity rates.[89] The results are reported in *Table 48*, *Appendix 7*. Stabile *et al.*[89] evaluated the learning curve for the probability of detecting CSPCa from three urologists, who each used a different biopsy approach on separate patient cohorts: transrectal cognitive biopsy (operator 1), transrectal SF biopsy (operator 2), and transperineal SF biopsy (operator 3). Each urologist had performed at least 200 prostate biopsies but were naive to targeted biopsy techniques. The total number of targeted biopsies performed by operator 1, 2 and 3 were 87, 70 and 87 respectively. Operator experience was defined as the progressive number of targeted biopsies performed by each operator. Stabile *et al.*[89] found that there was a sharp increase in the csPCa biopsy positivity rates in the first 60 procedures, where it plateaued, regardless of the biopsy approach. Operator experience was a significant predictor of the CSPCa biopsy positivity rate in targeted cores, which was more pronounced for the operator who conducted transrectal SF biopsy compared with the other two biopsy approaches.

Prostate imaging – reporting and data system

Six studies reported test positive rates of PCa stratified by PI-RADS score (3, 4 or 5). All four studies that reported any PCa rates for SF and CF found no statistically significant differences by PI-RADS score between the two methods.[31,85,88,95] Similarly, the two studies that compared CS rates between software and CF subgroups found no difference across PI-RADS subgroups.[31,95] One study[81] found that test positive rates of any PCa cancer and CSPCa were comparable between KOELIS Urostation and BioJet after stratifying for PI-RADS score except for PI-RADS Score 4, where the rate of any PCa was higher in the Urostation group compared with BioJet (80% vs. 58.1%, respectively for EF and RF groups, $p = 0.025$), and one study[84] found that rates of CSPCa were higher for PI-RADS 4 patients undergoing TP with BioJet compared with transrectal biopsy with ARTEMIS (43.4% vs. 33.3%), but similar for PI-RADS 3 and 5 subgroups. These results are all based on small ($n < 100$) subgroups and may not be reliable.

Clinical effectiveness results

Biopsy positivity rates

Four studies reported biopsy positivity rates outcomes;[31,84,88,98] their results are presented in *Table 49*, *Appendix 7*. Three studies compared SF with CF and one compared different SF biopsies. None of the studies reported what threshold was used to define biopsy positivity rates. Biopsy positivity rates varied widely, from 21.1% to 75% for SF, and from 33.3% to 67% for CF.

Overall, there is no evidence that biopsy positivity rates differ significantly between SF and CF. Evidence comparing biopsy positivity rates between SF devices is inconclusive, as it limited to one study at high risk of confounding.

Software fusion versus cognitive fusion

Of the three studies that compared SF with CF, two studies did not find any significant difference in biopsy positivity rates between the two methods;[31,88] one study found a statistically significant difference in biopsy positivity rates that favoured SF,[98] although its results may be confounded due to the lack of matching or adjustment between the two study arms.

Comparisons between software fusion technologies

One study[84] found that the biopsy positivity rate of BioJet was significantly higher than that of ARTEMIS (43.5% vs. 21.1% respectively, $p = 0.0002$). However, this finding is at high risk of confounding, due to

differences in biopsy route (transrectal for ARTEMIS, and transperineal for BioJet) and anaesthesia (local for ARTEMIS, and general for BioJet) between the two study arms.

Time taken for biopsy procedure

Two studies compared the time required to complete biopsies between different SF devices. The results of these studies are presented in *Table 6*. Procedure completion duration varied widely, from an average of 13 minutes to 41 minutes; this variation is likely due in part to differences in biopsy and anaesthesia methods.

Overall, there is evidence suggesting that duration of biopsy procedures performed transrectally under local anaesthesia, using BioJet or UroNav (rigid registration) is significantly shorter than with KOELIS Trinity (elastic registration). However, this finding is based on a single, small study and is not conclusive.

Both the studies found statistically significant differences in procedure time between SF devices. Sokolakis *et al.*,[83] found biopsies conducted transrectally under local anaesthesia were significantly faster using BioJet and UroNav devices (both with rigid registration), compared with the KOELIS Trinity device (elastic registration). In Rabah *et al.*[84] the time taken to conduct the biopsy procedure was significantly shorter using the ARTEMIS device, compared to the BioJet device, although this comparison is at high risk of confounding due to differences in biopsy route and anaesthesia method: biopsies conducted with ARTEMIS were performed transrectally under local anaesthesia, whereas biopsies with BioJet were done transperineally under general anaesthesia.

Sokolakis *et al.*,[83] also compared the time taken to conduct the biopsy procedure by operator experience. Four urologists [two trainees who had completed around 40 TRUS-guided biopsies (junior urologists) and two senior urologists who had completed more than 250 TRUS-guided biopsies, but none had any experience of SF] conducted five biopsies with each system. Overall, operative time for the rigid registration fusion devices was shorter for the senior urologists compared to the junior urologists, but there were minimal differences in operating time for the elastic registration fusion device.

Complications and adverse events

Five studies evaluated the AEs and complications arising from the prostate biopsy procedure.[31,83–85,90] Of those, three studies compared complication rates and AEs of SF and CF, and two compared different SF devices.

Overall, there is no evidence of a significant difference in safety outcomes between biopsies conducted with SF and CF, although the evidence is limited by poor reporting and at high risk of confounding due to differences in biopsy routes and anaesthesia methods.

Software fusion versus cognitive fusion

Table 50, *Appendix 7*, presents the results of the three studies that compared safety events between SF and CF. Of those, two found no difference in safety outcomes (severity NR) between the two fusion methods,[85,90] and one found higher rates of grade 1–2 AEs for patients undergoing CF transrectal biopsy under local anaesthesia compared with SF transperineal biopsy under spinal/general anaesthesia. As discussed in *Quality of included studies*, the comparison in this study is at high risk of confounding due to the different biopsy routes and anaesthesia methods.

Comparisons between software fusion technologies

Table 51, *Appendix 7*, summarises the results of the two studies that compared safety outcomes between SF technologies.[83,84] Both studies found similar rates of AEs. Rabah *et al.*[84] found no difference between the rates of urinary retention or haematuria ($p = 0.56$, $p = 0.6$, respectively) between two SF biopsy devices (ARTEMIS and BioJet), although these results are at high risk of confounding due to differences in biopsy route. Sokolakis *et al.*[83] found no severe peri- or post-operative AEs, but mild AEs were reported in most participants, although this was not evaluated statistically.

TABLE 6 Time taken for biopsy procedure

Study	Design	Pop.	Biopsy method			Sample size	*N* cores per ROI[a]	*N* ROI targeted	Effect estimates	*p*-value
			Type	Route	Anaesthesia					
Rabah (2021)[84]	RCT, between patient	BN, RB	SF: ARTEMIS, SF: BioJet	ARTEMIS: TR BioJet: TP	ARTEMIS: LA BioJet: GA	ARTEMIS: 165 BioJet: 142	2–4 cores	All ROI	Mean (SD) BioJet: 41.2 minutes (±0.7) ARTEMIS: 13 minutes (±2.3)	$p < 0.001$
Sokolakis (2021)[83]	Prospective cohort, between patient	BN, RB	SF: BioJet SF: KOELIS SF: UroNav	TR (all)	LA (all)	BioJet: 20 KOELIS: 20 UroNav: 20	2–3 cores	All ROI	Median (IQR) BioJet: 16 minutes (15–18) KOELIS: 28 minutes (26–29) UroNav: 17 minutes (15–20)	$p < 0.001$

BN, biopsy naive; IQR, interquartile range; LA, local anaesthesia; RB, repeat biopsy; ROI, regions of interest; TP, transperineal; TR, transrectal; GA, general anaesthesia.
a Number of cores and number of ROI targeted relate to both targeted biopsy method unless specified otherwise.

Operator preferences between software fusion technologies

One study[83] evaluated the usability of SF biopsy which found evidence suggesting that rigid systems (BioJet and UroNav) are easier to use, compared to the elastic registration system (KOELIS) for transrectal biopsies under local anaesthesia, although this finding is based on a single small study at high risk of bias and is therefore not conclusive.

Sokolakis *et al.*[83] compared the impact of operator experience on the usability of three SF devices, using a system usability scale: a 100-point scale measuring the learnability and user-friendliness of a given technology, with higher values indicating a device or technology is easier to use.[102] Senior urologists also found that the SF devices had better usability compared to the junior urologists. Sokolakis *et al.*[83] also compared the usability of the three SF devices and found that the rigid systems (BioJet and UroNav) were significantly easier to use compared to the elastic registration system (KOELIS). Further results are presented in *Table 52*, *Appendix 7*.

Other outcomes

No evidence was found for the following outcomes specified in the protocol: biopsy sample suitability/quality, number of repeat biopsies performed, procedure completion rates, software failure rate, time to diagnosis, length of hospital stay, re-biopsy rate, hospitalisation, overall survival (OS), PFS, patient- and carer-reported outcomes (including tolerability and HRQoL), barriers and facilitators to implementations, or cost outcomes.

Diagnostic accuracy and clinical effectiveness: summary and conclusions

The evidence identified by the systematic review included a total of 3733 patients who received SF and 2154 individuals with CF from 23 studies. Evidence was included for all devices specified in the protocol, except for Fusion Bx 2.0 and FusionVu. Overall, the evidence for all devices was at high risk of bias. Up to 14 studies were included in NMAs. Analyses compared the relative diagnostic accuracy of SF, CF, CF with concomitant systematic biopsies, SF with systematic biopsies, and systematic biopsies alone.

Our main NMAs looked at how CF compares to SF in classifying patients across the range of ISUP grades. Results must be cautiously interpreted due to the high risk of bias, but suggest that patients undergoing software biopsy may show: (1) a lower probability of being classified as not having cancer, (2) similar probability of being classified as having non-CS cancer (ISUP grade 1) and (3) higher probability of being classified at higher ISUP grades, particularly ISUP 2. Similar results were obtained when comparing between same biopsy methods where both were combined with systematic biopsy.

Additional meta-analyses of cancer detection rates suggest that, compared with CF biopsy, SF may identify more PCa (any grade) (OR 1.30; 95% CrI 1.06 to 1.61). Adding systematic biopsy to cognitive or SF may increase the detection of all PCa and of CS cancer, and from this evidence there is no suggestion that SF with concomitant systematic biopsy is superior to CF with systematic biopsy.

Meta-analyses by individual device showed that compared with CF biopsy, BioJet and Urostation are associated with a higher detection of PCa overall, and that BioJet is associated with more CS cancer, although only one study of BioJet was included. The evidence for all other software devices was insufficient to evaluate their accuracy compared with CF reliably, or to assess whether some SF technologies are more accurate than others.

There was large uncertainty in all estimates due to the limited evidence, particularly for higher ISUP grades and by individual device. Results from studies, excluded from the meta-analyses, broadly reflected these findings. Compared with CF, there was no evidence that the accuracy of SF may differ by lesion location, or between biopsy naive and prior negative biopsy patients, or according to operator experience.

The applicability of the evidence for KOELIS Trinity is uncertain, as it was almost entirely informed by evaluations of a previous version (KOELIS Urostation) without integrated ultrasound. The applicability of the evidence for BiopSee is also limited due to the lack of evaluations under local anaesthesia. There is no evidence comparing the accuracy of Fusion Bx 2.0 and FusionVu with CF, and no evidence for these devices was eligible for inclusion in the indirect comparisons.

Evidence for all other protocol specified outcomes was limited and inconclusive. Overall, there is no evidence that biopsy positivity rates differ significantly between SF and CF, or between SF devices. There was some evidence that systems with rigid registration (BioJet or UroNav) are easier and faster to use than elastic registration (KOELIS Trinity), although this is informed by a single, small study and is not conclusive. Overall, there is no evidence of a significant difference in safety outcomes between biopsies conducted with SF and CF or between SF devices, although the evidence is limited by poor reporting and at high risk of confounding.

No relevant evidence was found for the following outcomes: biopsy sample suitability/quality, number of repeat biopsies performed, procedure completion rates, software failure rate, time to diagnosis, length of hospital stay, time taken for MR image preparation, subsequent PCa management, re-biopsy rate, hospitalisation, OS, PFS, patient- and carer-reported outcomes (including tolerability and HRQoL), barriers and facilitators to implementations.

Additional evidence to inform model structure and parameterisation

Additional evidence was required to inform a number of economic parameters, including (1) PCa prevalence; (2) distribution of test results for cognitive and SF broken down by Gleason grade; (3) test accuracy of cognitive and SF and (4) long-term evidence on outcomes from management strategies for patients with PCa. In addition to the systematic review of diagnostic accuracy and clinical effectiveness, targeted reviews were conducted to identify the most relevant evidence to inform these parameters.

Review of additional prevalence, test results and diagnostic accuracy evidence

Studies included in the systematic review of diagnostic accuracy and clinical effectiveness were reviewed to identify suitable evidence to inform the following economic model parameters: (1) PCa prevalence, estimated from a 'gold-standard' test (template mapping or saturation biopsy with at least 20 cores) and with sufficient granularity (by ISUP grade); (2) distribution of test results for cognitive or SF MRI in PI-RADS 3 + by ISUP grade and (3) accuracy of cognitive or SF MRI in PI-RADS 3 + patients against a 'gold-standard' test, that is comparative studies against template mapping or saturation biopsy for which a composite end point could be derived from the results of both tests.

Due to the lack of evidence from 'gold-standard' tests identified in the systematic review, additional targeted, pragmatic searches were conducted. References from a recent Cochrane systematic review, which included studies on the diagnostic accuracy of MRI-targeted biopsy against template-guided biopsy, were checked for further evidence.[66] As the searches in the Drost *et al.*[66] review were limited to July 2018, pragmatic searches of PubMed and Google Scholar were conducted to identify more recent studies. This search included the following search terms: [(template mapping) OR (saturation) AND (biopsy) AND (prostate)] AND (fusion biopsy).

Studies were prioritised according to the applicability of their population to the NHS. Ten studies were considered potentially eligible to inform at least one of the model parameters of interest. Their characteristics are summarised in *Table 53*, *Appendix 8*. Further details on the prioritisation and limitations of studies informing each of the three model parameters are available in *Appendix 8*.

Review of long-term evidence

To inform economic model parameters on morbidity and mortality outcomes for PCa patients, a targeted, pragmatic review was conducted. Searches included reference checking of evidence reviews informing NICE guidance on the management of PCa (NG131),[10] references included in the PROMIS economic analysis, targeted searches for relevant Cochrane reviews in Cochrane Database of Systematic Reviews (CDSR) and citation searches to identify the most up-to-date follow-up data. Studies evaluating long-terms survival and disease progression outcomes in PCa patients according to prognosis status, either under active surveillance or receiving radical treatment recommended by NICE[12] and described in *Prostate cancer management: active surveillance, watchful waiting and radical treatment options*, were included. Priority was given to larger RCTs with at least 2 years of follow-up, individual patient data (IPD) meta-analyses and large UK cohort studies. Fourteen studies, including 12 RCTs,[55,59–61,103–110] 1 IPD meta-analysis[111] and 1 cohort study[112] were identified and are listed in *Table 60*, *Appendix 8*. *Table 61*, *Appendix 8*, provides a brief summary of key trials considered most reflective of current NHS practice. The process for prioritising the final set of studies included in the model is described in *Clinical effectiveness results*.

Three RCTs evaluated the effect of radical prostatectomy in relation to an observation-based strategy in clinically localised PCa: SPCG4, PIVOT and ProtecT.[55,109,110] The comparators differed across trials between observation (PIVOT), watchful waiting (SPCG4) and active monitoring (PROTecT). Both SPCG4 and PROTecT included patients with localised, non-metastatic cancer, and PIVOT included low-to high-risk PCa patients. PROTecT was conducted in the UK, PIVOT in the USA and SPCG4 in Sweden, Finland and Iceland. Follow-up duration ranged from 10 years (PROTecT) to 29 years (SPCG4). PROTecT was the most recent study (1999 to 2009, compared with 1994–2002 for PIVOT and 1989–9 for SPCG4). None of the studies used mpMRI to diagnose patients.

Only SPCG4 found a significant effect for prostatectomy on OS, with the more contemporary studies not identifying an effect on all-cause mortality. PROTecT, which compared radical prostatectomy, radiotherapy and a passive management strategy (active monitoring) found that despite surgery and radiotherapy being associated with lower incidences of disease progression and metastases than active monitoring, at a median of 10 years, PCa–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments.

Of the trials identified that focused on treatments for intermediate- to high-risk disease, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) was the largest, most recent and only study conducted in the UK.[59] STAMPEDE evaluated treatments for high-risk or metastatic or recurring cancer.[113] A large UK-based RCT of 2962 men, conducted between 2005 and 2013 with a median follow-up of 6.5 years, evaluated three drug treatment combinations for high-risk or metastatic cancer including zoledronic acid and DTX, as used in addition to SOC. While zoledronic acid showed no evidence of survival improvement, DTX led to improved survival and an increase in AEs.

Other trials with high-risk and/or metastatic disease included HYPO-RT-PC, GETUG-12 and TAX-3501.[60,61,107] HYPO-RT-PC compared hypofractionated radiotherapy with conventional radiotherapy in 1180 intermediate- to high-risk cancer patients and found that hypofractionated radiotherapy was non-inferior in terms of failure-free survival. GETUG-12 and TAX-3501. GETUG-12 evaluated the effectiveness of adding DTX, zoledronic acid/estramustine, or both to first-line long-term hormone therapy in patients with high-risk PCa (Gleason 8–10) and TAX-3501 evaluated the addition of DTX to leuprolide against leuprolide alone in metastatic patients following radical prostatectomy. Both were smaller (GETUG-12 included 413 participants, and TAX-3501 had 228 participants). At median follow-up of 12 years, GETUG-12 found that DTX chemotherapy reduces the risk of clinical relapse or mortality in high-risk PCa. TAX-3501 was terminated at 3.4 years and was underpowered to detect differences in PFS between study arms.

Additionally, evidence was sought on UK studies reporting outcomes by the five-stage CPG risk stratification system that currently supports treatment decisions in the UK NHS.[12] Only one large cohort study was identified.[112] The study included diagnostic data from 10,139 men with non-metastatic PCa from the Public Health England National Cancer Registration Service and had a median follow-up of 6.9 years, and found that a five-stratum risk stratification system outperformed the previous three-stratum risk stratification system used in the UK in predicting the risk of PCa death at diagnosis in men with primary non-metastatic PCa.

Overall, there is relevant evidence on the effectiveness of radical versus 'conservative' treatment options in delaying progression to metastatic disease, despite the limited observed impacts on mortality. The most contemporary and relevant evidence is from PROTecT, a recent, UK-based study.[114] Although there is UK-based evidence favouring the prognostic ability of a 5-level score for PCa mortality, there is no evidence on treatment effectiveness stratified by CPG scores.

Chapter 4 Assessment of evidence on the cost-effectiveness of software fusion biopsy

Overview

In the next sections, we provide an overview of published cost-effectiveness studies on the use of SF biopsy systems in comparison with CF for targeted prostate biopsy (see *Methodology of the cost-effectiveness of software fusion biopsy for suspected prostate cancer* and *Results of the review of the cost-effectiveness of* MRI *fusion biopsy for suspected prostate cancer*), to determine generalisability of the evidence to inform this assessment's decision problem. In addition, this chapter presents a targeted review of diagnostic cost-effectiveness studies (see *Methodology of the additional targeted reviews to support model conceptualisation* and *Results of the additional targeted reviews to support model conceptualisation*), which model prostate biopsy procedures to identify aPCa (same point in the diagnostic pathway as the interventions in this assessment). This targeted review is done with the aim to support the conceptualisation and parameterisation of a de novo decision-analytic model.

Methodology of the cost-effectiveness of software fusion biopsy for suspected prostate cancer

The methodology of the systematic review of published cost-effectiveness studies comparing SF biopsy systems with CF for targeted prostate biopsy in men with suspected PCa is described below. The review aimed to assess the generalisability of existing evidence to the decision problem defined by the NICE DAR scope, and provide a brief overview of the model structure, parameterisation and results. Titles identified for inclusion in this review, are subsequently included in the review to inform the conceptualisation and development of the de novo model alongside other studies.

Literature searches

The results of the systematic literature searches carried out to inform the clinical effectiveness of technologies described in *Systematic review methods (study selection, data extraction, quality assessment)* were used to identify relevant cost-effectiveness studies of SF systems compared to CF for targeted biopsy in men with suspected PCa.

Study selection

Full economic evaluations that consider both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses) were considered for inclusion. A broad range of economic evidence on the use of MRI fusion systems was considered eligible, including economic evaluations conducted alongside trials, studies using modelling approaches and analyses of administrative databased. The inclusion criteria also defined the:

- population as men with an elevated PSA level and/or abnormal DRE who had suspicious lesion(s) detected by (bi- or multiparametric) MRI
- interventions as targeted transperineal or transrectal prostate biopsy using MRI fusion software with or without systematic biopsy, under local or general anaesthesia intervention
- comparators as targeted transperineal or transrectal prostate biopsy using CF with or without systematic biopsy, under local or general anaesthesia.

Studies reporting only resource use, costs or HRQoL were excluded from the review, but considered to support the parametrisation of the de novo model.

The information submitted by the companies in response to NICE and the EAG's requests for information was also reviewed to identify economic studies that complied with the inclusion criteria described above.

Studies identified by the search strategies (see *Appendix 1*) were screened and selected through a two-stage process: (1) titles and abstracts identified by the bibliographic search were screened for possible inclusion, and (2) full texts of potentially relevant records were obtained and screened for inclusion. The process was performed independently by two researchers (HP and AD) with any disagreement resolved by consensus.

Quality appraisal

Cost-effectiveness evidence selected for inclusion was quality assessed using a checklist tool developed for the assessment of model-based economic evaluations of diagnostic tests.[115]

Synthesis of evidence

The characteristics and key findings of the included economic evidence were narratively summarised and tabulated for comparison. The extracted information included:

- the perspective of analysis;
- the comparators and its positioning in the diagnostic pathway, study population and setting, main analytic approaches (e.g. analysis of individual patient data/decision-analytic model), primary outcomes of the economic analysis;
- details of adjustment for HRQoL, resource usage (direct and indirect costs);
- estimates of incremental cost-effectiveness and how uncertainty was quantified (e.g. deterministic/probabilistic sensitivity analysis).

The relevance of existing economic evidence to the current decision problem in the NICE DAR scope was assessed based on:

1. consistency with the decision problem being considered in this assessment, including relevance to the UK
2. relevance of outputs for decision-making (i.e. to estimate long-term NHS costs and QALYs based on morbidity and mortality associated with PCa tailoring according to patient prognosis and preferences)
3. the model flexibility which allows the consideration of different subgroups (e.g. patients with previous negative biopsy results) and potential effect modifiers of diagnostic accuracy (e.g. operator experience).

Methodology of the additional targeted reviews to support model conceptualisation

Given an expected dearth of evidence on the cost-effectiveness of biopsies using SF biopsy systems compared to biopsies using CF in the UK context, we performed additional targeted reviews of cost-effectiveness evidence of diagnostic strategies at the point of biopsy to support the model conceptualisation. These aimed to (1) identify value components of the biopsy approaches, (2) characterise alternative mechanisms of evidence linkage from disease prevalence, diagnostic accuracy, choice of treatment to final outcomes and (3) identify any UK relevant sources of evidence.

Literature searches

We screened cost-effectiveness modelling studies identified by the main search described in *Systematic review methods (study selection, data extraction, quality assessment)* to identify evaluations of diagnostic strategies in the same diagnostic pathway position proposed for SF biopsy systems (i.e. at the point of biopsy), but which do not fulfil the full inclusion criteria for the population, interventions and comparators defined for the main cost-effectiveness review (see *Methodology of the cost-effectiveness of*

software fusion biopsy for suspected prostate cancer). We also considered for inclusion cost-effectiveness modelling studies identified in the cost-effectiveness reviews conducted for a previous assessment of the cost-effectiveness of TP for diagnosing PCa recently developed to inform NICE guidance.[116] Studies included in the review of cost-effectiveness studies in scope with this assessment (see *Methodology of the cost-effectiveness of software fusion biopsy for suspected prostate cancer*) were also included in the targeted review.

Study selection

We included 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. The relevance of these studies to inform the model conceptualisation under the current decision problem was assessed as described in *Results of the review of the cost-effectiveness of* MRI *fusion biopsy for suspected prostate cancer*.

Quality appraisal

Given the pragmatic nature of this review and its aims, identified studies did not undergo a formal quality appraisal.

Synthesis of evidence

The studies identified as potentially relevant were summarised in tabular form. A subset of the studies identified was selected for detailed extraction, if they were model-based cost-effectiveness studies which complied with at least the following criteria:

- UK-relevant evaluations of alternative prostate biopsy approaches
- UK policy-relevant assessments of diagnostic tests for PCa or
- evaluations comparing alternative MRI-influenced biopsy approaches.

The value of diagnostic technologies is to a large extent dependent on how downstream clinical management choices based on diagnostic information impact on final outcomes. Therefore, most of these value components rely on indirect mechanisms of value accrual to determine trade-offs in final outcomes, health system costs or both, the balance of which determines the net value of the technologies.

For the subset of studies considered most relevant for the conceptualisation, we synthesised narratively the following types of evidence:

1. key components of value, that is, ways in which the diagnostic technologies may lead to impacts on individuals' health and/or system cost compared to their alternatives (i.e. the comparators)
2. characterisation of the modelling/evidence-linkage approaches used to quantify the key indirect components of value, identifying underlying structural assumptions
3. value drivers, that is, factors expected to have a considerable impact on cost-effectiveness
4. main areas of uncertainty and evidence scarcity, as well as approaches taken to deal with these issues
5. sources of heterogeneity, and approaches taken to handle heterogeneity
6. data sources relevant to the UK decision making-context.

The focus of the narrative synthesis was placed on the characterisation of value accrual mechanisms that may be relevant to the current assessment of SF biopsy systems, rather than exhaustive characterisation of all value components.

Methodology of the review of economic evidence provided by the companies

We reviewed the economic evidence submitted by the companies in response to requests for information (RFIs) by NICE and the EAG. We listed this economic evidence grouped into three categories:

1. full economic evaluations that consider both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses)
2. resource use and cost data
3. other.

Full economic evaluations were considered for inclusion in one of the two other economic reviews (see *Methodology of the cost-effectiveness of software fusion biopsy for suspected prostate cancer* or *Methodology of the additional targeted reviews to support model conceptualisation*) as appropriate given their study characteristics.

Resource use and cost data were considered for the parametrisation of the de novo model.

Results of the review of the cost-effectiveness of magnetic resonance imaging fusion biopsy for suspected prostate cancer

Search and studies identified

Records from the searches described in *Systematic review methods (study selection, data extraction, quality assessment)* were examined to identify potentially relevant economic records. *Figure 17* in *Appendix 9* shows the PRISMA flow diagram for this review which details results at each stage of the review. A total of 27 studies were identified as being potentially relevant to the assessment of cost-effectiveness of SF biopsy versus CF biopsy. After screening the titles and/or abstracts, 26 studies were excluded. One full-text publication was retrieved and assessed for inclusion, Pahwa *et al.*[117] This study met the full set of inclusion criteria and was included in this review of SF biopsy for suspected PCa.

We note that the economic evidence submitted by the companies in response to information requests (RFIs) by NICE and the EAG largely consisted of resource use and cost data (mostly acquisition, maintenance, and training costs) on the SF they commercialise. This evidence was considered for the parameterisation of the model and is discussed in *Biopsy procedure adverse events costs*.

In addition to this, KOELIS and Kebomed also submitted economic evidence consisting of:

- a cost-analysis in a Japanese setting
- two business case analysis
- a slide set describing what is referred to as a cost–benefit analysis comparing MRI-influenced biopsy using KOELIS Trinity with TRUS-guided biopsy in the US healthcare setting.

This evidence is not considered further in this report, as the economic analyses did not comply with the inclusion criteria of this review. For example, the cost–benefit analysis presented in the slide set did not appear to include HRQoL outcomes (only cost and diagnostic outcomes). Furthermore, the evidence provided lacked sufficient detail to be informative for the model parameterisation (e.g. the methodology, sources of evidence and assumptions were not clearly described in the business case analyses) and it was not peer-reviewed.

Review of Pahwa et al.

The Pahwa *et al.*[117] study is summarised in *Table 7*. The quality assessment of this study is reported in *Table 62* (see *Appendix 9*).

TABLE 7 Summary of cost-effectiveness study of Pahwa *et al.*[117]

Study country, perspective	Population	Population characteristics	Diagnostic strategies	Analytical approach, time horizon	Outcomes
USA, not stated	Biopsy-naive men with indication for biopsy due to elevated PSA levels or CS DRE findings	Mean age 65 years PCa prevalence 50% Probability of CSPCa (given PCa) 50%	1. Systematic TRUS biopsy for all. 2–4. Non-contrast mpMRI for all followed by MRI-influenced biopsy (2. CF, 3. MRI fusion or 4. in-bore) for those with clinically suspect lesions on mpMRI. Those without mpMRI detected suspicious lesions do not receive biopsy. 5–7. Non-contrast mpMRI followed by MRI-influenced biopsy (5. CF, 7. MRI fusion or 7. in-bore) for those with clinically suspect lesions on mpMRI. Those without MRI detected lesions receive systematic TRUS biopsy	Cohort decision tree model Lifetime horizon	Costs QALYs NHB ICER

Pahwa *et al.*[117] evaluated the cost-effectiveness of mpMRI followed by MRI-influenced biopsy using alternative MRI-influenced methods (SF, CF and in-bore MRI biopsy) compared to systematic TRUS biopsy in individuals with suspected PCa in the US healthcare system. The study's perspective is not explicitly stated, but the costs included suggest a societal perspective.

The study population consisted of biopsy-naive men with elevated PSA levels and/or CS DRE findings. In the base-case analysis, the cohort had a mean age of 65 years, and a PCa prevalence of 50%; this prevalence estimate was varied in subgroup analyses by age groups. Cancer prevalence by age was sourced from a study which reviewed US cancer statistics and autopsy data; it is unclear if this estimate is reflective of a biopsy-naive population. The probability that PCa is CS cancer [defined as tumour volume > 0.5 cm^3, a GS higher than 6, or with a Gleason pattern of 4 or 5 (if GS ≤ 6) or not confined to the prostate] was assumed to be 50%, based on a previous cost-effectiveness study.

The study compared three diagnostic strategy types with the following test sequences: (1) systematic biopsy for all individuals, (2) mpMRI for all individuals followed by MRI-influenced biopsy for those with clinically suspicious lesions detected on mpMRI (positive mpMRI) and no further testing for those with negative MRI findings and (3) mpMRI for all individuals followed by MRI-influenced biopsy for those with a positive mpMRI result and TRUS systematic biopsy for those with a negative mpMRI result. Each strategy type with a MRI-influenced component (2 and 3) was evaluated separately for each alternative MRI-influenced method (SF, CF and in-bore MRI biopsy). Individuals who did not undergo biopsy or had a negative result did not receive treatment. Those who undergo biopsy and have a positive result are classified according to cancer significance and receive treatment consisting of a mix of active surveillance, watchful waiting, ADT and radical treatments. mpMRI was described as non-contrast and biopsy as TRUS; no further details on the specifications of the test were provided.

The decision model consisted of a cohort decision tree structure which characterised diagnostic pathways, treatment allocation and assigned lifetime payoffs by classification and treatment allocated. It started by classifying individuals according to their true disease status including clinical significance [no PCa, clinically non-significant (CNS) or significant PCa]. Individuals were subsequently classified according to the diagnostic accuracy of test sequences in each strategy according to diagnosis results and their true underlying disease status (including disease significance).

The metrics of diagnostic accuracy for the different biopsy approaches included the sensitivity to detect (1) cancer (for systematic biopsy only), (2) CS cancer (only for targeted biopsies), (3) clinically insignificant cancer (only for targeted biopsies) and (4) a probability of correctly identifying the tumour aggressiveness. In addition, all biopsy approaches were assumed to be 100% specific to detect PCa. The diagnostic accuracy of SF biopsy was NR as specific to any particular software fusion technology. The evidence used to inform the sensitivity of SF to detect clinically insignificant cancer was pooled from various MRI-fusion systems, while the sensitivity to detect CNS cancer was informed by evidence on ARTEMIS™ ProFuse.

The costs considered in the model included the costs of MRI, biopsies (systematic, CF, SF or in-gantry), histopathological evaluation, workdays lost, biopsy complications and lifetime treatment (cost payoffs). The cost of SF (mean US$ 731 including physician fees) applied in the model was not technology specific.

The model does not consider the impact on HRQoL of biopsy complications.

Treatments considered in the model included radical prostatectomy, external beam radiation therapy, brachytherapy, ADT, active surveillance and watchful waiting. Treatment distributions conditional on diagnosed clinical significance were sourced from a US registry and supplemented by assumptions.

The QALY pay-offs at each terminal node are conditional on the cancer presence (and its clinical significance), treatment status (treated, untreated), and type of treatment (independent of the clinical significance of cancer). The lifetime QALY pay-offs for treated patients are mostly derived from a previous cost-effectiveness study[118] which used a state transition Markov model to compare expectant management (active surveillance or watchful waiting) with initial treatments (brachytherapy, intensity-modulated radiation, radical prostatectomy) on men with low-risk, clinically localised PCa. The studies pooled to inform the treatment effectiveness in the external model are not clearly described. The Markov model captures disease progression and recurrence, short- and long-term AEs from treatment choice on lifetime quality-adjusted life expectancies (QALEs). The Pahwa *et al.*[117] model does not capture the probability of developing new cancer during the lifetime for men with NC.

The cost pay-offs are conditional on the diagnostic status (diagnosed, undiagnosed/later diagnosed), treatments received (for diagnosed patients) and the clinical significance of cancer (for undiagnosed or later diagnosed patients). The lifetime costs are also derived from Hayes *et al.* model.[118] As the risk of developing new cancer is not considered, no lifetime cost is assigned to men with NC.

Cost-effectiveness results are expressed as fully incremental cost-effectiveness ratios (ICERs) and net health benefits (NHBs) at US $50,000 per additional QALY. Sensitivity analysis included probabilistic sensitivity analysis, one-way sensitivity analyses and scenario analysis. The scenario analysis considers the cost-effectiveness of each strategy at three alternative Gleason cut-off scores for CS cancer (3 + 4, 4 + 3, ≥8). The authors also present subgroup analysis by three age subgroups (41–50 years; 51–60 years; and 61–70 years), with prevalence and life expectancy varying across subgroups.

Pahwa *et al.* cost-effectiveness results

The cost-effectiveness base-case results are summarised in *Table 8*. Strategy 4, consisting of mpMRI followed by in-bore biopsy for those who test positive on imaging and no further biopsy for those with a negative imaging result, had the highest NHB at US $50,000 per additional QALY.

Strategies with CF components (2 and 5) have higher NHB than the corresponding strategies with SF biopsy (3 and 6) than those of MRI-influenced fusion biopsy in both the base-case analysis and for scenario analysis where the definition of CS disease is varied. SF biopsy generally results in lower total QALYs and higher total costs compared to cognitive biopsy.

TABLE 8 Summary of cost-effectiveness results in Pahwa *et al.*

	Total costs (US$)	Total QALYs	ICER (US$ per QALY)	NHB (QALYs)[a] (95% CI)
Strategy 2: mpMRI, CF biopsy, no systematic biopsy if negative	17,630	9.250	–	8.997 (7.34 to 10.21)
Strategy 4: mpMRI, in-bore biopsy, no systematic biopsy if negative	17,870	9.308	$4147	8.950 (7.54 to 10.21)
Strategy 3: mpMRI, SF biopsy, no systematic biopsy if negative	18,608	9.198	Dominated	8.826 (7.33 to 10.19)
Strategy 5: mpMRI, cognitive biopsy, systematic biopsy if negative	18,802	9.269	Dominated	8.893 (7.45 to 10.18)
Strategy 7: mpMRI, in-bore biopsy, systematic biopsy if negative	19,042	9.326	$65,111	8.946 (7.60 to 10.17)
Strategy 6: mpMRI, SF biopsy, systematic biopsy if negative	19,780	9.217	Dominated	8.822 (7.43 to 10.16)
Strategy 1: Systematic biopsy	19,133	9.082	Dominated	8.699 (7.08 to 10.15)

a At US $50,000 per additional QALY.

The authors claimed that the one-way sensitivity analysis results suggest that the cost-effectiveness drivers are cancer prevalence, the proportion of CS cancer and the sensitivity of MRI. However, we note that results are not presented and that the ranges within which the model parameters were varied do not seem to follow any other rationale other than assuming great parameter uncertainty and testing extreme input values. Scenario and subgroup analysis results were consistent with those of the base-case analysis.

Generalisability and relevance of the Pahwa *et al.* study to the decision problem in the current assessment

The Pahwa *et al.*[117] study has several features that limit its generalisability and relevance to the decision problem in the current assessment.

Firstly, the study's perspective does not correspond to the NICE reference case, as it seems to take a US societal perspective rather than that of NHS and PSS. This difference in perspective implies that the opportunity costs considered in Pahwa *et al.*[117] are unlikely to be comparable to those relevant to this assessment. It also means that the range of included costs in Pahwa *et al.*[117] are not directly generalisable to this assessment.

Another area where there is a lack of alignment between this assessment and Pahwa *et al.*[117] is the study population considered and how this links to the position of the tests in the diagnostic pathway. Since the study predates the routine use of MRI to screen individuals with suspected PCa for biopsy, the study population is not limited to individuals with a MRI Likert or PI-RADS score ≥ 3. The study population is also limited to those individuals without a prior biopsy. Population characteristics such as prevalence, a cost-effectiveness driver in Pahwa *et al.*,[117] are, therefore, likely to differ between this study's population and the population defined by the scope of this assessment, thus limiting the generalisability of the study findings to this assessment.

The diagnostic pathway in the study also differs from the one currently recommended in UK clinical practice, as it does not allow for repeat biopsies.

The way in which diagnostic accuracy was modelled in Pahwa *et al.*[117] is another limitation, as the tests classified individuals according to PCa presence and its clinical significance. Clinical recommendations for management of PCa in the UK are made based on prognostic risk (characterised via a five-tier risk score), rather than clinical significance of disease alone. Therefore, the diagnostic classification in the study is insufficiently granular to allow linking classification to clinical management choices in the UK context.

Another issue in Pahwa *et al.*[117] is that it did not model a specific SF technology. The way in which the direct costs and diagnostic accuracy of SF were modelled implies that these estimates are equivalent across different technologies. This assumption is not justified, but the equivalence of the direct costs of alternative technologies is debatable, even if diagnostic accuracy can be assumed equivalent, given the similar functioning of these software systems. The study also does not model or discuss potential diagnostic accuracy and/or cost modifying factors, such as the method of estimation (rigid vs. elastic), the biopsy sampling method (targeted alone vs. combined), the biopsy approach (transperineal vs. transrectal, local anaesthesia vs. general anaesthesia), etc. These factors have been identified in the scope of this assessment as features of interest and may impact on the cost-effectiveness results.

Finally, the evidence linkage between clinical management and final outcomes in the Pahwa *et al.*[117] model lacks flexibility to allow adaptation to other jurisdictions, since these outcomes are modelled as pay-offs estimated from an external US-Markov model. It is unclear whether the distribution of treatments used to weigh the costs and QALYs pay-offs in the study is likely to match what is observed in a UK setting. However, even if the treatment distribution was reflective of UK clinical practice, the external Markov model also quantifies lifetime outcomes specific to the US setting. Therefore, it is not possible to easily implement alternative UK relevant treatment choices and reflect the impact of these on long-term cost and HRQoL outcomes.

Therefore, the EAG concludes that the Pahwa *et al.*[117] study cannot directly inform, or be adapted to inform, the decision problem in the current assessment.

Results of the additional targeted reviews to support model conceptualisation

The results of the searches are given in detail in *Appendix 1*. In total, 15 cost-effectiveness models[116,119–133] were considered potentially relevant to inform the de novo model conceptualisation for inclusion. These studies are summarised in *Table 63*, *Appendix 9*.

Of the 15 cost-effectiveness models identified at the first stage of the review, 9 were selected for a more in-depth review, as these were identified as the most appropriate to support the conceptualisation of the de novo model given the relevance of:

- the comparisons and position in the diagnostic pathway – studies which compared biopsies conducted with MRI-influence methods (i.e. targeted and/or combined biopsies) for PCa diagnosis;[119,120,124,129,130]
- UK policy relevance.[116,121,123,125,126]

Studies included in the model conceptualisation review

A summary description of the subset of identified studies[116,119–121,123–126,129,130] included in the model conceptualisation review is provided in this section, followed by a critical review (see *Critical review*). A summary table of these studies is presented in *Appendix 9* (*Table 64*) alongside further details on the studies.

Scope of the study

The population in the majority of studies comprises individuals with suspected PCa, who enter a secondary care diagnostic pathway,[116,119,121,123,125,126,129,130] while other studies consider patients being screened for PCa.[120,124]

A variety of biopsy approaches were compared in the studies; these differ by route of access (transrectal vs. transperineal), type of anaesthesia used (general vs. local), sample collection method (targeted vs. systematic vs. mapping or saturation biopsy) and MRI-influenced methods (SF, CF and in-bore MRI). Two models are of particular interest for UK policy. Souto-Ribeiro *et al.*[116] reports a previous DAR by the Southampton EAG. This study established two main comparisons between biopsy approaches: (1) local anaesthetic transperineal (LATP) biopsy (with any type of biopsy device) versus local anaesthesia transrectal ultrasound (LATRUS) biopsy and general anaesthesia transperineal (GATP) biopsy and (2) LATP with specific freehand devices versus LATRUS and versus transperineal transrectal biopsy conducted with a grid and stepping device conducted under local or general anaesthetic. The NICE CG131 model[123] evaluated alternative follow-up strategies of individuals with suspected PCa and placed little emphasis on alternative biopsy approaches.

Some studies modelled the possibility of repeat biopsies.[116,119,121,125,126] These studies varied in how they specified: who would receive a repeat biopsy, what proportion of those eligible would receive one (or more) repeat biopsies, the type of biopsy received, and the number of subsequent biopsies allowed (if more than one).

Classification

In most studies, the diagnostic accuracy of the biopsy procedure classifies individuals as not having PCa or having non-CS or CSPCa.[116,119,121,123–126,129,130] The exception was the study by Hao *et al.*, in which classification is done by ISUP grade.[120] Both types of classification are usually defined by histopathological features of the biopsied lesions (graded according to GSs).

The specificity of biopsy, to detect PCa, is assumed perfect across most models, therefore individuals without PCa cannot be misclassified as having the disease. However, some studies considered the possibility of individuals with CNS PCa misclassified as CS.[124,129,130]

Choice of clinical management

Decisions on patient management at diagnosis could be determined by the biopsy diagnostic outcomes alone[125,126,129,130] or with other factors also influencing treatment allocation.[116,119–121,123,124]

In three models[125,126,129,130] patient management was attributed according to individuals' classification in terms of disease presence and clinical significance of disease. This classification was established based on the diagnostic accuracy of the biopsy approaches. Some models tracked the individuals' underlying cancer prognostic risk and used this information, jointly with the diagnostic outcomes, to allocate treatment. For example, the Southampton DAR model[116] allocated treatments based on disease presence, clinical significance of disease and underlying cancer risk distribution.

For patients diagnosed with PCa, the primary treatment allocation was conditional on:

1. diagnosed clinical significance of disease, true cancer risk category and disease spread[116,123]
2. diagnosed disease clinical significance[125,126,129,130]
3. GS, PSA level and age[124]
4. type of biopsy (targeted or systematic), cancer risk category and age.[119]

A range of evidence sources were used to inform the distribution of treatments for diagnosed PCa. Amongst these, the following are relevant in the UK context:

- the Southampton DAR model[116] based treatment distribution by risk category on UK clinical guidance and observed treatment allocation from national audit data[134]
- the NICE NG131 model[123] used observed primary treatment distributions by risk category from UK registry data[112]
- the PROMIS trial[125,126] assumed that treatment choice was guided by diagnosed disease clinical significance alone.

Individuals diagnosed as not having PCa were discharged to follow-up,[121,123,125,126] or returned to the screening schedule.[120,124] One study[116] conditioned the individuals' subsequent management after a no PCa diagnosis on whether they had been misclassified [true negative (TN) results led to discharge and false negative (FN) results (patients with PCa of any risk category) to routine PSA monitoring]. This assumption was not justified, and it is not clear how in clinical practice the two groups of individuals (TN and FN) would be distinguished so that distinct treatment decisions could be made for each group.

Outcomes

The evidence linkage approaches applied in the identified studies to connect patient classification and subsequent treatment choices with longer-term outcomes differed in whether PCa progression was explicitly modelled as an intermediate outcome or not.

Only two studies did not model disease progression.[129,130] Pahwa *et al.*[129] conditioned lifetime QALYs and cost payoffs on diagnostic status (i.e. whether cancer had been diagnosed or remained undiagnosed), underlying true disease status (no PCa, CNS or CSPCa) and type of treatment received. Venderink *et al.*[130] used a long-term Markov model that only allowed for transitions from alive to death states, with survival conditional on type of treatment received and the underlying true disease clinical significance, with the diagnostic status (diagnosed vs. undiagnosed cancer) determining whether individuals received treatment.[130]

All other models considered disease progression from localised to metastatic disease, although health states and possible state transitions varied across models.[116,119,121,123–126] Some studies modelled progression from localised to metastatic disease, and conditioned disease progression on underlying risk category and being correctly diagnosed/treatment received.[119,121,125,126] Other studies modelled sequential disease progression across disease risk categories (from low- to intermediate-risk and from the latter to high-risk disease) for localised disease followed by progression from the high-risk localised to metastatic disease. In these models, the probabilities of transitioning to later disease stages were conditioned on the underlying true disease status (including risk category) and being diagnosed as having CS or non-significant disease.[116,123] The screening studies modelled progression differently in the preclinical stage and in the clinical states.[120,124]

All the disease progression models shared the assumption that PCa mortality only applied to patients with metastatic disease. Treatment for patients identified as having cancer reduced disease progression to metastatic cancer compared to untreated patients, and thus reduced the probability of dying from PCa for these patients. The transition probabilities for treated and untreated patients in the Markov disease progression were estimated by calibration or partially observable Markov model decision processes (as progression is an unobservable process). The data sources and calibration methods, used to estimate these transition probabilities, differed across models and are reviewed below for the two most relevant UK models. Details on the remaining models are in *Appendix 9*.

The PROMIS model[125,126] calibrated the probability of progressing from localised to metastatic disease by risk category and treatment received, combining risk-stratified survival data and proportion of patients with metastases from the PCa Intervention versus Observation Trial (PIVOT),[109] with the mortality in the metastatic subgroup of the STAMPEDE trial.[113] The PIVOT observation arm was used to inform the transition probabilities for individuals with PCa who did not receive active treatment (due to correct classification on misclassification depending on the risk category). The PIVOT radical prostatectomy arm was used to inform the transition probabilities for those treated with active treatment (true

positives with intermediate and high-risk cancer). The 'treatment' effects of being diagnosed on disease progression were thus informed by randomised comparative efficacy evidence.

The model used in the previous DAR[116] and in the NICE NG131 model[123] disaggregated disease progression by cancer risk categories and used calibration to estimate transition probabilities. The calibration method estimated transition probabilities first for the transition from high-risk to metastatic disease, then from intermediate- to high-risk disease, and finally from low-risk to intermediate-risk disease can be derived. The calibration was done separately for the undetected and detected cancers using different data sources. Transition probabilities for the undetected cancers used cumulative metastases risk rates by cancer risk category from the watchful waiting arm in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG4) trial[135] jointly with and Swedish life-table data (from 1999 to reflect background mortality in the trial). For the diagnosed cancers, the data sources for calibration included: cancer-specific survival by risk category sourced from a UK registry study,[112] all-cause survival for people with metastatic PCa from the STAMPEDE trial,[59] and UK life-table (from 2010 to 2022 to reflect background trial mortality in STAMPEDE). Thus, this calibration approach relies on an indirect naive comparison to derive the 'treatment' effects of being diagnosed on disease progression, which may introduce bias on the probabilities of disease progression used in the model.

In general, disease progression models, survival outcomes for individuals with PCa were conditional on having metastatic disease and age. Two models[116,123] further conditioned mortality on whether metastatic disease was diagnosed (and therefore, received treatment for metastatic cancer) or not. Metastatic mortality data sources of relevance to the UK context include different publications of the STAMPEDE study, a UK-based trial which compared the survival outcomes of men with newly diagnosed metastatic, high-risk or node-positive cancer treated with alternative cancer treatments. The PROMIS and related models estimated the probability of metastatic death using early (median follow-up of 20 months) survival data of men with newly diagnosed metastatic PCa from the control arm (who received SOC consisting of androgen depleting therapy) of the STAMPEDE trial. The NICE NG131 and related models used a later survival data cut (median follow-up 43 months) from the DTX and control arms of the STAMPEDE trial that includes individuals with metastatic and non-metastatic disease.[59]

Health-related quality-of-life outcomes of patients with PCa were most frequently conditioned on having metastatic disease,[116,119–121,123–126] age[116,119–121,123–126] and treatment received and time since treatment initiation,[120,124,130] although other factors having been considered in select models (see *Appendix 9*). The UK-relevant utility sources for patients with PCa in the long-term outcome models include Torvinen *et al.*[136] – for the disutility of metastatic disease, Ara and Brazier, 2010[137] – for the disutility of ageing, Mowatt *et al.*[133] – for the disutility of treatment-related AEs (combined with rates of AEs) from Donovan *et al.*[138].

Most models considered the cost of treatment for patients with diagnosed localised or locally advanced PCa (radical treatment or active surveillance)[116,119–121,123–126,129,130] and management of treatment AEs.[116,121,123,125,126] Patients with undiagnosed PCa would incur the costs of routine follow-up[116,119,121,123,125,126,129] or of delayed radical treatment.[129] The studies also considered the costs of metastatic disease treatment with or without staging and follow-up tests.[116,119,121,123–126] Two models assumed diagnosed metastatic disease would be treated differently if diagnosed (DTX would be added to androgen depleting therapy) compared to undiagnosed metastatic disease and that treatment with DTX would vary with age.[116,123] Some models included an end-of-life cost for patients who died from PCa,[116,119,120,123,124] with one study conditioning the end-of-life costs on age at death.[124]

The costs of individuals who did not have PCa were not clearly reported for most models, but, where reported, consisted of the costs of routine follow-up.[116,119,123,124]

In UK-relevant models, treatment and follow-up resource use was informed mainly by UK [clinical and technology appraisal (TA)] guidance, as well as other published data (e.g. a randomised control

trial informed AE rates of treatment[138]) and supplemented with assumptions. End-of-life costs were uprated to the relevant price year based on Round *et al.*[139] Unit costs were sourced mainly from national published sources.

Critical review

Value components

The value components of the biopsy tests, in the studies included in the conceptualisation review, are summarised in *Table 65* (see *Appendix 9*), which distinguishes between value components that require evidence linkage and those that are direct impacts of the tests. Direct value components of biopsy included the costs of the procedure, and its AEs (with associated complication costs and negative health impacts). The indirect value components identified here are linked to diagnostic accuracy.

All studies in the conceptualisation review modelled two common value components requiring evidence linkage to be quantified; these are an improvement of outcomes resulting from an increased and/or earlier detection of PCa and of CSPCa. To capture the value of increased/earlier detection of CSPCa, the majority of models determined a single clinical management strategy for each biopsy classification option. Classification (under an assumed clinical management strategy), together with true disease status (either true cancer risk category, e.g. NICE NG131 model[123]), or cancer grade, for example, Hao *et al.*[120] was then linked to the outcomes. Clinical management strategies either consisted of a single treatment option[125,126] or a particular mix of treatments.[123]

Only three studies explicitly modelled the impact on outcomes resulting from improved detection of CNS PCa.[124,129,130] Although the evidence linkage requirements for modelling this value component are similar to those described above for the increased and/or earlier detection of CSPCa, these are the only models in which the parameterisation of biopsy diagnostic accuracy allowed for CNS PCa to be misclassified as CS. Individuals who have been misclassified thus incur the costs and harms of unnecessary radical treatment but have limited ability to benefit in the long-term from treatment, compared to those who have CS disease.

Another value component relates to the costs and/or harms incurred for individuals who undergo a repeat biopsy conditional on the result of the index (or subsequent to index) biopsy. Although these costs and harms are a direct impact of the biopsy, this is classified as an indirect value component because the decision to repeat the biopsy is conditional on the classification of the index biopsy in the testing strategy and, therefore, requires evidence via linkage. Differences in diagnostic accuracy between biopsy approaches partially determine the proportion of individuals classified as eligible for a repeat biopsy, that is the proportion of those who will incur the costs and harms of an additional biopsy. In addition to the linkage via classification, modelling this value component also requires a decision rule to define who is eligible for a repeat biopsy (e.g. all or a proportion of the individuals classified as not having CS cancer at the previous biopsy in the test sequence). One study further assumed (in scenario analysis only) that with one type of biopsy a smaller proportion of individuals initially classified by the previous biopsy in the test sequence as eligible for a repeat biopsy would receive repeat biopsies compared to the alternative biopsy approach.[116]

The biopsy value components with direct impact on outcomes modelled in the studies included the costs of the biopsy procedure, and the costs of managing AEs of biopsy, as well as the detrimental health impacts of AEs.

Evidence linkage

The evidence linkage used to model the indirect value components relied in most studies on a common model structure whereby a decision tree approach to track individuals' diagnostic outcomes (and, in some models, biopsy AEs) was linked to a Markov model to capture long-term outcomes.

In most models, diagnostic classification categorised individuals (correctly or not) as having (1) no PCa, (2) CNS or (3) CSPCa. The definition of clinical significance differed across models but was generally defined in terms of a GS threshold or a three-tier cancer risk categorisation (defined in terms of GS, PSA levels and cancer stage). This stratification reflects differences in diagnostic accuracy and prognostic for individuals in the different risk categories. In general, the low-risk disease category was assumed to correspond to true non-CSPCa, while the intermediate- and high-risk cancer categories corresponded to CS disease.

Treatment allocation for each diagnostic classification group was usually determined. This could be a single treatment option for each group (such as in PROMIS[125,126] where all of those identified with CS cancer received radical treatment). Or it could be a pre-defined mix of treatments, where the distribution of treatments differs by group (e.g. with a higher proportion of radical treatments for those at higher cancer risk).[123] In either case, the linkage does not aim to disentangle the outcome for the diagnosed/treated by treatment received.

In most studies, the impact of being correctly or incorrectly classified by the biopsy was modelled as an effect on disease progression to metastatic cancer, and PCa death only affected individuals who were in metastatic disease health states.

Chapter 5 Independent economic assessment: York model

Diagnostic strategies

The model evaluated two strategies for two alternative comparisons: (1) targeted SF biopsy versus targeted cognitive biopsy and (2) combined (targeted and systematic) SF biopsy versus combined cognitive biopsy. The four strategies could not be incrementally compared due to the mechanism of evidence generation for the diagnostic accuracy, which relied on separate evidence networks.

The test sequence and clinical management for each strategy:

1. all patients receive the index biopsy:
   A. If biopsy result suggests no PCa or ISUP grade 1, a proportion of patients undergo repeat biopsy. Patients who do not undergo repeat biopsy are managed in accordance with their diagnosed ISUP grade/CPG or discharged to routine monitoring.
   B. If biopsy result suggests ISUP grade 2 or greater, the individual receives treatment according to CPG.
2. for the patients who receive repeat biopsy:
   A. Individuals are clinically managed according to the highest ISUP grade/CPG score between the two biopsy results or discharged to routine monitoring if the biopsy suggests no PCa.

Model development

Conceptualisation

The value components identified in the review supporting conceptualisation (see *Results of the additional targeted reviews to support model conceptualisation*) were:

- direct value components of biopsy, including the costs of the procedure and its AEs (with associated complication costs and negative health impacts) and
- indirect value components, including the increased or earlier detection of any PCa, of CSPCa, or of non-CS cancer, and the reduction of repeat biopsies.

From the review, supporting the conceptualisation (see *Results of the additional targeted reviews to support model conceptualisation*), we have identified several key aspects to consider in the conceptualisation of the de novo model, which we describe below and pertain to the diagnostic accuracy, the concept of under- and overdiagnosis, the modelling of disease progression and issues with outcome evidence sources.

The histopathological biopsy results are expressed in terms of GS (see *Description of health problem*) and sometimes including lesion core length or cores positivity. In order to estimate the diagnostic accuracy measures applied in the models, the results of the biopsy are typically collapsed into one no PCa and two PCa categories (CNS and CS). The collapse of diagnostic information into these categories implies an information loss, as the granularity of biopsy results is not preserved in the classification according to

biopsy accuracy (GS ranges from 2 to 10). It also implies a judgement on the definition of CS disease at a specific Gleason threshold, with some models using a Gleason threshold of 3 + 3 and others 3 + 4.

Furthermore, making clinical management choices between active surveillance and a range of radical surgical treatments and/or radiotherapy requires information provided by the biopsy diagnostic accuracy, but also information with prognostic value like PSA levels and disease stage at diagnosis. In clinical practice, patient preference is also another factor influencing the choice of management strategy. Due to this, several models made assumptions on how to map from the two PCa classification into three-tier risk cancer prognostic risk classifications. Current UK clinical guidance,[10] for the management of newly diagnosed localised or locally advanced PCa, recommends an even more granular prognostic risk classification, the CPG system, which uses the same type of information as the previous risk classification but classifies patients into five categories. The most recent update of the NICE CG131 defines four alternative clinical management strategies for individuals diagnosed in the different groups (same treatment strategy for CPG 4 and 5), whereas previous guidance defined three management strategies (one for each risk category).

The concepts of under-/overtreatment are not clearly defined in the literature. In general terms, overtreatment seems to arise when patients with PCa of favourable prognostic receive radical treatment (e.g. radical prostatectomy or radiotherapy) instead of active surveillance. In contrast, undertreatment would arise when patients with worse disease prognosis receive active surveillance, rather than radical treatment. So under-/overtreatment can occur if the clinical management approach taken is not commensurate with the true disease prognostic risk, which may be due to:

1. disease not been correctly classified in terms of its underlying prognostic risk; and/or
2. the prognostic risk categorisation not being accurately predictive; and/or
3. treatment decision rules not being followed due to clinical variation and/or patient preference.

The move from the three-tier to the five-group classification aims to improve the identification of patients who have slow progressing disease and should be managed with active surveillance. For these patients, the harms (and costs) of radical treatment are likely to offset its long-term benefits.

The misclassification of individuals in the lower-risk categories/groups as having a higher prognostic risk (overdiagnosis) may result in net health losses if it leads to unnecessarily radical treatment (overtreatment). Therefore, reducing overtreatment is an important value component of biopsy. The few previous studies which modelled this value component did so by capturing misclassification of CNS as significant cancer and linking this to the outcomes of more radically treated patients. This is an imperfect link, as it lacks the flexibility to identify individuals with CS who are at the lower end of the prognostic risk spectrum (i.e. CPG 2 or favourable intermediate risk), and, thus, quantify the net benefit of providing active surveillance to this group.

Most studies modelled the reduction of underdiagnosis, that is, the value of increased or earlier detection of PCa in individuals whose disease will progress at a faster rate if not managed with radical treatment. This value component was modelled by capturing misclassification of CS as non-significant cancer (or NC) and linking this to the outcomes of patients undiagnosed for CS cancer. Since this classification does not allow the identification of individuals with favourable intermediate risk, it may overestimate the net benefit of treating with more radical treatment individuals with true CSPCa.

While most studies modelled longer-term outcomes as a function of PCa disease progression, we identified two alternative structural choices to model the unobservable disease progression: (1) directly between localised (or locally advanced disease) to metastatic disease and (2) sequentially progression across three health states defined by category of true underlying prognostic risk. These two approaches also differ in terms of evidence requirements for parameterisation, with the second approach requiring more data and/or more structural assumptions to be imposed in the model. We also identified

alternative methods to estimate unobservable transitions probabilities, namely calibration and partially observed Markov process models.

We have also identified issues with outcomes evidence. Some models used naive/unadjusted comparisons, that is, used different data sources to describe outcomes for different groups. This may result on bias. Additionally, all models used data sources to describe outcomes according to true disease that use an imperfect reference standard (typically PSA results).

These key aspects grounded the de novo model conceptualisation, an overview of which is provided below.

Risk stratification: In terms of risk stratification, and given that the current UK clinical guidance[10] recommends a five-category prognostic risk classification, the CPG system, there is the need to consider this more granular classification system in the modelling. Despite this being a five-tier classification system, only four alternative clinical management strategies are recommended in the NICE Guideline (same treatment strategy for CPG 4 and 5), therefore CPG 4–5 can be reasonably collapsed in analysis. However, broader evidence does not typically use the CPG system, for example, we found no diagnostic studies reporting results using CPG, and therefore ISUP grade was used in the diagnostic component to reflect CPG tiers.

Determining diagnostic accuracy: The review work (see *Systematic review methods (study selection, data extraction, quality assessment)*) focused on identifying and synthesising studies (RCTs and within-patient comparisons) comparing CF and SF targeted prostate biopsy methods. The multinomial model used in the synthesis of this evidence (see *Multinomial synthesis model*) compares the alternative biopsy methods in how they classify individuals across the following categories: 1 (no PCa), 2 (ISUP grade 1), 3 (ISUP grade 2), 4 (ISUP grade 3) and 5 (ISUP grade 4 or 5 pooled together). This allows a more complete consideration of evidence across ISUP grades, extending from previous approaches that focus on either cancer detection rates (typically defined as NC vs. ISUP grade ≥ 1) or detection rates of CS cancer (typically defined as NC or ISUP grade 1 vs. ISUP grade 2 or above).[116,117,119–121,123–126,130]

The synthesis model considers the distribution of individuals by ISUP grades and relates this distribution across technologies using a set of odds ratios, the quantities pooled across studies. Note that such a model does not identify concordance between methods in biopsy test results (further explanation in *Appendix 10*). The application of the synthesised odds ratios to an externally derived distribution of probabilities of test results for one of the tests (say SF) retrieves the expected distribution of probabilities for the other test (CF). This calculation of absolute probabilities is described in *Appendix 10*

The evidence synthesis model does not consider the accuracy of either method in relation to a reference standard (by virtue of the evidence available for inclusion), that is, it does not consider the extent of misclassification with either any of the modelled methods. This has important implications for economic modelling as, in the absence of a robust and representative outcomes RCT, evidence linkage is required, facilitated by knowing the extent of misclassification of the different tests in relation to true disease status, to allow determine its consequences to health and economic outcomes.

To consider accuracy evidence, a structural approach is required that extends the synthesis model to integrate such evidence. The approach developed here is described in *Diagnostic pathway*.

Diagnostic pathway and repeat biopsy: The need and the accuracy of repeat biopsies is a potential value component for SF methods, in relation to CF. This may arise indirectly from improved diagnostic accuracy of the method used for the first biopsy, that is, a more accurate identification from a first biopsy can lead to a decreased pool of individuals eligible for re-biopsy. We did not identify comparative evidence suggesting differences in the rates of repeat biopsy between cognitive and SF. However, the clinical advisers to the EAG suggested that a potential value component for SF, is that by consulting the

stored cartograms produced by MRI systems, the MDT could better target re-biopsy. There is, however, a lack of evidence to parameterise impact beyond what can be captured via diagnostic accuracy. We will explore the potential value of such a case in scenario analyses.

Treatment of PCa: There is UK-relevant evidence on the distribution of treatments for patients identified at different CPG groups. Our model will therefore be reflective of the different mixes of treatments used at different CPG levels (see *Treatment of prostate cancer*).

Modelling of long-term outcomes: To reflect the value of increased/earlier detection, the long-term outcomes component of the model will need to condition on true disease status and the diagnosed disease category (given the PCa management strategy determined by the diagnosed disease category). None of the existing long-term models have been developed using the five-category prognostic risk classification based on CPG system, recommended in the current UK clinical guidelines.[10] Therefore, a de novo inference model will be developed for this assessment. For its structure, and given that this assessment focuses on the diagnostic pathway, considering PCa disease progression over time and incidence is not as relevant as for the NG131 model, which aimed to model monitoring strategies. Therefore, the increased complexity of the structure used in the NG131 model[123] (and in the Southampton DAR[116]) may not be justified for the purpose of modelling biopsy within the diagnostic pathway. Additionally, evidence to support such a complex structure is sparse (if existing at all), and therefore its parameterisation would rely on a number of assumptions that cannot be verified. However, the added complexity of such a structure would allow for the time profile of treatment costs on those that leave the diagnostic pathway under a monitoring strategy to be better captured.

In terms of evidence to quantify the impact of alternative treatments on outcomes, comparative effectiveness evidence will be preferred to avoid bias. The most contemporary evidence available will be used to inform the inference submodel.

Further details on the inference model and on how this will be incorporated in the cost-effectiveness decision model are provided in *Modelling of long-term outcomes*.

Model structure and parameterisation

Modelling of first biopsy results

Determining diagnostic accuracy

As identified above (see *Conceptualisation*), the fact that the evidence synthesis conducted as part of this assessment does not consider the accuracy of the different biopsy methods in relation to a reference standard has important implications for economic modelling. In the absence of a robust and representative outcomes RCT, economic modelling relies on evidence linkage facilitated by knowing the extent of misclassification of the different tests in relation to true disease status and determining its consequences to health and economic outcomes.

The extent of misclassification can, however, be made explicit by the accuracy matrix, the elements of which reflect the probabilities of obtaining a particular test result with one method conditional on a particular level of (true) disease status. Together with prevalence estimates, this matrix determines the distribution of test results, shown at the top of *Figure 8*.

Note that, due to the nature of biopsy and histological examination of the biopsy specimen, it is reasonable to assume that false-positive results are not possible, that is, if cancer is histologically identified, then it is present. This implies that biopsy methods cannot identify a higher category

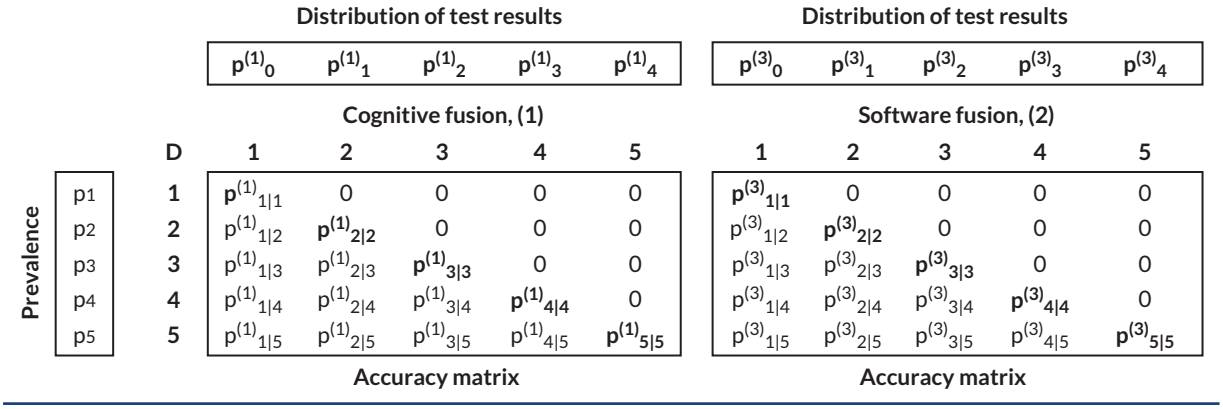


FIGURE 8 Illustration of the relationship between prevalence, and the accuracy and distribution of test results across five categories, for two hypothetical tests.

than true disease status, and therefore zero probability is attributed to such cases in the above accuracy matrices.

Where multiple methods are of interest, the problem becomes more complex for two reasons. First, the prevalence (i.e. the true distribution across categories) is independent of test results and therefore a common prevalence estimate needs to ground all distributions of test results, and be consistent with these. Second, explicit accounts of accuracy need to respect both the prevalence estimates and the marginal distribution of test results derived from the synthesis. Therefore, a structural approach is required for determining accuracy from the marginal distributions obtained through application of the synthesis model.

Summary of approaches used in previous cost-effectiveness models

From the conceptualisation reviews (see *Results of the additional targeted reviews to support model conceptualisation*), two cost-effectiveness reviews have focused on a similar context where no accuracy evidence was synthesised.

A previous DAR,[116] from now on referred as the Southampton DAR, conducted a meta-analysis on cancer detection rates [using relative risks (RRs)] including studies comparing the biopsy methods of interest to the decision problem (e.g. LATP vs. LATRUS), and did not include evidence comparing either method to a reference standard. In this work, the authors sourced the baseline distribution for LATRUS and its accuracy matrix, from an external diagnostic accuracy study (the PROMIS study[125,126]). The authors then applied the synthesised RRs of cancer detection for LATP biopsy (derived for marginal distributions) directly to both (1) the conditional probability of LATRUS identifying CS cancer conditional on true disease status, and to the (2) conditional probability of identifying CNS cancer (assumption imposed in the base case). The conditional probability of NC given true disease status was then adjusted to be one minus the remaining. The way the RRs were applied in the model is not consistent with the way in which they were derived, in that the RR derived from the synthesis model refers to the relative increase in detection rate with one method in relation to another; the RRs were therefore derived on marginal probabilities and not on conditional probabilities. Their application to conditional probabilities in such a way implies that the increase in accuracy of detecting cancer with a particular test is independent of whether the cancer was CS or non-CS, and that the increase in accuracy of detecting non-CS cancer given the patient has non-CS cancer is equal to the increase in accuracy of detecting CS cancer, given the patient has CS cancer.

An alternative study, Wilson *et al.*[121] also investigating LATP in relation to LATRUS, assumed no difference in the expected accuracy of the biopsy methods in the comparison of interest. Therefore,

the authors sourced prevalence and accuracy estimates for LATRUS from the PROMIS study[125,126] and used it to represent the expected results for both biopsy methods. In reflecting uncertainty, the authors sampled from the accuracy matrix directly, taking two independent samples to represent the two different biopsy methods, and therefore generate differences in the accuracy matrix between the methods, due to randomness only.

None of the existing approaches has direct applicability in the current assessment, where a disaggregation by ISUP grade is required.

Summary of methods

The approach used in the current assessment was designed to:

- be grounded on the results of the evidence synthesis model
- return a true distribution across ISUP grade categories (prevalence) that is internally valid, that is not lower than the estimated ISUP Grade detection rates of the different biopsy methods
- be grounded on available evidence on the likely accuracy of targeted MRI fusion conditional on ISUP grade
- define accuracy matrices for the remaining biopsy methods of interest that are consistent with both prevalence and the distributions of biopsy results from the evidence synthesis.

To achieve this, an extension to the synthesis model was developed, drawing on the broader evidence in *Review of additional prevalence, test results and diagnostic accuracy evidence*. To allow for an internally consistent approach, we grounded our methodology on the distribution of test results obtained with MRI-influenced methods and their accuracy. Given that disease prevalence is fully determined by these two results, the prevalence evidence identified in *Review of additional prevalence, test results and diagnostic accuracy evidence* will not be explicitly incorporated in our analyses but will instead be used qualitatively to put our results into context.

The methodology is summarised below. A more comprehensive description of the methods used is presented in *Appendix 10*.

Distribution of test results

The distributions of test results across the disease categories for the relevant biopsy methods within each disconnected component of the network in Model 1a were computed by applying network-specific baseline distributions to the results of the NMA. Building from the analyses in the evidence synthesis section, the baseline distributions were sampled from a multinomial likelihood with an uninformative Dirichlet prior distribution for its hyperparameters, to allow for uncertainty in describing the data from the empirical studies.

Accuracy matrix for software fusion

Evidence on the accuracy matrix for SF, sourced from the literature, was used to characterise the elements of the accuracy matrix probabilistically in the model. A multinomial likelihood was used to describe the distribution of test results conditional on each particular level of true disease status (each line in the matrix in *Figure 8*) with Dirichlet uninformative prior distributions.

Prevalence

The derivation of prevalence followed two steps, the first consisted of the analytical derivation of an initial prevalence estimate from the marginal distribution and accuracy matrix for SF. The second step entailed applying a constraint to ensure that the prevalence is always higher than the detection rates (by ISUP grade) observed across all tests.

Accuracy matrix for remaining biopsy methods

The diagonals of the accuracy matrices for the remaining biopsy methods were determined by the prevalence and the test-specific distribution of results. To define the remaining non-zero and free elements of the matrix, uninformative beta distributions were used, constrained so that their multiplication by the prevalence retrieves the test results estimated within the evidence synthesis.

Implementation The extension to the synthesis model, developed to determine accuracy, was implemented alongside the synthesis model in a Bayesian framework estimated through Markov chain Monte Carlo methods using WinBUGS 1.4.3.[140] Due to the sparseness of evidence in other networks, this was applied to Model 1a [see *Model 1a: Multinomial synthesis model (base case)*] which includes SF, CF and systematic biopsy in a first connected network, and the combination of software and CF with systematic biopsy in a second connected network. As in the evidence synthesis, model convergence was assessed where possible by running two independent chains with different starting values looking at a history plot and through inspection of Gelman–Rubin diagnostic plots. Model fit was assessed by comparing the mean total residual deviance to the number of independent data points contributing to the analysis.[71]

Sensitivity analysis Given that the approach proposed here is heavily data driven, sensitivity analyses focused on varying the data sources for the baseline distributions and accuracy matrix.

Results

The extension to the synthesis model reflects the data sources described in *Model 1a: Multinomial synthesis model (base-case)* for the baseline distribution of test results for SF, the reference method. The extension model also required data to characterise the accuracy matrix for the reference biopsy method, two sources for these data were available (see Section *Review of additional prevalence, test results and diagnostic accuracy evidence* and *Appendix 8*, *Distribution of test results obtained with cognitive fusion or software fusion biopsy*) and were used here. According to the data sources used, the following analyses were conducted:

- Main analysis, for the subgroup of biopsy-naive individuals: baseline distribution of test results for SF sourced from biopsy-naive data from Filson *et al.*[96] relative accuracy data from the multinomial evidence synthesis model (see *Multinomial synthesis model*) which was incorporated in this extension, and accuracy data from Mortezavi *et al.*[141] Mortezavi *et al.*[141] was chosen for the main analysis over Zhou *et al.*[142] as it more closely reflects the lower accuracy observed in UK-specific evidence sources.
- Subgroup analysis for previous negative-biopsy individuals: all sources were equal to those used in the main analysis except the baseline distribution of test results for SF which was sourced from previous negative-biopsy data from Filson *et al.*[96]
- Sensitivity analysis to data source on baseline distribution: all sources were equal to those used in the main analysis except the baseline probabilities, which were based on biopsy-naive data from PAIREDCAP (2019),[88] for network 1.
- Sensitivity analysis to data source on accuracy matrix: all sources were equal to those used in the main analysis except accuracy data which was sourced from Zhou *et al.*[142]

Note that given the two networks are disconnected, results are reported separately for comparisons of CF and SF – network 1, and for comparisons of combined cognitive/SF with systematic biopsy – network 2. Note that while network 1 includes systematic biopsy, results for this biopsy method are NR here.

Main analyses (biopsy naive)

Table 9 shows the results of the structured approach applied to the main analysis for the subgroup of biopsy-naive patients. Results are internally consistent, and consistent with the sources of evidence these drew upon. They mirror the high level of uncertainty in the evidence base.

TABLE 9 Distribution of test results, conditional accuracy and prevalence probabilities (mean and 95% CrI) according to ISUP grade for biopsy-naive individuals

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.516 (0.416 to 0.615)	0.186 (0.131 to 0.249)	0.136 (0.068 to 0.211)	0.098 (0.052 to 0.157)	0.064 (0.031 to 0.114)	0.457 (0.403 to 0.513)	0.173 (0.137 to 0.214)	0.196 (0.157 to 0.233)	0.108 (0.079 to 0.144)	0.066 (0.043 to 0.095)
		CF					SF				
		(Accuracy matrix)					(Accuracy matrix)				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.121 (0.007 to 0.238)	NC	1	0	0	0	0	1	0	0	0	0
0.318 (0.212 to 0.452)	1	0.829 (0.529 to 0.994)	0.171 (0.006 to 0.471)	0	0	0	0.671 (0.538 to 0.796)	0.329 (0.204 to 0.462)	0	0	0
0.262 (0.193 to 0.341)	2	0.300 (0.016 to 0.64)	0.362 (0.083 to 0.674)	0.338 (0.111 to 0.55)	0	0	0.251 (0.167 to 0.347)	0.204 (0.128 to 0.288)	0.544 (0.443 to 0.64)	0	0
0.183 (0.119 to 0.265)	3	0.189 (0.006 to 0.526)	0.140 (0.005 to 0.422)	0.192 (0.008 to 0.537)	0.479 (0.213 to 0.804)	0	0.224 (0.121 to 0.343)	0.059 (0.012 to 0.138)	0.207 (0.112 to 0.322)	0.510 (0.387 to 0.65)	0
0.116 (0.077 to 0.174)	4 or 5	0.125 (0.004 to 0.389)	0.111 (0.004 to 0.357)	0.111 (0.004 to 0.362)	0.101 (0.002 to 0.332)	0.552 (0.299 to 0.882)	0.111 (0.046 to 0.199)	0.047 (0.011 to 0.112)	0.130 (0.063 to 0.217)	0.140 (0.068 to 0.226)	0.573 (0.467 to 0.687)

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.460 (0.335 to 0.583)	0.250 (0.152 to 0.356)	0.127 (0.034 to 0.261)	0.131 (0.046 to 0.231)	0.033 (0.001 to 0.107)	0.348 (0.273 to 0.418)	0.223 (0.179 to 0.273)	0.232 (0.168 to 0.311)	0.115 (0.081 to 0.152)	0.082 (0.054 to 0.114)
		Combined CF and systematic biopsy					Combined SF and systematic biopsy				
		(Accuracy matrix)					(Accuracy matrix)				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.121 (0.007 to 0.238)	NC	1	0	0	0	0	1	0	0	0	0
0.318 (0.212 to 0.452)	1	0.709 (0.289 to 0.987)	0.291 (0.013 to 0.711)	0	0	0	0.528 (0.206 to 0.824)	0.472 (0.176 to 0.794)	0	0	0
0.262 (0.193 to 0.341)	2	0.249 (0.01 to 0.689)	0.437 (0.07 to 0.836)	0.314 (0.028 to 0.78)	0	0	0.078 (0.001 to 0.273)	0.152 (0.011 to 0.384)	0.770 (0.523 to 0.975)	0	0
0.183 (0.119 to 0.265)	3	0.126 (0.002 to 0.488)	0.124 (0.003 to 0.449)	0.134 (0.002 to 0.482)	0.616 (0.148 to 0.981)	0	0.132 (0.005 to 0.441)	0.135 (0.005 to 0.411)	0.130 (0.004 to 0.403)	0.603 (0.338 to 0.92)	0
0.116 (0.077 to 0.174)	4 or 5	0.195 (0.004 to 0.618)	0.187 (0.005 to 0.603)	0.173 (0.004 to 0.561)	0.163 (0.004 to 0.543)	0.281 (0.006 to 0.865)	0.069 (0.001 to 0.282)	0.070 (0.001 to 0.265)	0.066 (0.001 to 0.27)	0.071 (0.001 to 0.266)	0.724 (0.402 to 0.98)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of main analysis.

The prevalence estimates inferred by the extended synthesis model are in line with those available in the literature (see *Review of additional prevalence, test results and diagnostic accuracy evidence* and Appendix *Distribution of test results obtained with cognitive fusion or software fusion biopsy*), perhaps closer to the lowest available estimate of cancer prevalence (i.e. low probability of NC). This is, however, expected, as the inferred prevalence in the extended model is bounded by a composite of all five tests, and is sampled from a distribution that allows for even higher cancer prevalences than those identified by the composite of all five tests.

In terms of distribution of test results, the results obtained here (presented at the top of each accuracy matrix in *Table 9*) are consistent with those in the synthesis section (see *Tables 68–71*, *Appendix 10* for detailed comparisons). In summary, within network 1 (which includes cognitive and SF), the results suggest that SF may retrieve a higher detection of cancer at ISUP grade 2 and above when compared to CF, with the detection at ISUP grade 2 being highest. These results are not statistically significant, in that CrIs overlap significantly. *Table 10* presents the information on distribution of test results converted onto detection rates at thresholds of categories. This information highlights that: SF presents a similar level of detection at ISUP grades 4–5, slightly increased detection of ISUP grade 3 or above of 1.3%, increased detection of ISUP grade 2 or above of 7.1% and increased detection at ISUP grade 1 or above of 5.9%.

In terms of accuracy, the results for network 1 suggest that SF is more accurate at detecting the correct category (the diagonal of the accuracy matrix is always higher for SF), with higher differences at ISUP grades 1 and 2.

The accuracy matrix results show that despite cognitive presenting a higher likelihood of an ISUP grade 1 result, there is an increased accuracy of SF at ISUP grade 1. This is due to, with CF, individuals at higher ISUP categories being misclassified as grade 1. The accuracy matrix shows increased accuracy at ISUP grade 2 for SF, but retains a significant proportion inaccuratelyclassified as 'NC' [with a probability of 0.25 95% CrI (0.17 to 0.34)] which is higher than the proportion innacurately classified as ISUP grade 1 [with a probability of 0.20 95% CrI (0.13 to 0.29)]. A similar effect is observed in ISUP grade 3, where the likelihood of being classified as 'NC' is higher for SF than for CF – probabilities 0.224 95% CrI (0.121 to 0.343) versus 0.189 95% CrI (0.006 to 0.526). This is a result of the increased detection at ISUP grade 2 not being matched by a similar level of detection at ISUP grade 1.

By multiplying the prevalence by the respective element of the accuracy matrix, the joint probability matrix is obtained (see *Table 67*, *Appendix 10*). This matrix identifies, for a cohort with the mix of ISUP grades as per the prevalence estimates, the probability of both events, that is the probability of

TABLE 10 Proportion correctly identified and detection rates (mean and 95% CrI) with the different biopsy methods for biopsy-naive individuals

	Estimated detection rates with the different biopsy methods			
	Network 1		Network 2	
ISUP grade	CF	SF	Combined CF and systematic biopsy	Combined SF and systematic biopsy
4 or 5	0.064 (0.031 to 0.114)	0.066 (0.043 to 0.095)	0.033 (0.001 to 0.107)	0.082 (0.054 to 0.114)
3 to 5	0.162 (0.102 to 0.237)	0.175 (0.135 to 0.217)	0.164 (0.064 to 0.27)	0.197 (0.152 to 0.243)
2 to 5	0.299 (0.209 to 0.396)	0.370 (0.322 to 0.424)	0.290 (0.173 to 0.428)	0.429 (0.358 to 0.502)
1 to 5	0.484 (0.385 to 0.584)	0.543 (0.487 to 0.597)	0.540 (0.417 to 0.665)	0.652 (0.582 to 0.727)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of main analysis.

a particular 'true' ISUP grade and a particular test result. This matrix identifies that, at all grades, the probability of an accurate result is 0.524 95% CrI (0.411, 0.628) for SF – 0.12 at NC, 0.10 at ISUP grade 1, 0.14 at ISUP grade 2, 0.09 at ISUP grade 3 and 0.07 at ISUP grade 4 or 5. The probability of an accurate result is 0.413 95% CrI (0.256, 0.583) for CF – 0.12 at NC, 0.05 at ISUP grade 1, 0.09 at ISUP grade 2, 0.09 at ISUP grade 3 and 0.06 at ISUP grade 4 or 5. The highest difference between software and cognitive is observed at ISUP grades 1 and 2 (approximately 5% increase in each with software). Notably, in terms of misclassification, the overall proportion of ISUP grade 3 identified as 'no cancer' is higher with SF 4.2% than with CF (3.5%). This implies that the key trade-offs for SF are the benefits achieved by the general increase in detection, but particularly for ISUP grades 1 and 2, at the expense of a slightly higher proportion of grade 3s that will not be detected as cancerous.

Network 2 (including software and CF combined with systematic biopsy) shows higher identification in the distribution of test results (due to the baseline used) to but qualitative results are similar to those in network 1 to noting that there is substantial uncertainty in these results. Detection rates at thresholds of categories show that cancer detection is expected to be higher with combined software to at all levels to but particularly at ISUP grade 2 or above where detection is 13.9% higher than with combined CF and at ISUP grade 1 or above where detection is 9.2% higher that with combined CF.

In terms of accuracy to at all grades to the probability of an accurate result is 0.655 95% CrI (0.471 to 0.816) for combined SF and 0.438 95% CrI (0.218 to 0.665) for combined CF. For both combined strategies to the likelihood of a 'no cancer' result for ISUP grades 2 and 3 is still relatively high to but this is now comparable to the likelihood of an ISUP grade 1 result.

Subgroup analysis (previous negative biopsy)

We conducted a subgroup analysis to where the baseline distribution of test results for SF was sourced from Filson *et al.*[96] but using the group of individuals recruited into this study that had previous negative-biopsy results. However, the diagnostic accuracy evidence synthesis and the accuracy matrix are still sourced as per the main analysis to grounded on evidence over biopsy-naive and repeat biopsy patients. Summary results of distribution of test results for the subgroup analysis are presented in *Table 72* (*Appendix 10*) alongside their interpretation. Prevalence probabilities and results of the accuracy matrices are also presented in *Tables 73* and *74* to *Appendix 10*.

Sensitivity analysis

Sensitivity analyses change the main sources of evidence of the main analyses (on biopsy-naive patients): a first sensitivity analysis uses an alternative baseline distribution of test results for SF [from PAIREDCAP (2019)],[88] and a second analysis uses an alternative source for accuracy matrix evidence [from Zhou *et al.*].[142]

In both these analyses, results for the accuracy matrices could only be presented for the first network because of increased uncertainty.

The summary results in *Tables 75* and *76*, *Appendix 10*, for the first sensitivity analysis, indicate that results are sensitive to the distribution of test results. The PAIREDCAP study distribution showed a higher proportion of 'no cancer' identified with SF (31% vs. 46% in the main analysis grounded on Filson, *Table 9*), identical in ISUP grade 1, and higher proportions across all remaining ISUP categories (26%, 16% and 10%, respectively for ISUP grades 2, 3 and 4 or 5, vs. 20%, 11% and 7% in the main analysis grounded on Filson, *Table 9*). The distribution of test results for ISUP grade 4 or 5 are similar between software and CF, but are significantly increased for software at ISUP grade 2, slightly increased at ISUP grade 3 and slightly reduced for ISUP grade 1.

The summary results in *Tables 77* and *78*, *Appendix 10*, for the second sensitivity analysis indicate that results on the distribution of test results are only slightly sensitive to the source of evidence on the accuracy matrix in Filson (see *Table 9*). The main difference distribution of test results for ISUP grades

4 or 5 are slightly higher for SF in this analysis in relation to the main analysis in *Table 9*. The estimates of the accuracy matrices (in *Appendix 10*) show increased accuracy (in classifying individuals in the right category) for both technologies in relation to the main analysis in *Table 9*, which reflect the data from Zhou *et al.*[142] However, differences between the technologies in the accuracy matrices are encountered in individuals with true ISUP grade 4 or 5 where the misclassified have an equal chance across being identified across all other categories in cognitive but are slightly less likely to be identified as NC or ISUP grade 1 with SF. For those in ISUP grade 2, sensitivity analysis indicates a low likelihood of the misclassified being identified as grade 1 with SF (and therefore being more likely to be classified as 'no cancer'), which was not observed in the main analysis.

Diagnostic pathway

The diagnostic pathway is structured as a decision tree that captures AEs, repeat biopsies and classifies individuals according to the result of the biopsy (or biopsies), and the true disease status (see *Diagnostic pathway*), defined as ISUP grade for those with PCa (ISUP grades 1, 2, 3, 4–5). *Figure 9* shows a simplified schematic of the decision tree illustrating biopsy-related mortality, sequence of biopsies, and cost and HRQoL pay-offs which apply for each strategy. The diagram does not show the biopsy-related non-fatal events, as these do not modify the probability of moving forward in the diagnostic pathway. The probabilities of AEs are applied as weights to adjust the branch costs and HRQoL pay-offs. The diagram also does not show how the classification is established conditional on the true disease state and test accuracy at each biopsy, or how the classification conditions the probability of repeat biopsy; this is illustrated in *Appendix 11*, *Table 79*.

All individuals who undergo the first biopsy are at risk of biopsy-related non-fatal and fatal AEs. The mortality risk corresponds to the complement of probability (p1). For those who survive the first biopsy, the probability of receiving a repeat biopsy (p2) is conditional on the result of the first biopsy. Individuals who test positive at first biopsy (biopsy result ISUP grade ≥ 2) and survived the first biopsy receive no further testing (p2 = 0). Those who test negative (no PCa or ISUP grade 1) and survived the first biopsy have a probability of undergoing repeat biopsy (p2), with the remaining individuals receiving no further testing. The individuals who receive a repeat biopsy are again exposed to biopsy mortality risk (p1-p3), and to a probability of having non-fatal biopsy AEs. Time is not modelled within the decision tree, so events are assumed to occur instantaneously (or in rapid succession prior to long-term model entry); this is in line with the other cohort models examined in *Results of the additional targeted reviews to support model conceptualisation*.

The decision-tree models repeat biopsies for a proportion of individuals who have a negative-first biopsy result. In the base case, this proportion is not conditional on whether the strategy includes a cognitive or

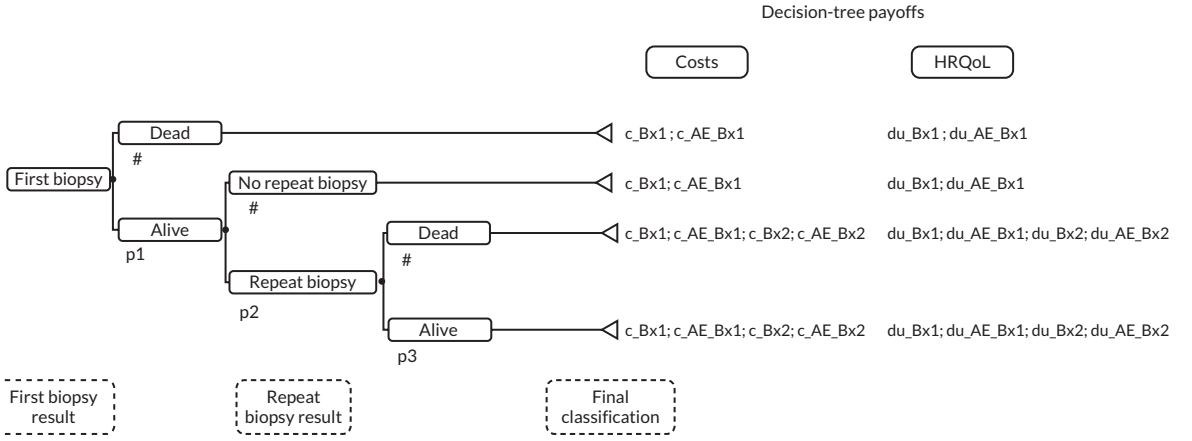


FIGURE 9 Decision-tree schematics. •, probability node; ◁, terminal node; #, complement probability (1-probability); Bx, biopsy; c_, cost; du_, disutility; p1, probability of surviving the first biopsy; p2, probability of repeat biopsy (is conditional on first biopsy result); p3, probability of surviving second biopsy.

SF component. The base-case analysis assumes that the proportion of repeat biopsy is only conditional on the result of the first biopsy (15.45% and 5%, if the result of the first biopsy indicated a lesion with ISUP grade 1 and no PCa, respectively) as per a previous DAR.[116]

Similar to a previous DAR,[116] we assume the same rates of biopsy complications per biopsy approach for the first and repeat biopsies. However, because we assume a different distribution between transperineal and transrectal biopsy, for the first and repeat biopsies in the diagnostic pathway, the repeat biopsy complication rates reflect a higher proportion of TP (10% GATP and 60% LATP) compared to first biopsy (65% LATP) (see *Biopsy procedure costs*).

In the base-case scenario, the diagnostic performance of the repeat biopsy is assumed the same as of the first biopsy. The model allows exploring a degradation in the diagnostic performance of repeat when compared to first biopsy; the impact of applying this alternative assumption is assessed through scenario analysis.

We note the (first and repeat) biopsy results are assigned in the decision tree immediately before the biopsy mortality risk is applied, meaning the proportion of individuals in each category is adjusted by the proportion who survived the biopsy procedure (assuming the same mortality risk applies to all individuals regardless of true disease category and biopsy result). Similarly, we assumed that the biopsy AEs apply to all individuals who undergo a biopsy procedure.

The costs and QALY pay-offs in the decision tree capture the short-term impacts of first and repeat biopsy. First biopsy cost pay-offs apply to all branches and include the cost of the biopsy procedure and of associated AEs. Similarly, the QALY pay-offs of the first biopsy also apply to all decision-tree branches. These QALY pay-offs aim to quantify the QALY loss associated with biopsy procedural complications. The repeat biopsy-related costs (including the same cost categories as for the first biopsy) and repeat biopsy complications QALY loss apply only to the decision-tree branches which include a repeat biopsy.

The costs of the biopsy procedure vary by strategy to reflect the differences in cost between CF and SF with each of the MRI fusion systems modelled (see *Biopsy procedure costs* for the estimation of biopsy procedure costs). The biopsy procedure and AEs costs are both specific to the biopsy approach (LATP, GATP or LATRUS); these costs are estimated as a weighted average of the costs by biopsy approach (where the weights correspond to the proportion of LATP, GATP and LATRUS for each biopsy in the strategy). The QALY loss from biopsy-related complications also varies by biopsy approach to reflect the different biopsy complication rates by biopsy route of access (transperineal or transrectal) and, therefore, is also estimated as a weighted average by biopsy approach.

Clinical management conditional on biopsy final classification

There are 15 possible final classifications at the end of the diagnostic pathway, which are as follows:

1. For individuals correctly classified:
    - A. Diagnosed as having no PCa and without PCa;
    - B. Diagnosed as ISUP grade 1 and with ISUP grade 1;
    - C. Diagnosed as ISUP grade 2 and with ISUP grade 2;
    - D. Diagnosed as ISUP grade 3 and with ISUP grade 3;
    - E. Diagnosed as ISUP grades 4–5 and with ISUP grades 4–5;

2. For individuals misclassified:
    - A. Diagnosed as having no PCa and with:
        - a. ISUP grade 1;
        - b. ISUP grade 2;
        - c. ISUP grade 3;
        - d. ISUP grades 4–5;

B. Diagnosed as ISUP grade 1 and with:
   a. ISUP grade 2;
   b. ISUP grade 3;
   c. ISUP grades 4–5;

C. Diagnosed as ISUP grade 2 and with:
   a. ISUP grade 3;
   b. ISUP grades 4–5;

D. Diagnosed as ISUP grade 3 and with:
   a. ISUP grades 4–5.

The clinical management for each of these possible classifications is dependent on the diagnosed category. As detailed in *Care pathways for the diagnosis and management of prostate cancer*, current clinical guidance[10] recommends that individuals, diagnosed as having localised or locally advanced disease (henceforth referred to as localised disease for simplicity), are involved in decisions about the management of their disease, with the range of management options offered varying as a function of their prognostic risk. Thus, patients with lower CPG scores (better prognosis) are offered more conservative management (active surveillance) with option to undergo radical treatment, while those with higher CPG scores are offered radical treatment as the preferred management option.

The diagnostic performance evidence only allows classifying patients according to their histopathological information (i.e. ISUP grade), which is only part of the prognostic information used to determine the CPG scores. Therefore, we made a simplifying assumption that ISUP grade can be used as a proxy for the individuals' CPG score (e.g. CPG1 = ISUP grade 1), to allow establishing the evidence linkage between classification and clinical management and subsequently from this to treatment outcomes. Henceforth, we refer to the classification in the model in terms of CPG score, assuming interchangeability between ISUP grades and CPG scores. The treatment options for localised disease include active surveillance or radical treatment. Radical treatment includes radiotherapy [consisting of the model of brachytherapy or external beam radiotherapy for costing purposes (see *Prostate cancer treatment costs – metastatic disease*)], and radical prostatectomy.

For individuals identified as having PCa, the model assigns varying proportions of active surveillance and radical treatment, according to diagnosed CPG score (see *Treatment of localised prostate cancer*). All patients in the localised disease health states receive monitoring, with the set of monitoring tests and schedule varying according to whether they are receiving active surveillance or radical treatment. Individuals without a PCa diagnosis also receive monitoring, but its regime is less intensive compared to individuals diagnosed with PCa and is time limited (maximum of 10 years).

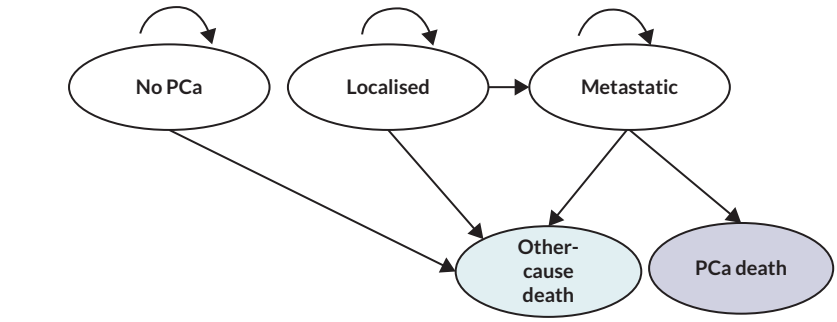
Prostate cancer treatment is associated with AEs, such as sexual, urinary and bowel dysfunction, with rates of AEs varying by treatment (see *Localised treatment adverse events*). AEs from PCa management are associated with disutility and costs of managing these events, which are quantified within the long-term model.

Modelling of long-term outcomes

Overview of the decision-analytic model

The long-term outcomes of the model cohort conditional on latent true disease status, the diagnosed disease category and PCa management assigned are quantified in a state transition Markov model. The model has yearly cycles (with a half-cycle correction applied) and a lifetime time horizon (40 years).

The core structure of the model is illustrated in *Figure 10*. Individuals who survived the biopsy procedure(s) in the diagnostic pathway can enter the model through the no PCa state if they are disease



Localised disease health states

True disease status	**No PCa**	CPG 1	**CPG 1**	CPG 2	CPG 2	**CPG 2**	CPG 3	CPG 3	CPG 3	**CPG 3**	CPG 4-5	CPG 4-5	CPG 4-5	CPG 4-5	**CPG 4-5**
Diagnosed	**No PCa**	No PCa	**CPG 1**	No PCa	CPG 1	**CPG 2**	No PCa	CPG 1	CPG 2	**CPG 3**	No PCa	CPG 1	CPG 2	CPG 3	**CPG 4-5**

FIGURE 10 Long-term outcomes Markov model structure.

free or the localised (and locally advanced) disease state if they have PCa. Patients with PCa at model entry can remain in the localised disease health state or transition to the metastatic disease state at each yearly model cycle. The individuals who died due to the diagnostic procedure enter the 'other cause' death state, one of the two absorbent states in the model (highlighted in grey in *Figure 10*). Transitions to the other-cause death state are possible from the 'no PCa', localised and metastatic disease health states, with the same probability as the general population (see *Other-cause mortality*). The only other possible transition for the 'no PCa' state is to remain in the same state (i.e. the model does not consider that individuals can develop PCa, so disease progression is not modelled for those who do not have the disease at model entry). The metastatic health state is modelled as three tunnel health states (not illustrated in this diagram, *Prostate cancer treatment adverse event costs – localised disease*, *Figure 12*), where individuals can only stay in the two first tunnels states for a maximum of 1 year. Patients who transition to the metastatic health state can only remain in that health state or die. PCa mortality only applies to patients in the metastatic disease states.

There are 15 possible localised disease health states (illustrated in the box below the model schematics), each reflecting the final classification (here expressed as CPG scores) attributed by the diagnostic pathway and the different treatments assigned conditional on the diagnosed category in the final classification.

Over the next subsections we provide details on the parameterisation of long-term transition probabilities.

Inference sub-model (disease progression by Cambridge Prognostic Group and treatment intensity)

The decision-analytic PCa model requires consideration of the impact of treatment decisions according to diagnostic accuracy. Treatment decisions are currently grounded on the identification of CPG groups, and therefore the outcomes component of the model aims to reflect: (1) differences in outcomes across the CPG risk groups that underlie treatment decisions in clinical practice and (2) the impact of different treatment intensities on each of these risk groups. Our conceptualisation review has not identified any previous cost-effectiveness model where treatment outcomes for five-level CPG groups have been considered (see *Results of the additional targeted reviews to support model conceptualisation*). Therefore, an estimation strategy was developed in this assessment grounded on the targeted review of evidence on the long-term outcomes of PCa (see *Review of long-term evidence*).

The brief overview of the wider literature highlights that, while there is evidence on the effectiveness of radical versus 'conservative' treatment options in delaying progression to metastatic disease, there are limited mortality benefits observed within the follow-up of clinical trials in this area. Also, we did not find evidence on treatment effectiveness stratified by CPG scores, despite the prognostic ability of the five-level score for PCa-specific death having been demonstrated in a large UK-based observational study.[112]

The aim of the inference model is therefore to pull existing evidence together to predict differences in progression to metastatic disease by five-level CPG score and by treatment. Given this has not been directly observed, a calibration model was developed to infer these. The calibration model uses the structure of the decision-analytic model in *Figure 10*, but without considering the 'no PCa' health state, which has, thus, been faded out in the diagram.

The model structure is underpinned by the following assumptions. All individuals are assumed to begin with localised disease. They can continue to have localised disease, progress to metastatic disease or die from causes other than PCa. The speed of progression to metastatic disease is expected to depend on CPG group and is given by λ_i, where the index *i* reflects the CPG group. Other-cause mortality is age-specific and is determined by δ_{age}. Those with metastatic disease may (1) continue to live with metastatic disease, (2) die from PCa or (3) die from other causes. Following the NICE NG131 model,[123] it was assumed that death from PCa could only occur after metastatic disease. The model was parameterised for each CPG score of interest to this assessment (CPG 1, 2, 3, and 4 and 5 combined).

The inference procedure is undertaken in two parts.

Part 1: identifying rates of progression to metastatic disease by CPG, λ_i

This part uses calibration. For any calibration process, two sets of parameters are of interest. The first concerns model parameters, some of which are unobserved and the target of inference, and others are observed and therefore evidence directly informs these. The second set concerns calibration targets, which are functions of the model parameters that have been observed and are used to identify the unobserved parameters under the model structure and other observed inputs. *Table 11* lists the calibration parameters and targets and presents the results of the calibration model. A more detailed description of these parameters and their evidence sources is presented in the subsequent subsections.

Calibration targets

Our calibration target is 10-year PCa-specific mortality according to CPG group at diagnosis of localised disease, as reported in Gnanapragasam *et al.*[112] Our analysis combines groups 4 and 5, as the recommended treatment is the same for both groups.[10] We used a single data point for each CPG group of interest, at 10-year follow-up, in the calibration model. We used WebPlotDigitizer[145] to extract point estimates and upper and lower CIs for PCa survival at 10 years (3652 days) from both training and validation sets in Gnanapragasam *et al.*[112] (from figures 1a and 2a). Standard errors (SEs) were calculated by considering the average distance between the point estimate and the upper and lower confidence limits (where both were available). The figures were then combined across data sets to derive a single estimate for each CPG, by weighting according to the inverse of their precision (analogously to a fixed-effect meta-analysis). Values for the combined CPG 4 and 5 group were derived by pooling the distributions, that is, assuming that the variance of the combined group is the weighted sum of the variances in each group. To describe the survival probabilities probabilistically, the parameters of beta distributions were specified using the method of moments. The estimates of 10-year PCa survival and the parameters of the beta distributions used to describe this in the calibration model are presented in *Table 11*. When simulating from the beta distribution to run the calibration, we preserved the ordering ensuring survival is highest in group 1 then group 2, group 3 and groups 4–5.

TABLE 11 Calibration model parameters and targets, and calibration results

	Description	Source	Parameter value	Results
PART 1	**Calibration targets**			
	10-year PC death by CPG group at diagnosis	Gnanapragasam *et al.*[112] pooled results for testing and training sets	10-year PC survival (SE) (a, b parameters of a beta distribution): G1: 0.968 (0.007) (586, 19) G2: 0.938 (0.010) (577, 38) G3: 0.871 (0.016) (356, 53) G4/5: 0.763 (0.052) (50, 16)	–
	Calibration model parameters			
	Unobserved rate of progression from localised to metastatic disease, by CPG: λ_1, λ_2, λ_3, λ_4	Unobserved (calibration parameters)	NA	Rate (SE): G1: 0.0101 (0.00236) G2: 0.0229 (0.00403) G3: 0.0645 (0.01058) G4/5: 0.1788 (0.08641)
	Observed rate of PC mortality from metastatic disease, γ	STAMPEDE[143]	Yearly rate of PC mortality in ADT arm of 0.162 (SE 0.0073), calculated from 5-year PC mortality	–
	Observed rate of death from other causes, age-specific	ONS life tables (2000–2)[144]	Assumed mean age for each CPG group G1: 66.2 G2: 68.14 G3: 71.13 G4/5: 72.18	–
PART 2	Proportions under radical treatment vs. conservative management, by CPG	Gnanapragasam[112]	G1: 0.53 G2: 0.70 G3: 0.81 G4/5: 0.95	–
	Rate ratio for the development of metastasis of radical vs. conservative treatment	ProtecT[55]	Rate ratio = 0.43 95% CI (0.26 to 0.72), log rate ratio mean = −0.834, SE = 0.2545	–
	Rate of progression from localised to metastatic disease, by CPG and by treatment	Unobserved	NA	Conservative management $\lambda_1^{(0)}$ = 0.0143 (0.00357) $\lambda_2^{(0)}$ = 0.0380 (0.00832) $\lambda_3^{(0)}$= 0.1197 (0.02812) $\lambda_4^{(0)}$ = 0.3950 (0.22287) Radical treatment: $\lambda_1^{(1)}$ = 0.0063 (0.00184) $\lambda_2^{(1)}$ = 0.0165 (0.00357) $\lambda_3^{(1)}$= 0.0516 (0.00964) $\lambda_4^{(1)}$ = 0.1674 (0.08066)

Calibration model parameters

The rates of progression from localised to metastatic disease by CPG score (λ_i, where *i* represent the CPG score groups of interest) were the unobserved parameters we sought to achieve inference on.

The remaining model parameters were observed. PCa specific mortality was assumed to only be possible after progression to metastatic disease, and therefore to inform this model parameter we used outcomes reported from STAMPEDE, a UK study.[143] Data from STAMPEDE's control arm were used, as long-term

hormonal treatment was the SOC at the time the study informing the calibration target was conducted. The individual patient data were reconstructed from the published Kaplan-Meier curve using the Guyot algorithm[146] and a Weibull distribution was fitted using the *flexsurv* package in R.[147] PCa survival at 5 years, predicted by the fitted Weibull function, was 40.6% (95% CI from 43.9 to 47.0%), which was converted onto a rate assuming constant hazard. This resulted in a mean hazard of 0.162 and a 95% CI from 0.1777 to 0.1492. Assuming a symmetrical distribution, this implies a SE of 0.0073.

Office for National Statistics (ONS) life tables for men[144] were used to parameterise the transitions to death from other causes (both from localised disease and from metastatic disease). Life tables were used for the years 2000–2 to approximate the mortality at the time of the Gnanapragasam study (2000–10). The average age at the start of that study differs by risk group according to data reported in the NICE model.[123] Using linear interpolation, we extended the three risk groups reported in the NICE report to the four risk groups we are considering. The ages assumed were: 66.2 years for Group 1; 68.14 years for Group 2; 71.13 years for Group 3 and 72.18 years for Groups 4–5. Due to the large sample size underlying the life tables, we did not consider this parameter uncertain.

Analysis methods

Using the parameters and targets described above, we ran the calibration analysis in the software package R, according to the algorithm below:

1. Sample a value from the uncertainty distribution for the target (PCa mortality at 10 years, for each risk group) and the known model inputs (metastatic mortality rate).
2. For each risk group, identify the value of the rate of transition from localised to metastatic disease (λ_i) that is consistent with the PCa mortality at 10 years sampled in step 1. Record the result.
3. Repeat steps 1 and 2, 10,000 times.

The *optim* function in R was used for the second step in this algorithm.[36] To find the rate consistent with the target, we defined a discrete time Markov model with the structure in *Figure 11*, and determined that its predicted 10-year survival should be compared against the target value. The loss function used was the squared distance from the proposed value to the target value. The Brent method was used with lower and upper bounds of 0 and 10, respectively.[148]

Results

The results from the calibration procedure regarding the unobserved rate of progression from localised to metastatic disease by CPG are shown in *Table 11*. Comparisons of calibration parameter estimates with those from recent UK cost-effectiveness models are presented in *Tables 80* and *81*, *Appendix 11*.

Part 2: identifying the effect of treatment on the rates of metastasis

The estimated rate of progression to metastatic disease from the calibration exercise above reflect outcomes with current practice, which comprises a mix of radical and conservative treatment. In part

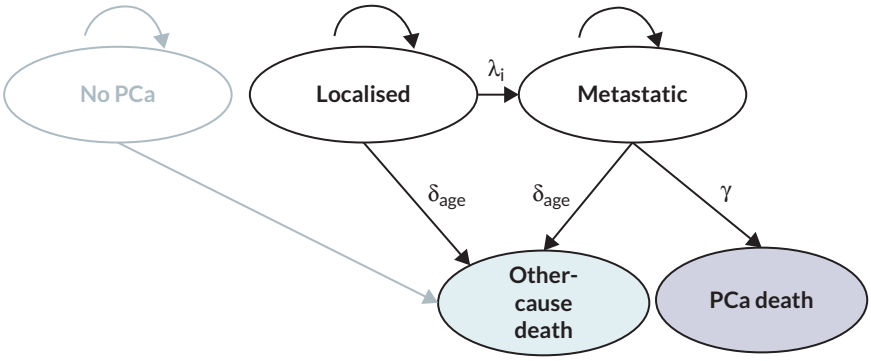


FIGURE 11 Calibration model structure and parameters.

2, we back-calculate how these rates differ for the proportions treated with radical and conservative treatment observed in Gnanapragasam *et al.*[112] using an external estimate of effect for radical treatment.

Gnanapragasam *et al.*[112] reported the treatment mix by risk group observed in UK clinical practice during the years 2000–10. The treatment categories considered were: conservative management, brachytherapy, primary ADT, radical prostatectomy and radical radiotherapy. We further grouped treatments into two categories: conservative management and all other options, which we considered 'radical treatment' (see *Appendix 11* for further details and comparison to NICE guidance). The split by risk group is shown in *Table 11*.

The rates of progression to metastatic disease inferred in the calibration step (part 1) reflect the treatment allocations in Gnanapragasam *et al.*[112] (see *Table 11*). To consider the rates of progression with and without radical treatment, we disentangle the effect of treatment by considering that the pooled estimate of the rate of progression is a weighted average of the rates under radical treatment and conservative management (weighted by the proportions treated). The rates under radical treatment are assumed to be the rates under conservative treatment multiplied by a rate ratio sourced from external evidence. For such, we use the treatment effect from ProTecT,[55] the most recent UK study identified in the targeted review of the literature (see *Review of long-term evidence*). The rate ratio data for radical treatment pooled the PROTecT results for radical prostatectomy and radiotherapy, retrieving an estimate of 0.43 (95% CI from 0.26 to 0.72). Note that this estimate is similar to the US-based PIVOT study which estimated a HR for developing bone metastasis for radical prostatectomy of 0.40 (0.22–0.70).

Results

The results from the second part of the inference model, regarding the rate of progression from localised to metastatic disease by CPG and by treatment, are shown in *Table 11*.

Parameterisation of the prostate cancer health states transition probabilities

The transition probabilities from each of the 15 localised disease health states to metastatic disease were informed by calibration as described above [see *Inference sub-model (disease progression by Cambridge Prognostic Group and treatment intensity)*]. The calibration estimated the transition rates by true disease status and treatment assigned (active surveillance or radical treatment). Transition probabilities were subsequently estimated by weighting the annual transition rates according to the treatments assigned based on diagnosed category (see *Treatment of localised prostate cancer*), and then converted to annual transition probabilities assuming constant hazards over time (i.e. an exponential time to event distribution).

For patients in the metastatic disease health state transitions to PCa death were informed by PCa-specific death from the UK-STAMPEDE trial.[143] As described previously, a Weibull distribution was fitted using the *flexsurv* package in R data to the reconstructed individual-level PCa mortality data for the SOC (ADT) arm (metastatic patient subgroup) in Clarke *et al.*[143] The choice of parametric distribution was in line with a recent NICE TA evaluating enzalutamide in combination with ADT for hormone-sensitive metastatic cancer and based on a visual fit assessment conducted by the EAG (a full assessment of survival curve fit was considered out of scope for this assessment, so a targeted approach was taken). This baseline probability was parametrised in the executable model based on the *flexsurv* estimated Weibull coefficients (with a multivariate normal distribution fitted using the corresponding Cholesky decomposition for the PSA) and then adjusted by the effectiveness of contemporaneous combination treatments (i.e. in addition to ADT) weighted HR according to the current treatment distribution (see *Treatment of localised prostate cancer*). The weighted hazard ratios (HRs), for three combinations used in current clinical practice for first-line metastatic PCa compared to ADT alone, were applied to the baseline probability of PCa death to derive the metastatic to PCa death transition probability. The combination treatments considered in the model included DTX (HR vs. ADT 0.78, 95% CI: 0.66 to 0.93),[143] enzalutamide (HR vs. ADT 0.66, 95% CI: 0.53 to 0.81)[149] and apalutamide (HR vs. ADT 0.65, 95% CI: 0.53 to 0.79).[150] Lognormal distributions were fitted to each HR in the probabilistic model setup.

Other-cause mortality

Age-dependent other-cause mortality rates for men from Office for National Statistics (ONS) lifetables (2018–20 collection period)[144] was used to estimate other-cause death probabilities in the long-term model. Parameter uncertainty was not considered for these inputs, due to the large sample size of the source data set.

Treatment of prostate cancer

In *Prostate cancer management: active surveillance, watchful waiting and radical treatment options*, we stated that the clinical management (choice component) of individuals with a localised and locally advanced PCa diagnosis in the model was conditional on (1) diagnosed CPG score for the treatment component and (2) on the type of PCa treatment (active surveillance or radical treatment) received for the routine monitoring component. For those in the metastatic health state, treatment includes androgen deprivation alone or in combination with other treatments. Here we present further details on the treatment distribution inputs in the model for (1) localised disease and (2) metastatic disease.

Treatment of localised prostate cancer

National Institute for Health and Care Excellence NG131 makes separate treatment recommendations by CPG score and conditional on patient preference and/or suitability for radical treatment (see *Prostate cancer management: active surveillance, watchful waiting and radical treatment options*) for individuals diagnosed with localised and locally advanced PCa. In order to reflect treatment allocation based on the diagnosed CPG score and the patient-level factors, we have sourced treatment allocation from Parry *et al.*[151] a study on the differences in localised and locally advanced treatment according to CPG in clinical practice in England. Our approach parameterising the treatment distribution contrasts to the approach taken in a previous DAR.[116] First, in the York model the distribution of active surveillance and radical treatments is conditional on the diagnosed disease status, whereas the Southampton DAR model conditioned this distribution on the 'true' disease category. Second, this previous model sourced the treatment distribution mostly from Gnanapragasam *et al.*[112] with further assumptions imposed on this distribution based on NPCA data. Both, Parry *et al.* [151] and Gnanapragasam *et al.*[112] reported treatment distribution by CPG for cohorts of newly diagnosed with non-metastatic cancer. However, we preferred to source the treatment distribution from Parry *et al.* [151] to Gnanapragasam *et al.*[112] because the data collection period is more recent (2014–7 vs. 2000–10) and had a higher sample size (61,999 vs. 10,139). Furthermore, Parry *et al.*[151] collected evidence from England, whereas Gnanapragasam *et al.*[112] was limited to data collected within the East of England Cancer Network area. We therefore considered the evidence in Parry *et al.*[151] study to be more contemporaneous and likely to be more reflective of current clinical practice than Gnanapragasam *et al.*[112]

Table 12 contrasts the PCa management options distribution in the current and previous DAR. We note that the estimates applied in the York model, for individuals diagnosed with CPG 2 and 3, suggest less use of radiotherapy and more use of radical prostatectomy compared to what was applied to individuals with intermediate risk disease in the Southampton DAR model.[116] There are also differences between studies in the proportion of individuals receiving active surveillance and watchful waiting.

In the York model, we assumed that individuals would not be treated with watchful waiting, because this is a monitoring strategy for individuals for whom potentially curative treatment is not suitable (or do not wish to undergo this type of treatments). mpMRI to inform prostate biopsy decisions is currently only recommended for people who can undergo radical treatment,[10] so the exclusion of this treatment option was considered clinically plausible. We, therefore, assumed that individuals who were not treated with radical treatment underwent active surveillance.

Parry *et al.*[151] did not report the proportion of individuals who were treated with brachytherapy, a radiotherapy that is more costly than external therapy. We assumed that the proportion of individuals treated with radiotherapy who underwent brachytherapy by CPG was the same as in Gnanapragasam *et al.*[112] with the remaining patients receiving external therapy. Furthermore, we

TABLE 12 Localised disease treatment distribution

	Southampton DAR model[116]			York model			
	'True' disease status			Diagnosed disease status			
Treatment choice based on	Low-risk[a] (%)	Intermediate-risk[a] (%)	High-risk[a] (%)	CPG1 (%)	CPG2 (%)	CPG3 (%)	CPG4–5 (%)
Active surveillance	95	12.7	0	88.7	51.6	33.7	24.1
Radical prostatectomy	2	21.9	17.6	6.6	27.2	26.3	22.8
Radiotherapy	3	52.8	52.4	4.7	21.3	40.0	53.1
External radiotherapy	2.3	48.7	52.5	3.6	19.0	38.2	52.3
Brachytherapy	0.7	4.1	0.9	1.1	2.3	1.8	0.8
Watchful waiting	0	12.7	29	0	0	0	0

a Low-risk assumed to correspond to CPG 1, intermediate-risk to CPG 2 and 3 (grey highlight) and high-risk to CPG 4 and 5.

assumed that all patients treated with radiotherapy also received ADT (length of treatment conditional on diagnosed CPG score), as per the Southampton DAR.[116] We note that current clinical guidance recommends 6 months of ADT before, during or after radiotherapy for individuals with CPG 2 to 5, and for treatment to continue for up to 3 years for people with CPG 4 and 5.

There is also an important structural difference in the choice component of the York model compared to the Southampton DAR.[116] As stated in *Inference sub-model (disease progression by Cambridge Prognostic Group and treatment intensity)* and *Parameterisation of the prostate cancer health states transition probabilities*, the York model has flexibility to reflect different treatment distributions between conservative (active surveillance) and radical treatment on disease progression, as the calibration model estimates disease progression rates by type of treatment and the derived transition probabilities for each localised disease health state are adjusted as a function of the treatment distribution per diagnosed CPG. In contrast, the calibrated disease progression probabilities in the Southampton DAR model[116] reflect the treatments received by the individuals in the outcome data used to derive them [i.e. Gnanapragasam *et al.*[112] for the diagnosed states and Bill-Axelson *et al.*[135] (observation arm)] and changes in the parameterisation of the treatment distribution only change how the cost and disutility of localised disease management are weighed in the model.

We fitted a Dirichlet probability distribution to the disaggregated observed count data by treatment type in Parry *et al.*[151] in the probabilistic parameterisation of the model.

Treatment of metastatic prostate cancer

Metastatic disease is treated initially with ADT alone or in combination, while disease is hormone-sensitive. Once disease progresses to hormone resistance, ADT is stopped and individuals will receive subsequent treatments.

Initial metastatic disease treatment (hormone-sensitive metastatic cancer) was assumed to consist of a mix of ADT alone and in combination with DTX, enzalutamide and apalutamide, similarly to a previous DAR.[116] We updated the distribution of metastatic treatments in the Southampton DAR to reflect the 74% reduction in the use of DTX between 2019 and 2020 suggested by the NPCA 2021 report.[4] Therefore, in the York model we assumed that 9% of individuals with hormone-sensitive metastatic cancer would be treated with DTX in combination with ADT (in contrast with the 36% in the Southampton DAR). We assumed that the difference in the proportion of treated with DTX between

the two models (27%) would receive enzalutamide instead, since the NPCA 2021 report[4] also suggested a considerable increase on the use of this alternative treatment. We have sourced the proportion of treatment with ADT alone and in combination with apalutamide directly from the Southampton DAR.[116] The metastatic treatment distribution applied in the two models is reported in *Table 82*, *Appendix 11*.

As mentioned in *Parameterisation of the prostate cancer health states transition probabilities*, the distribution of hormone-sensitive metastatic cancer treatments was reflected in the transition probability from metastatic to PCa death, by weighing the treatment of effect of combination therapy according to the relative distribution of treatments. This was also in contrast with the Southampton DAR model,[116] which did not link metastatic treatment distribution to the metastatic treatment effectiveness.

Subsequent metastatic treatment (for hormone-resistant metastatic cancer) was also considered in the York model, for the proportion of individuals who survived the first 2 years in the metastatic health state (see *Treatment of metastatic prostate cancer*). The treatments considered included monotherapy with abiraterone, DTX and enzalutamide, and best supportive care, and the treatment distribution was conditional on the type of treatment received at first line (i.e. for hormone-sensitive metastatic cancer). We sourced the hormone-resistant metastatic treatment distribution from the Southampton DAR model[116] (see *Table 82*, *Appendix 11*). While the hormone-sensitive metastatic treatment distribution is linked to treatment costs, treatment effectiveness and AE costs, the hormone-resistant metastatic treatment distribution in both models is applied only to estimate the costs of metastatic treatment. While this structural decision was not justified in the Southampton DAR,[116] we considered that extending the model to establish these additional links would be of limited value to this assessment. Therefore, the York model does not consider the effectiveness and safety of hormone-resistant metastatic treatment.

Given that the distribution of metastatic cancer treatments was informed by assumptions, these parameters were not set up probabilistically (i.e. probability distributions were not fitted to these parameters).

Adverse events

Biopsy procedure-related adverse events

The biopsy procedure is associated with AEs such as urinary retention, infections, sepsis, haematuria and death. The cost and HRQoL impacts of these AEs vary according to their severity and the level of healthcare resource use required to treat them.

The review in *Systematic review methods (study selection, data extraction, quality assessment)* could not establish differences in the type and the rates of AEs (i.e. the safety profile) between software and CF, as well as between different SF systems. This was because either comparative safety evidence was not presented, was confounded by the biopsy route of access or the observational nature of the studies limited the ability to attribute differences to the intervention. Furthermore, there is a clear biological mechanism (e.g. clear difference in the number of cores for each MRI-influenced method or a marked increase in procedural time that might increase the likelihood of AEs from anaesthesia) that suggests the safety profile of cognitive and SF is different.

The Southampton DAR[116] modelled differences in safety profile between biopsy procedure by route of access and type of anaesthesia. In their revised base case, the biopsy complications considered for LATP/GATP and LATRUS were mild AEs (more frequent with transperineal biopsies), AEs leading to non-elective hospital admission within 28 days of the procedure and peri-procedural death (also within 28 days of the procedure). Transperineal biopsies had a higher rate of mild AEs and slightly lower rates of non-elective admission and peri-procedural death.[116,152] *Table 83* in *Appendix 11* summarises the AE rates and sources used to parameterise the current report base-case analysis (which correspond to the revised base-case estimates in the Southampton DAR).[116]

We note that the AE rates estimated for the Southampton DAR[116,152] did not distinguish between biopsies in terms of sample collection method, so it is unclear whether these estimates are reflective of the safety profile of systematic, targeted or combined biopsies. In the base case, we assume that the biopsy safety parameterisation of the Southampton DAR is applicable to targeted biopsies and that there are no differences in biopsy complications between these and combined biopsies; this assumption is relaxed in sensitivity analysis.

Parameter uncertainty in the AE rates was modelled by fitting beta distributions to these parameters.

Localised treatment adverse events

Individuals diagnosed as having PCa will receive treatment for localised disease (active surveillance or radical treatment) in the long-term model according to their diagnosed CPG category, while those diagnosed as not having the disease are assumed to receive monitoring (see *Treatment of localised prostate cancer*). Both radical and conservative (active surveillance) treatment are assumed to have associated AEs.

In line with the Southampton DAR and the NICE NG131 model,[116,123] our base-case analysis includes the following categories of AEs for radical and conservative treatment: (1) erectile dysfunction, (2) urinary incontinence and (3) bowel dysfunction. The rates of AEs for radical prostatectomy, radiotherapy and active surveillance were sourced from *Table 64*, in the Southampton DAR,[116] which was informed by a single trial comparing all three treatments (PROTecT trial[138]). While all patients receiving radiotherapy are assumed to also received ADT (see *Treatment of localised prostate cancer*), the Southampton DAR assumed no AEs from hormone therapy;[116] we also applied this assumption in the York model.

Parameter uncertainty in the AE rates was modelled by fitting beta distributions to these parameters.

Metastatic disease treatment adverse events

Similarly, to the Southampton DAR model,[116] we only modelled AEs of treatment for hormone-sensitive metastatic disease. AE rates per type of AE were sourced from *Table 64*, in the Southampton DAR,[116] which obtained the rates from three pivotal trials[59,150,153] comparing ADT alone to each of the three combination therapies modelled.

Parameter uncertainty in the AE rates was modelled by fitting beta distributions to these parameters.

Health-related quality of life

Health-related quality of life outcomes, estimated from an NHS and PSS perspective, in the model are expressed as QALYs and discounted at 3.5% annual rate.

Biopsy procedure disutility

The model considers the disutility of biopsy-related AEs. In line with the Southampton DAR[116] a disutility weight was attributed to each type of AE (mild, leading to non-elective hospital admissions and death) and then adjusted for duration of the event to generate a QALY loss per type of AE. The biopsy procedure QALY loss in the model is then adjusted to reflect the different safety profile between transperineal and transrectal biopsy. The disutility weights and AE duration per type of AE are reported in *Table 84* in *Appendix 11*, and were sourced from the Southampton DAR.[116] We did not consider parameter uncertainty in the disutility weights or AEs duration inputs, given lack of information on their variance.

Health state utilities and treatment disutilities

Health state utilities and treatment disutilities were applied as per the Southampton DAR,[116] but adapted for the delayed radical treatment at 2 years in the model for misdiagnosed cases.

Resource use and costs

The resource use and costs, considered in the diagnostic pathway, include those associated with the biopsy procedure and its adverse eves. The long-term model quantifies the costs of monitoring individuals following the diagnostic procedures in the diagnostic model, the costs of PCa treatment and end of life. Costs in the model are expressed as 2020–1 Great British pounds, estimated from a NHS and PSS perspective, and discounted at a 3.5% annual discount rate.

The resource use and cost in the long-term model (costs associated with monitoring, PCa treatment, treatment AEs and end of life) was largely informed by the Southampton DAR,[116] as were the unit costs sources (updated or inflated to 2020–1 price year as appropriate). Therefore, descriptions of these categories of cost and resource use are brief and refer back to the Southampton DAR model.[116] Emphasis is put into describing elements where our assumptions and/or parameter sources differ from those of the Southampton DAR model.[116]

Parameter uncertainty in resource use and costs inputs was not considered for the large majority of the inputs due to lack of information on their variance and the reliance on assumptions to define parameter quantities.

Biopsy procedure costs

This section reports the costs associated with the biopsy procedure, which include the following components:

1. Cost of the SF system – costs of the fusion software and, in some cases, a workstation (or cart). This cost only applies to the diagnostic strategies which include a SF component.
2. Cost of the ultrasound – cost of the ultrasound probe/transducer, and any required software. This cost applies to diagnostic strategies with either software or cognitive function components, but some SF systems are not compatible with third-party ultrasounds.
3. Cost of SF system installation – cost of connecting the SF system to the NHS trust IT system. This cost only applies to the diagnostic strategies which include a SF component.
4. Cost of SF system maintenance – costs of service contracts to maintain the technology and keep software up to date. This cost only applies to the diagnostic strategies which include a SF component.
5. Costs of SF system training – staff time costs required to train NHS professionals to perform biopsies. The use of SF methods requires additional training compared to CF, but the cost of training also varies across biopsy approaches (by route of access).
6. Cost of staff time to perform the biopsy procedure – cost of urologists, nurses and anaesthetist (for procedures requiring general anaesthesia). This cost varies across biopsy approaches (by route of access and type of anaesthesia), but there is also a difference in procedural time between SF and CF.
7. Cost of the biopsy setting – costs of the setting in which the biopsy procedure takes place (outpatient room, theatre session); it varies by route of access, type of anaesthesia, and MRI-influenced method.
8. Costs of other biopsy devices and consumables – cost of (a) devices and equipment (e.g. freehand needle positioning devices, lithotomy beds and biopsy guns) and (b) needles and other materials requiring replacement (immediate or after a certain number of uses). These costs are often specific to the biopsy approach [transrectal or transperineal (stabilised, freehand or double freehand)], and may differ across MRI-influenced methods and across SF systems, due to compatibility issues.
9. Cost of histopathology analysis and report – costs of processing the biopsy sample and communicating the results to the patient in a consultation. This cost applies to all strategies but may differ for strategies using different sampling methods (combined vs. targeted-only biopsy), as these may result in different number of cores being sampled.

The evidence considered to estimate these components of costs (and their calculation) is detailed in *Tables 85–95*, *Appendix 11*. *Table 13* summarises the aggregated cost per biopsy for each technology and by biopsy approach, with further breakdown of costs in *Tables 96–98* in *Appendix 11*.

As stated in *Modelling of long-term outcomes*, we assumed for the first biopsy in the diagnostic pathway, 65% of biopsies were conducted with LATP and the remainder with LATRUS. For the repeat biopsy, we assume that 60% are LATP, 30% are LATRUS and 10% are GATP (to reflect those individuals where there was concern that first biopsy may not have been accurate due to patient moving excessively during the procedure). We weighted the costs per biopsy approach by the corresponding proportions for first and repeat biopsy to estimate their costs in the model; these costs are reported in *Table 14*.

There are a number of uncertainties in the biopsy procedure costs. These pertain to:

- the set of essential components that are integral part of each technology and the lifespan for all components

TABLE 13 Cost per biopsy by technology and biopsy approach

		Biopsy approach		
	Technology	**LATRUS (£)**	**GATP (£)**	**LATP (£)**
Technology specific	bkFusion	147.48	380.67	231.68
	FusionVu	169.47	402.67	253.68
	KOELIS Trinity	150.37	384.86	235.87
	BiopSee	89.51	323.52	179.18
	Fusion Bx 2.0	158.10	391.72	242.73
	CF	48.44	260.00	133.07
Non-technology specific		209.95	634.15	239.25
Total cost per biopsy	bkFusion	356.53	914.82	470.93
	FusionVu	378.53	936.82	492.93
	KOELIS Trinity	359.43	919.01	475.12
	BiopSee	298.56	857.67	418.43
	Fusion Bx 2.0	367.15	925.87	481.98
	CF	257.49	794.15	372.32

GATP, general anaesthesia transperineal biopsy; LATRUS, local anaesthesia transrectal ultrasound.

TABLE 14 Cost of first and repeat biopsy in the model

Technology	1st biopsy cost (£)	Repeat biopsy cost (£)
bkFusion	430.89	481.00
FusionVu	452.89	503.00
KOELIS Trinity	434.62	484.80
BiopSee	376.47	426.39
Fusion Bx 2.0	441.79	491.92
Average cost SF	427.33	477.42
CF	332.13	380.05

- the potential commercial discounts that may be offered by the companies, what is included in the commercial arrangements and how do these apply to each technology
- what additional costs may stem from compatibility issues with existing equipment and accessories in use in the NHS
- the additional time required to perform SF
- how training for the use of SF is delivered (to whom and for how long), and if the training requirements differ substantially between SF technologies.

Given these uncertainties and that it was not possible to calculate diagnostic performance evidence by individual SF devices at the granularity of classification (ISUP G1, ISUP G2, ISUP G3, and ISUP G4 or 5) required by the economic model, it was considered the biopsy procedure costs for each individual technology was potentially misleading to decision-makers. Thus, we apply the average biopsy cost across all SF technologies in this assessment for which cost data were submitted by the companies. Given this and the numerous uncertainties in the cost estimation of each SF technology, it was not considered appropriate to compare each SF technology against each other and CF in the model. Instead, in the base-case analysis, we apply the average cost per biopsy across all SF. Individual SF technology costs are presented alongside the base-case analysis results to illustrate how their individual costs would impact on the estimates of cost-effectiveness.

Biopsy procedure adverse events costs

The biopsy procedure-related AE costs, considered in the diagnostic pathway model, were estimated by multiplying the AE rate by the unit cost for each type of AE. The unit costs for each type of AE were derived from the Southampton DAR sources {updated for the 2020–1 price year by either using the corresponding versions of national tariffs [e.g. Personal Social Services Research Unit (PSSRU) and NHS reference costs] or inflating costs using the NHS Cost Inflation Index (NHSCII),[154] as appropriate} and using the same assumptions (e.g. on resource use required to treat a mild AEs);[116] further details are presented on in *Table 99* in *Appendix 11*.

Monitoring costs

Routine monitoring costs at model entry apply to all patients who enter the long-term model. In the model, the set of monitoring tests and schedule varying according to whether the individuals have been diagnosed:

- localised and locally advanced PCa, and if so, monitoring also varies with:
  - the diagnosed CPG category (CPG 1, CPG 2–3 or CPG 4–5)
  - treatment assigned (active surveillance or radical treatment)
  - and time in the model (first, second or subsequent years).
- or not, and if so, monitoring only varies with the underlying true disease status (no PCa or CPG1–5).

Table 100 in *Appendix 11* summarises the resource use and cost per year of the monitoring tests considered in the model for patients in the diagnosed as localised (and locally advanced) disease health states. These costs are applied from model entry (cycle 0) and while individuals remain in the localised disease health states.

We assumed that individuals without a PCa diagnosis would also undergo routine monitoring, regardless of whether they had PCa. In contrast, the Southampton DAR[116] only attributed a cost of monitoring to those with localised PCa who had not been identified as having PCa. We changed this assumption in the York model, because in principle these two groups of individuals would be indistinguishable, as true disease status would be unknown to clinicians. We assume that in both groups individuals receive the same monitoring schedule when they are discharged to primary care: an annual PSA test (velocity test at a threshold of 75 ng/ml/year) for up to 10 years, performed at a 10-minute nurse-led appointment, and followed by a CF biopsy (costed at £477.75; assumes 35% LATRUS and 65% LATP) if the PSA test results is positive. As per the Southampton DAR,[116] the probability of testing positive in the PSA test

for those with PCa was assumed to be 0.69, which corresponds to the sensitivity of the corresponding PSA velocity test used in NICE NG131 model. We further assumed that the probability of testing positive in the PSA test for those without PCa corresponded to one minus the specificity of the same test (1–0.56 = 0.44). The testing schedule is similar to what was modelled in the Southampton DAR[116] for those with PCa who were diagnosed as not having the disease, but the first PSA test is assumed in the York model to occur within 1 year in the long-term model (rather than 6 months). The annual cost per year of monitoring applied in the York model was £342.50 and £223.06 for those with and without PCa, respectively. These costs are applied from model entry (cycle 0) and for up to 10 years in the entry health states.

After 2 years in the model, individuals in the local disease health states are assumed to be correctly identified at their true disease status, and move to the monitoring regime that matches their true disease status.

Individuals who enter the metastatic health state incur a one-off monitoring cost of £577.83, corresponding to the same resource use as in the Southampton DAR[116] (i.e. one CT and bone scan).

Prostate cancer treatment costs – localised disease

Individuals identified as having localised PCa are assumed to receive treatment at long-term model entrance according to their diagnosed CPG (see distribution of treatments by diagnosed CPG in *Treatment of localised prostate cancer*). Individuals who receive active surveillance is assumed to not incur any treatment costs (only monitoring costs as detailed in *Prostate cancer treatment costs – localised disease*), so costs of treatment are only incurred by those who undergo radical treatment.

Radical treatment resource use and costs vary according to the type of radical treatment (radical prostatectomy, external radiotherapy or brachytherapy). The cost of each type of radical treatment procedure applied in the York model is reported in *Table 101*, *Appendix 11*, alongside details on resource use and unit costs. We note that the cost of brachytherapy has increased considerably in relation to the one used in the Southampton model (£9156.96 vs. £3106.02); these differences are driven by an increase in the unit cost of delivering brachytherapy in an outpatient setting (as well as increased activity for the corresponding currency code) in 2020–1 compared to 2019–20. The costs of the radical treatment procedures were applied as one-off costs at long-term model entry (cycle 0). For those who were misdiagnosed and treated with conservative treatment, it is assumed that they receive radical treatments according to their true disease status after 2 years in the model.

In addition to the medical procedures, we also included the cost of ADT for those patients who treated with radiotherapy, according to NICE guidance.[10] ADT in the localised disease setting was assumed to consist of the same treatments as in the Southampton model, that is, bicalutamide 50 mg for 21 days followed by luteinising hormone-releasing hormone (LHRH) agonists [either leuprorelin 11.25 mg (every 3 months), triptorelin 11.25 mg (every 3 months) or goserelin 3.6 mg (every 28 days)]. Similarly, to the Southampton model, the duration of LHRH treatments was varied according to category of prognostic risk; we assumed LHRH treatment duration would be 3 and 6 months for those diagnosed in CPG 1 and CPG 2–3 categories. For those diagnosed in the CPG 4–5 category, we updated the duration of treatment for 3 years, in line with the current NICE guidance for that prognostic risk group (see *Care pathways for the diagnosis and management of prostate cancer*).[10] The costs of ADT included drug acquisition and administration costs and were costed as per the Southampton DAR (updated to the current price year).

Prostate cancer treatment costs – metastatic disease

Metastatic disease treatment was assumed to consist of hormone-sensitive disease treatment for the first 2 years in the metastatic health states, followed by hormone-resistant disease treatment. Costs of metastatic treatment are summarised in *Table 102*, *Appendix 11*; these include drug acquisition and administration costs.

In line with the Southampton DAR, hormone-sensitive metastatic treatment was modelled as a blended treatment consisting of ADT alone (but not identical to the regimes described for the localised disease setting, as course of bicalutamide 50 mg is longer), or in combination with either DTX, apalutamide or enzalutamide. We updated the distribution of treatments for the hormone-sensitive metastatic treatment, as described in *Treatment of metastatic prostate cancer*. We note that yearly costs of metastatic treatment have increased considerably in the York model compared to the Southampton model (e.g. metastatic hormone-sensitive first year cost increased to £15,603.87 from £8388.63), due to the increased proportion of individuals treated with ADT combined with enzalutamide, due to the high cost of enzalutamide. Furthermore, although we apply the same DTX treatment regimen [i.e. six cycles (delivered every 3 weeks) at a dose of 75 mg/m^2; body surface area 1.91] as in the Southampton model, in the York model the 2-year DTX treatment costs are assumed to be distributed evenly between two model cycles (constant annual cost).

The Southampton DAR states that ADT alone or in combination was taken until disease progression, which was assumed to occur after 2 years. We also make their stated assumption, but we implemented it in a different way. In the Southampton model, a cost for first and second year is estimated for metastatic treatment (both treatment for hormone-sensitive and hormone-resistant disease) and applied to individuals in the metastatic disease state at first and second year (modelled in a way akin to tunnel states), respectively. Thus, in the Southampton model the cost of hormone-sensitive and hormone-resistant treatment is applied to the same set of individuals. In the York model, we explicitly model a set of three tunnel health states representing the first, second and subsequent years of metastatic disease (*Figure 12*). We applied the costs of hormone-sensitive metastatic treatment to individuals in the first and second year of metastatic tunnel health states, and the costs of hormone-resistant metastatic treatment costs are applied as a one-off cost to individuals who enter the 'metastatic subsequent years' health state.

Another difference between models is that in the York model metastatic treatment (and monitoring) is assumed to apply to all patients with metastatic disease, as we do not distinguish between diagnosed and undiagnosed metastatic disease (the latter does not appear to incur treatment costs in the Southampton model). Thus, we implicitly assume that all individuals with metastatic disease have been diagnosed.

All metastatic treatments costs are applied as an average of the costs of the different types of treatments weighted by their treatment distribution (see treatment distribution in *Table 12*, *Treatment of localised prostate cancer*).

Prostate cancer treatment adverse event costs – localised disease

The model considers the costs of managing the AEs from active surveillance, radical prostatectomy and radiotherapy for localised PCa. These costs were estimated by multiplying the AE rates (see *Localised*

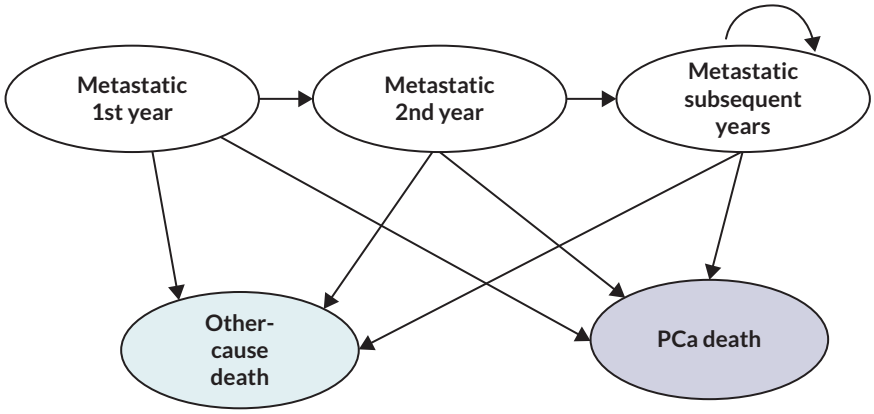


FIGURE 12 Diagram of metastatic tunnel health states and death states.

treatment adverse events) by the unit cost of the corresponding AE (see *Table 103*, *Appendix 11*). The costs are applied in the model as a one-off at localised disease health states to the proportion of patients who receives each treatment (see treatment distribution in *Table 12*, *Treatment of localised prostate cancer*).

Prostate cancer treatment adverse event costs – metastatic disease

The costs of managing metastatic treatment-related AEs was applied in the model. Similarly, to the Southampton model only AEs of treatment for hormone-sensitive metastatic disease were included. The AE costs for androgen therapy alone and in three alternative combinations (with DTX, apalutamide or enzalutamide) were estimated by applying the unit cost per type of AE (see *Table 103*, *Appendix 11*) by the corresponding rate (see *Metastatic disease treatment adverse events*). The resulting costs per treatment were then applied as a one-off cost at entrance to the 'metastatic 1st year' health state. The one-off cost was estimated by weighing each treatment cost by the metastatic treatment distribution (see treatment distribution in *Table 82* in *Appendix 11*).

End-of-life costs

End-of-life costs are applied to all individuals who die in the model of other-cause or PCa death, but not to those who have died of peri-procedural biopsy complications (see *Biopsy procedure related adverse events*). This one-off cost is applied to individuals who enter the death states at each cycle in the model, and it was sourced from Round *et al.*[139] and inflated to 2020–1 price year.[154]

Analytic methods

Overview

The diagnostic and long-term model is evaluated deterministically and probabliistically for the base-case analysis (1000 Monte Carlo simulations) to incorporate the joint parameter uncertainty across all of the model inputs according to the probability distributions assigned to each. The parameters set up probabilistically in the model are identified in *Table 104* in *Appendix 11*.

Following conventional decision rules for cost-effectiveness, the mean costs and QALYs for the two strategies (cognitive or software fusion) for two set of comparisons (targeted biopsy alone or combined with systematic biopsy) are presented and cost-effectiveness compared by estimating the ICERs, as appropriate. A NHB approach is also applied, for which the unambiguous decision rule. Net benefits can be expressed on the effect scale (NHB), which is calculated at the two cost-effectiveness thresholds at the lower and upper bound of the range used by NICE to guide decision-making (i.e. £20,000 and £30,000 per additional QALY). The formula to estimate NHBs is presented below:

$$\text{Net health benefit (NHB)} = \text{QALYs} - \frac{\text{Costs}}{\text{Cost} - \text{effectiveness threshold}}$$

Heterogeneity is partly explored in a subgroup analysis detailed in *Subgroup analysis*. Uncertainty regarding the appropriate source of data, and other assumptions are explored by scenario analysis and threshold analysis, as detailed in *Threshold analysis on costs of software fusion* and *Scenario analyses*.

Base-case analysis

The base-case analysis considers two alternative set of comparisons. The first comparison is established between targeted SF and targeted CF, while the second is established between combined SF and combined CF. Therefore, we consider a dual base-case analysis with results presented separately for (1) targeted biopsy alone and (2) combined (targeted + systematic) biopsy.

The dual base case is defined by the following data sources and assumptions:

- the main analysis extension to the evidence synthesis for the subgroup of biopsy-naive individuals, which uses:
  - the baseline distribution of test results for SF sourced from biopsy-naive data from Filson *et al.*;[96]
  - relative accuracy data from the multinomial evidence synthesis model (Model 1a) which was incorporated into the extension to the evidence synthesis – network 1 was used to inform the targeted biopsy comparison, while network 2 informed the combined biopsy comparison;
  - accuracy data from Mortezavi *et al.*[107] extension to the evidence synthesis;
- the only differences between combined and targeted biopsy stem from the data used in the extension to the evidence synthesis [i.e. they are assumed to have the same profile of AEs and biopsy procedure costs (note that both set of comparisons consider SF and CF biopsy)];
- the cost of first and repeat biopsy with SF is modelled as an average of these costs for each technology (headline cost-effectiveness results for the individual technologies are presented for the base case analysis) and
- the cost of first biopsy assumed procedures are conducted as a mix of LATP and LATRUS; similarly, repeat biopsy is a mix of LATP, GATP and LATRUS. These proportions were assumed the same for SF and cognitive biopsy.
- Structural assumptions:
  - only individuals classified in the CPG 1 or 'no cancer' categories are eligible for repeat biopsy, and of those a fixed proportion received repeat biopsy in the model (15.45% and 5% for those classified CPGI and 'no cancer', respectively);
  - while the model considers different progression rates by true CPG (as modified by radical treatment effect in accordance with the diagnosed CPG), progression across CPG scores is not modelled – only progression between each local disease status and the metastatic health state are possible;
  - after 2 years in the misclassified localised disease health status, all individuals who remain in the corresponding states and have not yet received radical treatment will receive radical treatment according to their true disease status, incurring the costs and disutility of radical treatment then and receiving monitoring commensurate with their true disease status from that point onwards.

Threshold analysis on costs of software fusion

We highlighted in *Resource use and costs* uncertainties and areas of evidence scarcity, relating to the costs of the biopsy procedure, particularly for the SF technologies. We reiterate that given these uncertainties and that it was not possible to calculate diagnostic performance evidence by individual SF devices with the necessary classification granularity required by the economic model, it was considered the biopsy procedure costs for each individual technology were potentially misleading to decision-makers.

Thus, we apply the average biopsy cost across all SF technologies in this assessment for which cost data were submitted by the companies. We also perform a threshold analysis in which we estimate what is the cost per biopsy procedure with SF at which it is no longer likely that the new technologies will be cost-effective at the conventional range of opportunity costs considered by NICE. This threshold analysis applies the same assumptions and data sources of the base-case analysis, but assumes that:

- all biopsies are LATP procedures
- excludes the cost of the third-party ultrasounds from the biopsy cost calculations (to disentangle the cost of cognitive and SF).

These assumptions are necessary in order to run a threshold analysis varying a single parameter (i.e. cost of SF biopsy).

Subgroup analysis

As mentioned in *Results*, the extension of the evidence synthesis included a subgroup analysis for previous negative-biopsy individuals. We performed a subgroup analysis for the same group of patients, which mirrors the subgroup analysis in *Results*. In brief, this subgroup analysis used the same evidence

sources to inform the extension to the synthesis, except the baseline distribution of test results for SF. This was sourced from previous negative biopsy data from Filson *et al.*[96]

Scenario analyses

The scenario analyses are summarised in *Table 15*. In brief, the aim of the scenario analysis is:

- Scenario analyses 1 and 2: to mirror the sensitivity analysis performed around the sources of data informing the sensitivity analyses of the evidence synthesis extension (see *Results*), and explore their impact on the cost-effectiveness estimates.

TABLE 15 Description of the scenario analyses

Scenario number and label	Element of uncertainty	Base case	Scenario variation
1. PAIREDCAP (2019) baseline	Extension of the evidence synthesis model	Data sources for the extension to evidence synthesis: • baseline distribution of test results for SF from biopsy-naive data in Filson *et al.* • Relative accuracy data from the multinomial evidence synthesis model (Model 1a, network 1 + 2 – targeted and combined biopsy). • Accuracy data from Mortezavi *et al.*	Data sources for the extension to evidence synthesis: • baseline distribution of test results for SF from biopsy-naive data in biopsy-naive data from PAIREDCAP (2019) for network 1. • Relative accuracy from the multinomial evidence synthesis model (Model 1a, network 1 only – targeted biopsy). • Accuracy data as for base-case analysis.
2. Zhou (2018) diagnostic			Data sources for the extension to evidence synthesis: • Baseline distribution of test results for SF as for base-case analysis. • Relative accuracy from the multinomial evidence synthesis model (Model 1a, network 1 only – targeted biopsy). • Acccuracy data from Zhou *et al.*[142](2018)
3. Degradation of repeat biopsy accuracy	Diagnostic performance of MRI-influenced repeat biopsy	Repeat biopsy is as accurate as first biopsy for both cognitive and SF.	• Probability of correctly classifying individuals as having cancer at each CPG category is reduced by 80% at repeat biopsies (changes in diagnostic accuracy are distributed equally across all other possible CPG classifications for each true disease CPG).
4. SF as quality assurance	Diagnostic performance of MRI-influenced biopsy and selection for repeat biopsy	Diagnostic performance of MRI-influenced biopsy is informed by the extension of the evidence synthesis model 1a (network 1 and 2) and only a proportion of those classified at first biopsy as having NC or CPG1 receive repeat biopsy.	• No difference in overall diagnostic performance of CF vs. SF • Individuals eligible for repeat biopsy are those: ○ Who have been misclassified as CPG1or NC at first biopsy with SF ○ Who have been classified (correctly or not) as CPG1or NC at first biopsy with SF
5. Radical treatment for all identified CPG ≥ 2 and conservative treatment for CPG 1	Distribution of treatment for localised disease	The distribution of radical treatment for localised disease is sourced from Parry *et al.*[151]	All individuals diagnosed CPG ≥ 2 are treated at long-term model entrance with radical treatment (maintaining the distribution between radical prostatectomy and radiotherapy as per the base case) and those diagnosed with CPG1 receive conservative treatment (and do not switch for radical treatment).
6.1 Throughput (150/year)	Annual biopsy throughput	300 biopsies per year	• 150 biopsies per year: 50% lower than base case
6.2 Throughput (450/year)		300 biopsies per year	• 450 biopsies per year: 50% higher than base case

- Scenario analysis 3: to explore the impact of lowering the diagnostic accuracy of repeat biopsy, as considered in the PROMIS, NICE NG131 and Southampton DAR models.
- Scenario 4: to model the use of SF biopsy as quality assurance, as this was suggested by clinical advisers to the EAG as a potential value component of software. The clinical advisers commented that they would be more confident that a negative biopsy result with SF biopsy following a positive MRI result would not require a confirmatory biopsy compared to CF, and that this confidence did not arise from any perceived gains in diagnostic accuracy of SF versus CF biopsy. Thus, we set the diagnostic accuracy of SF to be equal to the base-case accuracy for CF (implying that the sole value of SF is to inform the selection of cases for repeat biopsy), and we changed the eligibility criteria for repeat biopsy with SF as described in *Table 15*.
- Scenario 5: aims to approximate the assumptions on localised disease treatment conditional on final classification to those of the PROMIS model.
- Scenarios 6.1 and 6.2: aim to explore the impact of using SF in NHS trusts with lower (6.1) and higher patient throughput (6.2) than that assumed to correspond in the base-case analysis to the national average throughput.

Results

Base-case analysis

The deterministic and probabilistic cost-effectiveness results for the base-case analysis are presented in *Tables 16* and *105*, *Appendix 12*, respectively. Base case results for each individual technology are also presented in *Tables 114* and *115*, *Appendix 12*. The data sources used to derive prevalence and true disease status (see *Table 110*, *Appendix 12*) in this analysis refer to a biopsy-naive population. For both the targeted biopsy (informed by network 1 of Model 1a) and the combined biopsy (informed by network 2 of Model 1a) comparisons, the SF strategy seems to on average be costlier and to yield greater QALYs than the CF strategy, resulting in a deterministic ICER of £5623 and £1826 per additional QALY, respectively. These ICERs are below the lower bound of the cost-effectiveness threshold range recommended by NICE, suggesting that it may be cost-effective compared to CFs in both the targeted and the combined comparisons. However, these results should be interpreted cautiously given the uncertainties in the relative diagnostic accuracy evidence which informs the model.

The probabilistic analysis suggests a higher probability of cost-effectiveness for SF versus CF at the range of cost-effectiveness thresholds recommended by NICE (0.64 and 0.68 at £20,000 and £30,000 per additional QALY for targeted SF biopsy). The probabilistic and deterministic cost-effectiveness results for each set of comparisons are similar. Henceforth and for subsequent analysis, we focus on the deterministic results, as these are easier to compare across base case, threshold, subgroup and scenario analyses.

For the targeted biopsy (network 1), the SF strategy results in average higher costs (£543 vs. £443) and slightly lower QALY loss due to biopsy AEs (–0.00175 vs. 0.00176) compared to CF in the diagnostic model. The higher costs are driven by the cost of performing biopsy with SF, which on average costs £92 and £97 more than with CF, for first and repeat biopsy, respectively. The SF strategy appears to lead to fewer repeat biopsies due to its higher correct detection rate at categories CPG 2 to CPG 4–5 compared to CF; this has a small impact on incremental costs and QALY loss. This small impact on costs and benefits is due to the reduction in repeat biopsy with SF compared to CF being small (0.055 vs. 0.050) and the only differences in rates of biopsy AEs between MRI-influenced methods stemming from differences in the proportion of repeat biopsy for each strategy.

The targeted SF strategy appears to increase correct classification (see *Table 106*, *Appendix 12*) across all CPGs compared to targeted CF at the end of the diagnostic pathway (final classification), particularly for CPG 2 (correctly classified 15% vs. 10%, out of a true disease prevalence for this category of 26%) and to a lesser extent for category CPG 1 (correctly classified 0.108 vs. 0.057, out of a true disease prevalence for this category of 32%). This is consistent with the results of the extension to the evidence

TABLE 16 Deterministic cost-effectiveness results of the base-case analysis: (1) targeted and (2) combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**ICER[b]**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
Targeted CF	−0.00176	£445	11.45	8.29	£27,919	11.45	8.29	£28,364		6.87	7.34
Targeted SF	−0.00175	£543	11.46	8.30	£27,885	11.46	8.30	£28,428		6.88	7.35
Targeted	**Inc QALY loss**	**Inc costs**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00001	£98	0.02	0.01	−£34	0.02	0.01	£63	£5623	0.01	0.01
Strategy	**QALY loss**	**Total costs**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**ICER[b]**	**NHB at, £20,000[b]**	**NHB at £30,000[b]**
Combined CF	−0.00177	£448	11.44	8.28	£27,889	11.44	8.28	£28,337		6.86	7.33
Combined SF	−0.00176	£544	11.49	8.31	£27,840	11.49	8.30	£28,384		6.89	7.36
Combined	**Inc QALY loss**	**Inc costs**	**Inc Lys[a]**	**Inc QALYs[a]**	**Inc costs[a]**	**Inc Lys[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00002	£95	0.05	0.03	−£49	0.05	0.03	£47	£1,826	0.02	0.02

a Discounted at 3.5% per annum.
b Per additional QALY; INHB, incremental net health benefit; Inc, incremental; LYs, life years.

synthesis (see *Results*) and suggests that even with repeat biopsy for the cases classified as CPG 1 or no PCa at first disease, the remaining true disease CPG 2 cases misclassified are likely to be largely classified as having no PCa. For those with true disease CPG 3 (prevalence for this category of 18.3%), the increase in correct detection with SF versus CF is modest (from 9% to 9.5%). The likelihood of being CPG 3 and being misclassified by the CF strategy as NC, CPG 1 or CPG 2 is 33%, 23% and 36%, respectively, whereas with SF these proportions are 40%, 10% and 39%, respectively (results not shown; extracted directly from model). Disaggregated results for the diagnostic model are presented in *Table 107*, *Appendix 12*.

In the long-term model, the targeted SF strategy appears to be accompanied by small life-year and QALY gain (0.02 life years and 0.01 QALYs) compared to CF in the long-term model. Some of the higher incremental diagnostic costs of the SF biopsy strategy versus CF appear to be offset by the lower costs accrued for this strategy compared to CF in the long-term model (£28,885 vs. £27,919, costs disaggregated by CPG are shown in *Table 108*, *Appendix 12*). The higher health outcomes with the SF technology compared to CF are likely to stem from a slight increase in time spent in the localised disease health state (as suggested by the higher life years and baseline QALYs accrued in the model and lower metastatic disease QALY loss; see *Table 109*, *Appendix 12*), which is partially offset by the higher upfront QALY loss from immediate localised radical treatment with the SF strategy versus CF. This is due to more patients being correctly identified in the diagnostic model with the SF strategy. The increased correct classification with SF also results in higher upfront costs from radical treatment and its AEs, but lower costs of managing metastatic disease and of monitoring.

For combined biopsy (network 2), the incremental costs and QALY loss of the SF strategy versus CF in the diagnostic model are fairly similar to those observed for the targeted biopsy. However, there seems to be greater cost savings and health outcomes benefits in the long-term model for SF compared to CF in the combined biopsy analysis, which result in cost-effectiveness results more favourable to the SF strategy. Disaggregated results for combined biopsy are presented in *Tables 111–113*, *Appendix 12*.

The level of correct classification across all grades in the combined biopsy diagnostic pathway is increased for the SF strategy compared to CF (45.5% vs. 68%, more so than for targeted biopsy). The results suggest that when compared to combined CF strategy, SF retrieves a higher proportion of CPG 4–5 (8.5% vs. 3.4%), CPG 2 (20.7% vs. 8.9%), CPG 1 (15.4% vs. 9.6%). Overall, this suggests that 16.8% more individuals are correctly identified with combined SF versus CF at CPG 2 or above, the threshold above which radical treatment is a treatment option according to current clinical guidance.

The correct higher detection at CPG results warranting radical treatment results in higher costs of upfront radical treatment for combined SF compared to CF, but also the health benefits in the long-term model (due to slower disease progression). It also reduces the costs of metastatic treatment for the SF strategy versus CF. The impact on total costs and QALYs in the long-term model is still limited, as the increased correct detection concentrates on those who have a true CPG 2 and are less likely to benefit from radical treatment than those at CPG 3–4 (where increases in correct classification for combined SF vs. CF are less marked). Nevertheless, the cost savings (–£49) and small incremental increase on QALYs (0.03 QALYs) for combined SF compared to CF result in an ICER favourable to combined SF (see *Table 16*).

Further exploration of the base-case analysis

This subsection reports further results from the base-case model on the comparison of targeted strategies, that aim to identify the cost-effectiveness drivers and aid decision-making when trying to integrate the uncertainties over the clinical evidence with the overall cost-effectiveness.

This is important because of the complexity of the classification of disease, treatment allocation rules, combined with the impacts of the different treatments, makes it difficult to establish how the misclassification of suspected PCa lesions across different categories drives the value of SF compared

to CF. To clarify this issue we present the final diagnostic accuracy for the strategies as implied by the test sequences modelled, the disaggregated cost-effectiveness results (corresponding to aggregated results for targeted biopsy in *Table 16*) by true CPG, and the trade-offs between different degrees of misclassification and correct classification. The results presented here are deterministic.

Diagnostic accuracy of the test sequences in the decision model

Table 17 illustrates the distribution of test results and conditional accuracy probabilities at final classification for cognitive and SF biopsies (includes first biopsy and repeat biopsy for a proportion of individuals). The difference in diagnostic accuracy between SF and CF by each classification is shown in brackets in *Table 17* (increased and detection are highlighted in green and red, respectively).

The diagnostic accuracy at final classification is consistent with the results for the first biopsy for both strategies (targeted CF and SF), suggesting that SF increases the correct classification across all CPGs (cells along the diagonal line) compared to CF, particularly for CPG 2 (21% more) and CPG 1 (16% more). For those with true CPG 2, the greatest reduction in misclassification is observed at diagnosed CPG 1 (16% less).

Estimation of disaggregated base-case results

Table 18 presents the base-case analysis incremental NHB (INHB) at £20,000 per additional QALY of SF versus CF as a total estimate [0.01 QALY (0.00810 with further decimal cases), as in *Table 16*] and disaggregated by true disease category (where the prevalence for each true disease category is set to 100%). The total INHB corresponds to the sum of the INHB by true disease category weighted by its corresponding prevalence.

The results suggest:

- The disaggregated INHB estimates are negative for the 'no cancer' and CPG 1 categories, which suggests that the increased correct detection of CPG 1 with SF does not result in net health gains in relation to CF.
- The disaggregated INHB estimates suggest higher net health gains for SF compared to CF for CPG ≥ 2. Once prevalence is considered (column 3), the largest effective contribution to the total INHB arises from CPG 2.

To aid interpretation of these results, in *Table 19* further disaggregates the base-case results by model component, and within the long-term model component by health state. The grey shading highlights estimates unweighted by prevalence (totals correspond to prevalence weighted values).

In the diagnostic model, the INHB of SF is negative across all CPGs. Since the INHB of SF in the model overall (diagnostic + long term) is positive, this suggests that the costs and harms of SF in the diagnostic model are only offset by long-term costs HRQoL outcomes that result from the subsequent clinical management of individual conditional on final biopsy classification. The different diagnostic INHB for each category reflect only differences in the proportion of repeat biopsies across true disease categories.

The long-term model INHB estimates follow the same pattern across true disease categories as observed for the full model results (see *Table 18*). For true disease categories CPG 2 and above, the INHB for SF versus CF is positive; the greater contribution to the INHB stems from the CPG 2 category. Compared to CF, QALY gains occur for CPG 2 and above with SF, and these are accompanied by cost savings for CPG 2 and 3.

The INHB for CPG 1 is negative in the long-term model due to higher costs and lower QALYs compared to CF; this is due to the increased correct detection of CPG 1 leading to more individuals receiving immediate (conservative or radical) treatment of localised disease with associated costs and AEs (if they had been misclassified as NC they would have received only monitoring in the first 2 years in the model) for SF compared to CF, which are not offset by the benefits of early treatment. The annual probability of

TABLE 17 Final classification: distribution of test results, conditional diagnostic accuracy and prevalence probabilities

		Distribution test results					Distribution of test results				
		50.5%	18.3%	14.4%	10.2%	6.6%	44.6%	17.2%	20.3%	11.1%	6.7%
		CF biopsy					SF biopsy				
		Accuracy matrix					Accuracy matrix				
Prev (%)	CPG	NC (%)	1 (%)	2 (%)	3 (%)	4 or 5 (%)	NC (%)	1 (%)	2 (%)	3 (%)	4 or 5 (%)
12	NC	100					100 (0)				
32	1	82	18				66 (−16)	34 (+16)			
26	2	29	35	36			24 (−5)	19 (−16)	57 (+21)		
18	3	18	13	20	49		22 (+3)	5 (−7)	21 (1)	52 (+3)	
12	4 or 5	12	10	11	10	56	11 (−1)	4 (−6)	13 (+2)	14 (+4)	58 (+2)

prev, prevalence.
Note
Results do not consider biopsy-related mortality.

TABLE 18 Base-case analysis results by CPG category

CPG	Prevalence (weights) (%)	INHB by CPG	INHB by CPG × prevalence[a]
NC	12.1	−0.00500	−0.00061
1	31.8	−0.01631	−0.00519
2	26.2	0.02890	0.00757
3	18.3	0.01907	0.00349
4 or 5	11.6	0.02435	0.00283
Total INHB[a]			0.00810

a Estimates weighed by the prevalence for each true disease category.

TABLE 19 Base-case analysis results by CPG category for the diagnostic and long-term model results

	Diagnostic model	Long-term model				
	INHB	INHB	Inc	Inc	INHB	INHB
CPG	Total	Total	QALYs	Costs	Localised	Metastatic + EoL
NC	−0.0050	–	–	–	–	–
1	−0.0056	−0.0107	−0.0017	£180	−0.0075	−0.0032
2	−0.0043	0.0332	0.0198	−£268	0.0636	−0.0304
3	−0.0046	0.0237	0.0178	−£117	0.0327	−0.0090
4 or 5	−0.0046	0.0289	0.0290	£2	0.0392	−0.0103
Total[a]	−0.0049	0.0130	0.0113	−£34	0.0248	−0.0118

a Estimates weighed by the prevalence for each true disease category; EoL, end of life; Inc, incremental.

Note
INHB for the localised disease health states included costs and disutilities of localised disease monitoring, treatment and associated AEs. INHB for the metastatic disease health states included costs and disutilities of metastatic disease monitoring, treatment and associated AEs. For simplicity, end-of-life costs were also included in the metastatic INHB.

progression from localised to metastatic disease is similar for CPG 1 misclassified compared to correctly classified CPG 1 (0.14 vs. 0.13), so the benefits from increased correct detection at this category are limited.

The localised and metastatic INHB estimates also suggest that the increased correct detection in category CPG 2 with SF is contributing more to the total long-term model INHB. We note that while the metastatic INHB is negative across all cancer categories, this does not mean that there are higher net health losses with SF compared to CF in the metastatic health states because the INHBs are not estimated by individual in the model. Since individuals spend less time in the metastatic health states with SF compared to CF due to overall slower progression to metastatic disease with SF (e.g. for CPG 2, 3.55 and 3.70 undiscounted life-years are accrued in the metastatic health states for SF and CF, respectively), SF accrues overall fewer QALYs than CF in the metastatic health states. Despite the lower costs accrued with SF in the metastatic states, the metastatic INHB is always negative.

Disaggregated estimates of cost-effectiveness by final classification category

We estimated the NHB that could be achieved in the long-term model if all individuals were identified in a particular final classification category (see *Table 20*) to understand how shifts in classification may impact on cost-effectiveness estimates.

TABLE 20 Long-term model NHB at each final classification category

CPG	NC	1	2	3	4 or 5
No cancer	8.966 (9.435, −0.469)				
1	7.996 (8.121, −0.125)	7.930 (8.074, −0.145)			
2	7.072 (6.756, 0.316)	6.855 (6.578, 0.277)	7.066 (6.927, 0.139)		
3	5.215 (4.077, 1.139)	5.117 (4.027, 1.090)	5.468 (4.571, 0.897)	5.707 (4.925, 0.782)	
4 or 5	3.476 (1.740, 1.737)	3.408 (1.689, 1.719)	3.642 (2.007, 1.635)	3.816 (2.245, 1.571)	3.912 (2.385, 1.527)

Note
NHB by health state are reported between brackets (localised disease NHB, metastatic disease NHB). Results are not specific to SF or CF.

Results suggest that there will be more (long-term) NHB loss in misclassifying CPG ≥ 2 as CPG 1 than as 'no cancer'. The highest increase in NHB for CPG ≥ 2 can be achieved with technologies that shift misclassification from CPG 1 to the correct classification. When shifting between adjacent categories, the highest NHB gain can be generated when someone with CPG 3 misclassified as CPG 1 with one technology is identified as CPG 3 with the alternative (+0.351 QALYs). The lowest NHB gain between adjacent categories is generated for those with true CPG 4–5, when they 'move' from a CPG 3 to a correct diagnosis (+0.096 QALY).

The incremental value of one technology will depend on how it changes the distribution across classification categories for each true disease category compared to the alternative technology, and on the prevalence per true disease category. For SF compared to CF, the INHB will be positive for the classification categories where it increases detection and negative for those where detection is decreased (see *Table 17* for differences between diagnostic accuracy matrices).

This can be illustrated with an example for true disease category CPG 2. For SF versus CF:

- the reduction in detection of CPG 2 as 'no cancer', the category with highest NHB for CPG 2 (7.072 QALYs) is small (−5%), so the INHB is −0.339 QALYs
- the reduction in detection of CPG 2 as CPG 1 (NHB = 6.885 QALYs) is −16% resulting in an INHB of −1.086 QALYs
- the increased correct detection of CPG 2 (+21%, NHB = 7.066 QALYs) is sufficient to offset the negative INHBs from the alternative classifications (as 'no cancer' and CPG 1), and the total INHB across this disease category is 0.033 QALYs
- since the prevalence of CPG 2 is 26%, the relative contribution from changes in detection rates for this category is 0.009.

The NHB gains for correctly identifying lesions at CPG3 and CPG 4–5 compared to missing them (i.e. identifying them as CPG 0) is positive (> 0.4 QALYs for both CPG groups). This suggests that it is worth radically treating individuals with CPG ≥ 3 PCa early, as radical treatment reduces disease progression proportionally more for these individuals compared to those with lower CPG. This delay to disease progression translates into longer time spent in the localised PCa state with higher HRQoL and lower mortality compared to the metastatic disease state, and without incurring the costs of metastatic treatment. These benefits off set the costs and harms of early radical treatment.

Given the uncertainties and limitations of the clinical evidence informing the diagnostic accuracy NMA and its extension, the information in *Tables 18–20* can be used by decision-makers to consider how their judgements on what are the plausible differences in the prevalence and relative diagnostic accuracy between SF and CF can be translated into cost-effectiveness impacts.

Threshold analysis on costs of software fusion

Given the uncertainties in the costing of SF we conducted a threshold analysis to identify the SF biopsy cost at which there would be a shift in the decision to accept SF as a good use of NHS resources. Since the base-analysis suggests that the SF strategy might be cost-effective compared to CF, the point of decision shift is identified as the cost per SF (holding the cost of CF constant) at which the incremental of NHB of the SF biopsy compared to CF becomes negative (i.e. SF is not likely to be cost-effective). The threshold analysis is conducted under the assumption that all biopsies are LATP and excluding the cost of the ultrasound components from the cost of CF. Under these assumptions the cost per biopsy is £448.50 and £331.00 per SF and cognitive fusio biopsy, respectively.

The threshold analysis results (see *Figure 18*, *Appendix 12*) suggest that the decision inversion point is located at a cost per targeted SF biopsy of £586 and £695 at £20,000 and £30,000 per additional QALY, respectively. For combined SF biopsy (see *Figure 19*, *Appendix 12*), the inversion point cost per biopsy was estimated as of £874 and £1116 at £20,000 and £30,000 per additional QALY, respectively.

Subgroup analysis

The deterministic cost-effectiveness results of the subgroup analysis for previous negative biopsy individuals are presented in *Table 21* with full breakdown presented in *Table 116–123*, *Appendix 12*. We note that this analysis only differs from the base-case analysis in the source for the baseline distribution of test results for SF (sourced from previous negative biopsy data from Filson *et al.*[96] rather than the biopsy naive in the base-case analysis). The estimated prevalence of PCa disease in this subgroup is lower than in the base-case analysis (57% vs. 88%), while the diagnostic accuracy matrices for both targeted and combined biopsies in the subgroup analysis (see *Appendix 10*) are similar to those estimated for biopsy-naive individuals (as expected).

In the subgroup analysis, there is an increased likelihood of correctly classifying individuals with PCa across all CPGs for software versus CF in both the targeted and combined biopsy analysis. However, the lower prevalence means that there are fewer individuals in the model who are more likely to benefit from radical treatment (e.g. prevalence at CPG 4–5 for the prior biopsy subgroup is 8.5% compared to 11.6% in the biopsy naive). Consistently with this, the prior biopsy subgroup cost savings and QALY gains in the long-term model for SF versus CF strategies appear to be smaller than for the base case (particularly so for combined biopsy strategies), resulting in increased ICERs compared to the biopsy naive.

Scenario analysis

The summary results of the scenario analysis are presented in *Table 22*, with full breakdown presented in *Table 124–139*, *Appendix 12*.

The cost-effectiveness results for both set of comparisons (targeted and combined biopsy) appear to be robust to variations of the elements of uncertainty in all scenario analyses, with the exception of scenario 5. We discuss below the scenarios in which data sources of the evidence synthesis extension were modified and scenario 5 given its high impact on the estimates of cost-effectiveness. The remaining scenarios are not discussed further.

In scenario 1, the prevalence of PCa is higher (at all CPGs except CPG1) than for the corresponding base-case analysis (targeted comparison), which means that there are proportionally more individuals who can potentially benefit from early treatment. The diagnostic accuracy of the targeted SF is also higher than that of CF strategy, but more so to correctly identify those with CPG2. Overall, this translates into increased cost savings in the long-term model for the targeted SF versus CF compared to the base case (–£58 vs. –£34), which lead to a lower ICER.

In scenario 2, the prevalence of PCa is lower (at all CPGs except CPG2) than for the corresponding base case analysis (targeted comparison), but the diagnostic accuracy is higher for SF compared to CF for

TABLE 21 Deterministic cost-effectiveness results for prior biopsy subgroup: (1) targeted and (2) combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**ICER[b]**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
Targeted CF	−0.00176	£444	11.75	8.68	£22,014	11.75	8.68	£22,457		7.56	7.93
Targeted SF	−0.00175	£542	11.76	8.69	£21,994	11.76	8.69	£22,536		7.56	7.94
Targeted	**Inc QALY loss**	**Inc costs**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00000	£99	0.01	0.01	-£20	0.01	0.01	£79	£9285	0.00	0.01
Strategy	**QALY loss**	**Total costs**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**ICER[b]**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
Combined CF	−0.00177	£446	11.75	8.68	£22,001	11.75	8.68	£22,447		7.55	7.93
Combined SF	−0.00176	£545	11.77	8.69	£22,000	11.77	8.69	£22,545		7.57	7.94
Combined	**Inc QALY loss**	**Inc costs**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00001	£98	0.03	0.02	-£1	0.03	0.02	£98	£5946	0.01	0.01

INHB, incremental net health benefit; Inc, incremental; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 22 Scenario analysis cost-effectiveness results: (1) targeted and (2) combined biopsy

Scenario	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)	ICER per QALY (£)
Targeted biopsy				
Base case	0.02	0.01	63	5623
1. PAIREDCAP (2019) baseline	0.02	0.01	39	4428
2. Zhou *et al.*[142] diagnostic	0.03	0.03	83	3105
3. Degradation of repeat biopsy accuracy	0.02	0.01	63	5477
4. SF as quality assurance	0.000100	0.000099	87	875,042
5. Radical treatment for all identified CPG ≥ 2	0.04	0.03	−117	Dominates
6.1 Throughput (150/year)	0.02	0.01	129	11,425
6.2 Throughput (450/year)	0.02	0.01	42	3689
Combined biopsy				
Base case	0.04	0.02	49	2199
1. PAIREDCAP (2019) baseline	–	–	–	–
2. Zhou *et al.*[142] diagnostic	–	–	–	–
3. Degradation of repeat biopsy accuracy	0.05	0.03	46	1801
4. SF as quality assurance	0.000141	0.000139	81	582,123
5. Radical treatment for all identified CPG ≥ 2 and conservative treatment for CPG 1	0.08	0.05	−300	Dominates
6.1 Throughput (150/year)	0.05	0.03	110	4275
6.2 Throughput (450/year)	0.05	0.03	26	1009

a SF compared to CF; cost and health outcomes discounted at 3.5% per annum over the model time horizon.

all categories of CPG, which overall reduces the ICER for the targeted SF strategy compared to CF to £3689 per additional QALY.

Scenario 5 shows that if there is no difference in diagnostic accuracy between SF and CF, even if some repeat biopsies can be avoided with SF due to it being less prone to operator inexperience, the ICERs for SF compared to CF (targeted and combined biopsy analysis) are far above the upper bound of the cost-effectiveness threshold range recommended by NICE. This is because the small incremental benefits from fewer repeat biopsies are insufficient to offset the higher costs of SF biopsy compared to CF.

Chapter 6 Discussion

Statement of principal findings

The systematic review of clinical evidence included a total of 3733 patients who received SF and 2154 individuals with CF from 23 studies. Evidence was included for all devices specified in the protocol, except for Fusion Bx 2.0 and FusionVu. Fourteen studies were included in the network meta-analyses.

Overall, the evidence for all devices was at high risk of bias and therefore the quantitative synthesis results must be interpreted with caution. Results from our main analysis (looking across ISUP grades) suggest that patients undergoing software biopsy may have: (1) a lower probability of being classified as not having cancer, (2) similar probability of being classified as having non-CS cancer (ISUP grade 1) and (3) higher probability of being classified at higher ISUP grades, particularly ISUP 2. Similar results were obtained when comparing between same biopsy methods where both were combined with systematic biopsy.

Additional meta-analyses of cancer detection rates suggest that, compared with CF biopsy, SF may identify more PCa (any grade) (OR 1.30; 95% CrI 1.06, 1.61). Adding systematic biopsy to cognitive or SF may increase the detection of all PCa and of CS cancer, and from this evidence there is no suggestion that SF with concomitant systematic biopsy is superior to CF with systematic biopsy.

Meta-analyses by individual device showed that compared with CF biopsy, BioJet and Urostation may be associated with a higher detection of PCa overall, and BioJet may be associated with a higher rate of CS cancers, although only one study of BioJet was included in the meta-analyses. Evidence for all other software devices was insufficient to reliably compare their accuracy with CF, or to determine whether some SF technologies are more accurate than others. Evidence for bkFusion, iSR'obot Mona Lisa and KOELIS Trinity was included in the systematic review but not in the meta-analyses. Compared with CF, there was no evidence that the accuracy of SF may differ by lesion location, or between biopsy-naive and prior negative-biopsy patients, or according to operator experience, although the number and quality of the studies informing the potential effect modifiers were limited.

Overall, there is no evidence that biopsy positivity rates and safety outcomes differ significantly between SF and CF, or between SF devices. There was some evidence that systems with rigid registration (BioJet or UroNav) are easier and faster to use than elastic registration (KOELIS Trinity), although this is informed by a single, small study and is not conclusive.

The base-case cost-effectiveness analysis suggests for the targeted biopsy and the combined biopsy comparisons, that SF strategy is on average costlier and yields greater QALYs than the CF strategy, resulting in a probabilistic ICER of £6197 and £2199 per additional QALY for each comparison, respectively. These ICERs are below the lower bound of the cost-effectiveness threshold range recommended by NICE, suggesting that SF may be cost-effective compared to CFs in both the targeted and the combined comparisons. However, these results should be interpreted cautiously, given the uncertainties in the relative diagnostic accuracy evidence which informs the model. The probabilistic analysis suggests a higher probability of cost-effectiveness for SF versus CF at the range of cost-effectiveness thresholds recommended by NICE (0.64 and 0.68 at £20,000 and £30,000 per additional QALY for targeted SF biopsy).

The key findings on the drivers of economic value of SF compared to CF are:

1. The costs (and harms) of SF biopsy in the diagnostic model component can only be offset in the long-term model component, which will only arise from differences in diagnostic accuracy between software and CF.
2. The value gains for SF appear to stem from increased detection at CPG ≥ 2 and, once we adjust for prevalence by CPG category, the greatest contribution to the cost-effectiveness of SF compared to cognitive results from increased correct detection at CPG 2.
3. Increased detection at CPG 1 due to reduced detection of 'no cancer' results in value losses at all cancer grades [i.e. there are net losses from shifting classification from 'no cancer' to CNS cancer (CPG 1)].
4. The magnitude of value realised for SF versus CF from the balance between different degrees of misclassification and correct classification with the two technologies also depends on the prevalence at each cancer grade.

Given the uncertainties in the costing of SF, we conducted a threshold analysis to identify the SF biopsy cost at which there would be a shift in the decision to accept SF as a good use of NHS resources. This suggested that at the cost of each the five individual technologies for which there was cost data, the recommendation decision would not change.

The base-case cost-effectiveness results were not sensitive to variations to alternative data sources and assumptions, except when no difference in diagnostic accuracy is assumed between SF and CF. Under this assumption, the ICERs for SF compared to CF (targeted and combined biopsy analysis) far exceed the upper bound of the cost-effectiveness threshold range recommended by NICE.

Strengths and limitations of the assessment

This is the first systematic review to formally compare the relative accuracy of SF and CF, with and without systematic biopsy, as well as different SF devices, using both direct and indirect evidence in a formal NMA. In order to best estimate differences between biopsy methods for each PCa grade, a multinomial logistic regression model was fitted, where the odds of being categorised in each of the different ISUP grades were allowed to vary by biopsy type.

Our findings are consistent with those of recent systematic reviews that found no significant difference between SF and CF at detecting non-CSPCas,[51–53] although unlike recent evidence,[51,53] our NMA found that SF increased detection of CS cancer compared with CF. This result might be explained by differences in review and synthesis methods.

Our review has a number of limitations. Despite attempts to reduce bias by excluding unpaired, non-randomised studies, the evidence included in the meta-analysis remains at high risk of bias. Although within-patient comparisons remove much of the risk of confounding from imbalances in participant characteristics, true blinding from tracks of preceding biopsy methods within the same examination is not feasible (or would require two separate biopsy sessions per patient, which would be unethical). So far, no high-quality RCTs have been published.

There was variation across the studies in patient characteristics. In particular, a number of studies included patients with prior negative-biopsy and biopsy-naive patients, who form the large majority of patients eligible for targeted biopsy, were under-represented. Some variation and gaps in reporting were observed in MRI acquisition methods, criteria for referral to biopsy, biopsy routes and anaesthesia methods. Definitions of PCa and CS cancer varied across the studies. There was insufficient evidence to explore the impact of a number of potential effect modifiers, including lesion location, operator experience, biopsy routes and anaesthesia methods.

The results of the synthesis models require careful interpretation, as they refer to comparisons between different cancer grades. The interpretation of the multinomial models on the absolute probability scale results is more intuitive and directly relevant to clinical practice. Overall, results are concordant across analyses and concordant with the data. Only the multinomial results are used in the economic model, as the value of diagnostic information provided by each test is dependent on the subsequent clinical decisions based on test results, and clinical management is conditional on cancer grades (jointly with other prognostic information).

Most estimates from the NMAs were imprecise, particularly in the multinomial synthesis and at higher ISUP grades where data were most sparse. The NMA relied on a number of assumptions. CF was assumed to be equivalent across studies. The risk and extent to which the accuracy of CF may vary by centre and operator experience are uncertain due to lack of evidence. It was also assumed that data from within-patient studies were independent. A model that accounted for the full structure of the data was not available, although it could have added precision to the estimates.

There were few studies per comparison and not all studies reported outcomes by all cancer grades. Therefore, only fixed-effect models were fit to the data. Data were sparse for most SF devices, and few studies included more than one SF technology, making it difficult to draw conclusions for relative accuracy of individual devices.

While our review identified several relevant studies, many could not be included in the synthesis due to lack of reporting of key data. For example, studies comparing software and CF to systematic biopsy reported data on both targeted technologies jointly, and few studies reported a sufficient breakdown of biopsy results by ISUP grades (or equivalent breakdown) to inform the evidence synthesis required for the economic model. In addition, where studies included a mixed population of patients, a lack of reporting of biopsy results for the relevant population led to their exclusion from the meta-analysis. We were therefore limited in the models we could consider due to data sparseness, and results are uncertain.

Studies not included in the meta-analyses mostly reported test-positive rates (positive cases as percentage of all patients). As this measure is dependent on disease prevalence rather than diagnostic accuracy, results from these studies may be influenced by differences in PCa rates between cohorts and may not be reliable.

The above-mentioned limitations in the evidence are not captured in the quantitative evidence synthesis, which is used to inform the economic analysis.

The cost-effectiveness analysis relies on the evidence informing it. Beyond the evidence sourced from the synthesis, this includes evidence on the long-term outcomes of treating PCa and the cost data on each SF technology. This evidence is limited.

Uncertainties

No evidence was found for most of this assessment's prespecified outcomes: biopsy sample suitability/quality, number of repeat biopsies performed, procedure completion rates, software failure rate, time to diagnosis, length of hospital stay, time taken for MR image preparation, subsequent PCa management, re-biopsy rate, hospitalisation, OS, PFS, patient- and carer-reported outcomes (including tolerability and HRQoL), barriers and facilitators to implementations.

There was large uncertainty in all estimates due to the limited evidence. Meta-analyses showed moderate heterogeneity that could not be explained by differences in individual SF devices. The

evidence for all SF devices was at high risk of bias, and the diagnostic accuracy of systematic biopsy relative to SF and cognitive may have been overestimated in the meta-analyses. The applicability of the evidence for KOELIS Trinity and BiopSee is uncertain. There is no evidence comparing the accuracy of Fusion Bx 2.0 and FusionVu with CF, and no evidence for these devices were eligible for inclusion in the indirect comparisons.

None of the studies included in the systematic review of diagnostic accuracy used template mapping biopsy as a reference standard, and many studies did not use standard 12-core systematic biopsy in addition to targeted biopsy methods. This means that the absolute true rate of PCa lesions was underestimated and is uncertain. However, the lack of a gold-standard test is likely to have affected comparisons between all devices similarly, and therefore is unlikely to have biased relative estimates of PCa detection.

The evidence supporting recent consensuses for classifying the clinical significance of PCa is not without limitations, despite recent improvements in imaging.[34,112,151] Trial evidence indicates that survival outcomes for some patients with more severe grades of localised PCa (CPG 3 and above) are favourable, and that the detriment associated with active monitoring may be small.[55,114] This raises further uncertainty regarding the added clinical (and economic) value of SF. Where reported, the number of targeted cores performed with software and CF were broadly comparable between the studies. However, not all studies reported data on number of targeted cores to fully assess the risk of confounding from a possible difference in number of targeted cores between software and CF. Evidence for all other protocol-specified outcomes was limited and inconclusive.

The economic value of SF seems to be driven by (1) comparative diagnostic accuracy derived where evidence is particularly sparse (cancer grades above 2), and (2) by prevalence, which is also affected by evidence sparsity.

Structural assumptions were applied to allow estimating the economic value of SF given the evidence gaps in the diagnostic accuracy of SF and in the longer-term outcomes of PCa. The structural uncertainty of these assumptions was explored in scenario analysis, but could not be jointly captured with parameter uncertainty. This means that the probabilistic results presented in this report are likely to underestimate the overall uncertainty.

Other relevant factors

Participants of studies included in the systematic review of diagnostic accuracy and clinical effectiveness had elevated PSA and/or abnormal DRE results and were referred to targeted biopsy following a PI-RADS or Likert score of three or more on MRI. This is reflective of NICE guidance, which recommends that men should be referred for mpMRI if their PSA levels are above the age-specific reference range or if their prostate feels malignant on DRE. However, other organisations have recommended that PSA levels should be used as part of a risk prediction tool, potentially leading to better targeting of patients referred to mpMRI. It is unclear how a change in referral criteria may affect the applicability of this assessment's findings.[13]

Equality, diversity and inclusion

This study was carried out by a multidisciplinary team, consisting of an information specialist, a statistician, systematic reviewers and health economists. Junior members of staff contributed according to their skills and had the opportunity to undertake tasks that furthered their training. Clinical experts that provided advice included a nurse and senior consultants.

This report was prepared to support NICE guidance to help reduce health inequalities, improve access to health care and encourage health improvement (www.nice.org.uk/about/who-we-are/policies-and-procedures/nice-equality-scheme).

Patient and public involvement

This report was prepared to support NICE guidance. Lay people, and organisations representing their interests, have opportunities to contribute to developing NICE guidance, advice and quality standards, and support their implementation (www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme/patient-public-involvement-policy).

Chapter 7 Conclusions

Compared to CF biopsy, patients undergoing SF biopsy may have a lower probability of being classified as not having cancer, similar probability of being classified as having non-CS cancer, and a higher probability of being classified at higher ISUPs, particularly ISUP 2. Both SF and CF biopsy can miss CS cancer lesions, and the addition of a standard-systematic biopsy increases the detection of all PCa and CS cancer for both fusion methods. There is insufficient evidence to conclude on the relative accuracy and clinical effectiveness of different software devices.

Cost-effectiveness estimates comparing software to CF were generally favourable to SF, except where the technologies were assumed to have the same diagnostic accuracy. The drivers of economic value of SF, comparative diagnostic accuracy and prevalence, are affected by unquantified uncertainty. Judgements on the economic value of SF require integration of the uncertainties over the clinical evidence with the overall cost-effectiveness.

Suggested research priorities

High-quality, sufficiently powered RCT evidence, comparing SF and CF with or without systematic biopsy in trained operators, is needed to address the limitations of the diagnostic accuracy evidence identified in this study. Ideally, a trial should be sufficiently powered to detect long-term oncological outcomes (PFS, PCa mortality, overall mortality), although we acknowledge that such a study may not be feasible. IP7-PACIFIC (NCT05574647),[155] a large UK-based randomised trial, will aim to determine whether SF biopsy is superior to CF at detecting CSPCa in patients with suspicious MRI in patients randomised to either mpMRI or bpMRI. It is hoped that this trial will provide more precise diagnostic accuracy estimates, although it is not clear which specific SF devices will be used, and the protocol indicates that estimates of diagnostic accuracy will not be informed by a gold standard test.

Full reporting of ISUP grades for each randomised arm is recommended, and for within-patient comparison studies, full reporting of cross-tabulation tables, where the classification of patients' cancer by ISUP grade for each biopsy type is described and the relative accuracy of the interventions can be derived. In mixed population studies, reporting by key patient characteristics, such as PI-RADS score, whether biopsy naive or experienced, and route of referral for MRI (e.g. following clinical concerns, routine surveillance, screening etc.) are required to inform decision-making. Availability of more granular data, from already published studies, would enable future syntheses to make use of a larger body of evidence. Qualitative evidence on the acceptability of SF to patients, notably where biopsy procedure time might be significantly increased, is needed.

Additional information

Contributions of authors

Alexis Llewellyn (https://orcid.org/0000-0003-4569-5136**)** (Systematic Reviewer) contributed to the protocol, performed the systematic review, wrote the background and most of the sections on clinical effectiveness.

Thai Han Phung (https://orcid.org/0000-0001-6193-4673**)** (Health Economist) assisted with the economic evidence reviews and with the development of the economic model, its analyses and validation, and contributed to the writing of the cost-effectiveness sections.

Marta O Soares (https://orcid.org/0000-0003-1579-8513**)** (Health Economist) developed the methods to extend the evidence synthesis for use in the economic model and conducted the required analyses over the extended synthesis model. She provided oversight and contributed to the development of the inference sub model to inform the economic model. She wrote the cost-effectiveness sections of the protocol and main report, and provided leadership support to the economic sections.

Lucy Shepherd (https://orcid.org/0000-0001-6803-5566**)** (Systematic Reviewer) contributed to the protocol, performed the systematic review and wrote parts of the clinical sections.

David Glynn (https://orcid.org/0000-0002-0989-1984**)** (Health Economist) reviewed the prostate cancer long-term outcome evidence and developed the inference sub model to inform the economic model.

Melissa Harden (https://orcid.org/0000-0003-2338-6869**)** (Information Specialist) designed and ran all searches for the study, managed the library of references, and wrote the search sections of the report.

Ruth Walker (https://orcid.org/0000-0003-2765-7363**)** (Systematic Reviewer) contributed to the protocol and background materials.

Ana Duarte (https://orcid.org/0000-0002-0528-4773**)** (Health Economist) developed the economic model, conducted analyses over this model and validated it. Ana had overall responsibility for the cost-effectiveness sections of the report. She wrote the cost-effectiveness sections of the protocol and of the report.

Sofia Dias (https://orcid.org/0000-0002-2172-0221**)** (Statistician) contributed to the protocol, adapted the network meta-analysis model and performed the meta-analyses, wrote up the meta-analysis section results, and oversaw the conduct and writing of the clinical effectiveness sections and the report as a whole. Sofia has overall responsibility for the clinical effectiveness sections of the report.

Acknowledgements

We would like to thank specialist DAC members Dr Oliver Hulson, Consultant Radiologist at Leeds Teaching Hospital Trust, Ms Lillian White, Clinical Nurse Specialist at NHS Ayshire and Arran, and Mr Hide Yamamoto, Consultant Urological Surgeon at Maidstone and Tunbridge Wells Trust for providing helpful advice during this study. We also thank Ms Lillian White for commenting on an early draft of the report. We would also like to thank Prof Hashim Ahmed for providing helpful advice during this study; Mr Connor Evans, Research Trainee at CRD, for helping to edit the final version of this report; and Prof Stephen Palmer for advice on the conceptualisation of the economic model.

We thank Dr Bhash Naidoo and the NICE Centre for Guidelines who developed the NICE NG131 health economics model and for sharing it. The review of the electronic version of the model contributed to inform the York-model conceptualisation. Similarly, we would like to thank Dr Joanne Lord and the Southampton TAR group who developed the Southampton model and for sharing it. The electronic version of the Southampton model was used to support both model conceptualisation and parameterisation of the York model.

Data-sharing statement

All data are provided in appendices to this report. Additional requests for access to data should be addressed to the corresponding author.

Ethics statement

Due to the nature of this study (systematic review of aggregate data and economic analysis), no ethical approval was required.

Information governance statement

This study did not handle any personal information.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/PLFG4210.

Primary conflict of interest: Marta O Soares is a member of the NIHR Health Technology Assessment (HTA) General Committee.

References

1. Cancer Research UK. *Ten Most Common Cancers in Males*. 2021. URL: www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-One (accessed 20 June 2022).
2. Public Health England. *Cancer Registration Statistics, England: Final Release, 2018*. Public Health England; 2020. URL: www.gov.uk/government/statistics/cancer-registration-statistics-england-2018-final-release/cancer-registration-statistics-england-final-release-2018 (accessed 2 April 2022).
3. Cancer Research UK. *Prostate Cancer Statistics: Prostate Cancer Incidence*. 2017. URL: www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero (accessed 23 March 2022).
4. National Prostate Cancer Audit (NPCA) Team. *Eighth Year Annual Report of the NPCA Prospective Audit in England and Wales for Men Diagnosed from 1 April 2019 to 31 March 2020 and the Impact of COVID-19 in England During 2020*. London: Royal College of Surgeons; 2022.
5. Jones AL, Chinegwundoh F. Update on prostate cancer in black men within the UK. *Ecancermedicalscience* 2014;**8**:455.
6. Kiciński M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. *PLOS ONE* 2011;**6**:e27130.
7. Guo Z, He J, Pan J, Huang L, Cao J, Bai Z, *et al.* Prevalence and risk factors for incidental prostate cancer in patients after transurethral resection of the prostate with negative results on prostate biopsy: a retrospective study. *Investig Clin Urol* 2022;**63**:201–6.
8. Moynihan R, Doust J, Henry D. Preventing overdiagnosis: how to stop harming the healthy. *BMJ* 2012;**344**:e3502.
9. McCaffery K, Nickel B, Pickles K, Moynihan R, Kramer B, Barratt A, Hersch J. Resisting recommended treatment for prostate cancer: a qualitative analysis of the lived experience of possible overdiagnosis. *BMJ Open* 2019;**9**:e026960.
10. National Institute for Health and Care Excellence. *Prostate Cancer: Diagnosis and Management. [I] Evidence Reviews for Risk Stratification of Localised Prostate Cancer.* NICE Guideline NG131. London: NICE; 2021.
11. National Institute for Health and Care Excellence. *Diagnostics Assessment Programme. Diagnostics Consultation Document: Transperineal Biopsy for Diagnosing Prostate Cancer*. London: NICE; 2022.
12. National Institute of Health and Care Excellence. *Prostate Cancer: Diagnosis and Management*. NICE Guideline [NG131] (last updated: 15 December 2021). London: NICE; 2019.
13. Prostate Cancer UK. *Consensus Statements on PSA Testing in Asymptomatic Men in the UK: Information for Health Professionals – Prostate Cancer UK*. 2016. URL: https://prostatecanceruk.org/PSAconsensusHP (accessed 24 October 2022).
14. National Institute for Health and Care Excellence. *Suspected Cancer: Recognition and Referral NICE Guideline [NG12]*. London: NICE; 2015.
15. NHS England. *Faster Diagnosis Standard*. NHS England. URL: www.england.nhs.uk/cancer/faster-diagnosis/#:~:text=The%20Faster%20Diagnosis%20Standard%20(FDS,cancer%20have%20a%20timely%20diagnosis (accessed 24 October 2022).

16. National Institute for Health and Care Excellence. *Quality Statement 1: Direct Access to Diagnostic Tests – Suspected Cancer: Quality Standard [QS124]*. NICE; 2016. URL: www.nice.org.uk/guidance/qs124/chapter/Quality-statement-1-Direct-access-to-diagnostic-tests (accessed 24 October 2022).

17. NHS England. *Implementing a Timed Prostate Cancer Diagnostic Pathway: A Handbook for Local Health and Care Systems*. London: NHS England; 2018.

18. Ahmed HU, Bosaily AES, Brown LC, Kaplan RS, Colaco-Moraes Y, Ward K, *et al.* The PROMIS study: a paired-cohort, blinded confirmatory study evaluating the accuracy of multi-parametric MRI and TRUS biopsy in men with an elevated PSA. *J Clin Oncol* 2016;**34**:5000.

19. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, *et al.*; PRECISION Study Group Collaborators. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;**378**:1767–77.

20. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, *et al.*; European Society of Urogenital Radiology. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012;**22**:746–57.

21. Turkbey B, Choyke PL. Prostate magnetic resonance imaging: lesion detection and local staging. In: Klotman ME, editor. *Annual Review of Medicine, Vol. 70*. Palo Alto: Annual Reviews; 2019. pp. 451–9.

22. 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.

23. West of Scotland Cancer Network. *Audit Report: Prostate Cancer Quality Performance Indicators – Clinical Audit Data: 01 July 2019 to 30 June 2020*. Glasgow: West of Scotland Cancer Network; 2021.

24. North Cancer Alliance. *Quality Performance Indicators Audit Report: Prostate Cancer*. Aberdeen: North Cancer Alliance; 2022.

25. Barrett T, Slough R, Sushentsev N, Shaida N, Koo BC, Caglic I, *et al.* Three-year experience of a dedicated prostate mpMRI pre-biopsy programme and effect on timed cancer diagnostic pathways. *Clin Radiol* 2019;**74**:894.e1–894.e9.

26. Alabousi M, Salameh JP, Gusenbauer K, Samoilov L, Jafri A, Yu H, Alabousi A. Biparametric vs. multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naïve patients: a diagnostic test accuracy systematic review and meta-analysis. *BJU Int* 2019;**124**:209–20.

27. 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.

28. National Institute for Health and Care Excellence. *NICE Recommends New Diagnostic Devices for Men with Suspected Prostate Cancer in Draft Guidance*. NICE; 2022. URL: www.nice.org.uk/news/article/nice-recommends-new-diagnostic-devices-for-men-with-suspected-prostate-cancer-in-draft-guidance (accessed 9 May 2022).

29. National Institute for Health and Care Excellence. *Transperineal Biopsy for Diagnosing Prostate Cancer: In Development [GID-DG10043]*. NICE. URL: www.nice.org.uk/guidance/indevelopment/gid-dg10043 (accessed 23 May 2022).

30. Kucur M, Goktas S, Kaynar M, Apiliogullari S, Kilic O, Akand M, *et al.* Selective low-dose spinal anesthesia for transrectal prostate biopsy: a prospective and randomized study. *J Endourol* 2015;**29**:1412–7.

31. Wegelin O, Exterkate L, van der Leest M, Kummer JA, Vreuls W, de Bruin PC, *et al.* The FUTURE trial: a multicenter randomised controlled trial on target biopsy techniques based on magnetic resonance imaging in the diagnosis of prostate cancer in patients with prior negative biopsies. *Eur Urol* 2019;**75**:582–90.
32. Bjurlin MA, Taneja SS. Standards for prostate biopsy. *Curr Opin Urol* 2014;**24**:155–61.
33. Das CJ, Razik A, Sharma S, Verma S. Prostate biopsy: when and how to perform. *Clin Radiol* 2019;**74**:853–64.
34. European Association of Urology. *EAU Guidelines on Prostate Cancer*. Arnhem: The Netherlands: EAU Guidelines Office; 2022.
35. Fulgham PF, Rukstalis DB, Rubenstein JN, Taneja SS, Carroll PR, Pinto PA, *et al. Standard Operating Procedure for Multiparametric Magnetic Resonance Imaging in the Diagnosis, Staging and Management of Prostate Cancer*. American Urological Association; 2019. URL: www.auanet.org/guidelines-and-quality/guidelines/other-clinical-guidance/mri-of-the-prostate-sop (accessed 24 October 2022).
36. Prostate Cancer Foundation. *About Prostate Cancer*. Prostate Cancer Foundation; 2022. URL: www.pcf.org/about-prostate-cancer/ (accessed 24 October 2022).
37. Rouviere O, Puech P, Renard-Penna R, Claudon M, Roy C, Mege-Lechevallier F, *et al.*; MRI-FIRST Investigators. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naïve patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019;**20**:100–9.
38. van der Leest M, Cornel E, Israel B, Hendriks R, Padhani AR, Hoogenboom M, *et al.* Head-to-head comparison of transrectal ultrasound-guided prostate biopsy vs. multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. *Eur Urol* 2019;**75**:570–8.
39. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, *et al.* The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. *Eur Urol* 2021;**80**:682–9.
40. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, *et al.*; PROMIS Study Group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017;**389**:815–22.
41. Thompson J, Savdie R, Ponsky L, Brenner P, Shnier R, Moses D, *et al.* Magnetic resonance imaging detects significant prostate cancer and could be used to reduce unnecessary biopsies: initial results from a prospective trial of MRI in men planned for diagnostic biopsy. *Urology* 2013;**82**:S26–7.
42. Parry MG, Boyle JM, Nossiter J, Morris M, Sujenthiran A, Berry B, *et al.* Determinants of variation in radical local treatment for men with high-risk localised or locally advanced prostate cancer in England [Published online ahead of print September 7 2021]. *Prostate Cancer Prostatic Dis* 2021;**26**:257–63. https://doi.org/10.1038/s41391-021-00439-9
43. Morris M. *Exploring the Use of a New Risk Grouping to Assess 'Over-Treatment' for the National Prostate Cancer Audit*. National Prostate Cancer Audit, Royal College of Surgeons of England; 2022. URL: www.npca.org.uk/news/exploring-the-use-of-a-new-risk-grouping-to-assess-over-treatment-for-the-national-prostate-cancer-audit/ (accessed 22 August 2022).
44. Bjurlin MA, Rosenkrantz AB, Taneja SS. MRI-fusion biopsy: the contemporary experience. *Transl Androl Uro* 2017;**6**:483–9.

45. Yan P, Wang XY, Huang W, Zhang Y. Local anesthesia for pain control during transrectal ultrasound-guided prostate biopsy: a systematic review and meta-analysis. *J Pain Res* 2016;**9**:787–96.

46. Lee D, Chung BH, Lee KS. Effect of training and individual operator's expertise on prostate cancer detection through prostate biopsy: implications for the current quantitative training evaluation system. *Investig Clin Urol* 2021;**62**:658–65.

47. Costa DN, Pedrosa I, Donato F Jr, Roehrborn CG, Rofsky NM. MR imaging-transrectal US fusion for targeted prostate biopsies: implications for diagnosis and clinical management. *Radiographics* 2015;**35**:696–708.

48. Cash H, Gunzel K, Maxeiner A, Stephan C, Fischer T, Durmus T, *et al.* Prostate cancer detection on transrectal ultrasonography-guided random biopsy despite negative real-time magnetic resonance imaging/ultrasonography fusion-guided targeted biopsy: reasons for targeted biopsy failure. *BJU Int* 2016;**118**:35–43.

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

50. Bott SRJ, Young MPA, Kellett MJ, Parkinson MC; Contributors to the UCL Hospitals' Trust Radical Prostatectomy Database. Anterior prostate cancer: is it more difficult to diagnose? *BJU Int* 2002;**89**:886–9.

51. Watts KL, Frechette L, Muller B, Ilinksy D, Kovac E, Sankin A, Aboumohamed A. Systematic review and meta-analysis comparing cognitive vs. image-guided fusion prostate biopsy for the detection of prostate cancer. *Urol Oncol* 2020;**38**:734.e19–25.

52. 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 Prostatic Dis* 2019;**22**:39–48.

53. 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. *Prostate Cancer Prostatic Dis* 2021;**25**:174–9.

54. 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.

55. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, *et al.*; PROTecT Study Group. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med* 2016;**375**:1415–24.

56. Kishan AU, Sun Y, Hartman H, Pisansky TM, Bolla M, Neven A, *et al.*; MARCAP Consortium Group. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: an individual patient data meta-analysis. *Lancet Oncol* 2022;**23**:304–16.

57. National Institute for Health and Care Excellence. *Low Dose Rate Brachytherapy for Localised Prostate Cancer (IPG 132)*. London: NICE; 2005.

58. Morris WJ, Tyldesley S, Rodda S, Halperin R, Pai H, McKenzie M, *et al.* Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;**98**:275–85.

59. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, *et al.*; STAMPEDE Investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;**387**:1163–77.

60. Fizazi K, Faivre L, Lesaunier F, Delva R, Gravis G, Rolland F, *et al.* Androgen deprivation therapy plus docetaxel and estramustine vs. androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. *Lancet Oncol* 2015;**16**:787–94.

61. Schweizer MT, Huang P, Kattan MW, Kibel AS, de Wit R, Sternberg CN, *et al.* Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. *Cancer* 2013;**119**:3610–8.

62. 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 vs. magnetic resonance imaging-transrectal ultrasound fusion vs. cognitive registration. Is there a preferred technique? *Eur Urol* 2017;**71**:517–31.

63. Drost F, Osses D, Nieboer D, Steyerberg E, Bangma C, Roobol M, *et al.* Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. *Cochr Datab Syst Rev* 2019;**4**:CD012663.

64. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;**75**:40–6.

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

66. Drost FJ, Osses D, Nieboer D, Bangma C, Steyerberg E, Roobol M, Schoots IG. Prostate MRI, with or without targeted biopsy, and standard biopsy for detecting prostate cancer: a Cochrane systematic review and meta-analysis. *J Urol* 2019;**18**:e728–9.

67. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.*; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;**155**:529–36.

68. Yang B, Mallett S, Takwoingi Y, Davenport CF, Hyde CJ, Whiting PF, *et al.*; QUADAS-C Group. QUADAS-C: a tool for assessing risk of bias in comparative diagnostic accuracy studies. *Ann Intern Med* 2021;**174**:1592–9.

69. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 1: Introduction to Evidence Synthesis for Decision Making*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

70. Dias S, Caldwell DM. Network meta-analysis explained. *Arch Dis Child Fetal Neonatal Ed* 2019;**104**:F8–F12.

71. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-analysis of Randomised Controlled Trials*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

72. R Core Team. *R: A Language and Environment for Statistical Computing [Software]*. Foundation for Statistical Computing; 2022. URL: www.R-project.org/ (accessed 25 October 2022).

73. Rücker G, Schwarzer G, Krahn U, König J. *netmeta: Network Meta-analysis Using Frequentist Methods. Version 2.5-0 ed. [Software]*. 2022. URL: http://CRAN.R-project.org/package=netmeta (accessed 25 October 2022).

74. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. *Bayesian Data Analysis*. 3rd edn. Boca Raton, FL: CRC Press; 2013.

75. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS Book*. Boca Raton, FL: CRC Press; 2013.

76. van Valkenhoef G, Kuiper J. *gemtc: Network Meta-analysis Using Bayesian Methods. R Package. 1.0-1 ed. [Software]*. CRAN; 2021. URL: https://CRAN.R-project.org/package=gemtc (accessed 25 October 2022).

77. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. *NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2011.

78. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, *et al.* Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890.

79. Thangarasu M, Jayaprakash SP, Selvaraj N, Bafna S, Paul R, Mahesh C, *et al.* A prospective study on the efficacy of cognitive targeted transrectal ultrasound prostate biopsy in diagnosing clinically significant prostate cancer. *Res Rep Urol* 2021;**13**:207–13.

80. Alberts AR, Schoots IG, Bokhorst LP, Drost FH, van Leenders GJ, Krestin GP, *et al.* Characteristics of prostate cancer found at fifth screening in the European randomized study of screening for prostate cancer Rotterdam: can we selectively detect high-grade prostate cancer with upfront multivariable risk stratification and magnetic resonance imaging? *Eur Urol* 2018;**73**:343–50.

81. Ferriero M, Tuderti G, Muto GL, Fiori C, Bove AM, Mastroianni R, *et al.* Diagnostic performance of fusion (US/MRI guided) prostate biopsy: propensity score matched comparison of elastic vs. rigid fusion system. *World J Urol* 2022;**40**:991–6.

82. Izadpanahi MH, Elahian A, Gholipour F, Khorrami MH, Zargham M, Mohammadi Sichani M, *et al.* Diagnostic yield of fusion magnetic resonance-guided prostate biopsy vs. cognitive-guided biopsy in biopsy-naïve patients: a head-to-head randomized controlled trial. *Prostate Cancer Prostatic Dis* 2021;**24**:1103–9.

83. Sokolakis I, Pyrgidis N, Koneval L, Krebs M, Thurner A, Kubler H, Hatzichristodoulou G. Usability and diagnostic accuracy of different MRI/ultrasound-guided fusion biopsy systems for the detection of clinically significant and insignificant prostate cancer: a prospective cohort study. *World J Urol* 2021;**39**:4101–8.

84. Rabah D, Al-Taweel W, Khan F, Arafa M, Mehmood S, Mokhtar A, Farhat K. Transperineal vs. transrectal multi-parametric magnetic resonance imaging fusion targeted prostate biopsy. *Saudi Med J* 2021;**42**:649–54.

85. Liang L, Cheng Y, Qi F, Zhang L, Cao D, Cheng G, Hua L. A comparative study of prostate cancer detection rate between transperineal COG-TB and transperineal FUS-TB in patients with PSA <=20 ng/mL. *J Endourol* 2020;**34**:1008–14.

86. Kulis T, Zekulic T, Alduk AM, Lusic M, Bulimbasic S, Ferencak V, *et al.* Targeted prostate biopsy using a cognitive fusion of multiparametric magnetic resonance imaging and transrectal ultrasound in patients with previously negative systematic biopsies and non-suspicious digital rectal exam. *Croat Med J* 2020;**61**:49–54.

87. Wajswol E, Winoker JS, Anastos H, Falagario U, Okhawere K, Martini A, *et al.* A cohort of transperineal electromagnetically tracked magnetic resonance imaging/ultrasonography fusion-guided biopsy: assessing the impact of inter-reader variability on cancer detection. *BJU Int* 2020;**125**:531–40.

88. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, Marks LS. Comparison of targeted vs systematic prostate biopsy in men who are biopsy naïve: the prospective assessment of image registration in the diagnosis of prostate cancer (PAIREDCAP) study. *JAMA Surg* 2019;**154**:811–8.

89. Stabile A, Dell'Oglio P, Gandaglia G, Fossati N, Brembilla G, Cristel G, *et al.* Not all multiparametric magnetic resonance imaging-targeted biopsies are equal: the impact of the type of approach and operator expertise on the detection of clinically significant prostate cancer. *Eur Urol Oncol* 2018;**1**:120–8.

90. Monda SM, Vetter JM, Andriole GL, Fowler KJ, Shetty AS, Weese JR, Kim EH. Cognitive vs. software fusion for MRI-targeted biopsy: experience before and after implementation of fusion. *Urology* 2018;**119**:115–20.

91. Kaufmann S, Russo GI, Thaiss W, Notohamiprodjo M, Bamberg F, Bedke J, *et al.* Cognitive vs. software-assisted registration: development of a new nomogram predicting prostate cancer at MRI-targeted biopsies. *Clin Genitourin Cancer* 2018;**16**:e953–60.

92. Fourcade A, Payrard C, Tissot V, Perrouin-Verbe MA, Demany N, Serey-Effeil S, *et al.* The combination of targeted and systematic prostate biopsies is the best protocol for the detection of clinically significant prostate cancer. *Scand J Urol* 2018;**52**:174–9.

93. Cornud F, Roumiguie M, de Longchamps NB, Ploussard G, Bruguiere E, Portalez D, *et al.* Precision matters in MR imaging-targeted prostate biopsies: evidence from a prospective study of cognitive and elastic fusion registration transrectal biopsies. *Radiology* 2018;**287**:534–42.

94. Albisinni S, Aoun F, Noel A, El Rassy E, Lemort M, Paesmans M, *et al.* Are concurrent systematic cores needed at the time of targeted biopsy in patients with prior negative prostate biopsies? *Prog Urol* 2018;**28**:18–24.

95. Hansen NL, Barrett T, Kesch C, Pepdjonovic L, Bonekamp D, O'Sullivan R, *et al.* Multicentre evaluation of magnetic resonance imaging supported transperineal prostate biopsy in biopsy-naïve men with suspicion of prostate cancer. *BJU Int* 2018;**122**:40–9.

96. Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, *et al.* Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. *Cancer* 2016;**122**:884–92.

97. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, *et al.* A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: the PROFUS trial. *Eur Urol* 2014;**66**:343–51.

98. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, *et al.* Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. *J Urol* 2013;**189**:493–9.

99. Gomez-Ortiz D, Garza-Gangemi AM, Oropeza-Aguilar M, Rangel-Suarez S, Espinosa-Cruz V, Villegas-Hernandez AC, *et al.* Routine systematic prostate biopsies not replaced by magnetic resonance imaging-targeted biopsy [published online ahead of print June 7 2022]. *Rev Invest Clin* 2022;**74**:212–8. https://doi.org/10.24875/RIC.22000084

100. Lockhart K, Martin J, White M, Raman A, Grant A, Chong P. Fusion vs. cognitive MRI-guided prostate biopsies in diagnosing clinically significant prostate cancer [published online ahead of print May 13 2022]. *J Clin Urol.* https://doi.org/10.1177/20514158221085081

101. Kaufmann S, Russo GI, Bamberg F, Lowe L, Morgia G, Nikolaou K, *et al.* Prostate cancer detection in patients with prior negative biopsy undergoing cognitive-, robotic- or in-bore MRI target biopsy. *World J Urol* 2018;**36**:761–8.

102. Jordan PWTBMIL, Weerdmeester B, Brooke J. SUS: a 'quick and dirty' usability scale. In: *Usability Evaluation in Industry*. London: CRC Press; 1996. pp. 189–94.

103. Rodda S, Tyldesley S, Morris WJ, Keyes M, Halperin R, Pai H, *et al.* ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2017;**98**:286–95.

104. Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, *et al.* Hypofractionated vs. conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;**17**:1061–9.

105. Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, *et al.* Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017;**35**:1884–90.

106. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, *et al.*; CHHiP Investigators. Conventional vs. hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;**17**:1047–60.

107. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, *et al.* Ultra-hypofractionated vs. conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* 2019;**394**:385–95.

108. Marzi S, Saracino B, Petrongari MG, Arcangeli S, Gomellini S, Arcangeli G, *et al.* Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional vs. hypofractionated scheme for localized prostate cancer. *J Exp Clin Cancer Res* 2009;**28**:117.

109. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, *et al.*; Prostate Cancer Intervention vs. Observation Trial (PIVOT) Study Group. Radical prostatectomy vs. observation for localized prostate cancer. *N Engl J Med* 2012;**367**:203–13.

110. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, *et al.*; SPCG-4 Investigators. Radical prostatectomy vs. watchful waiting in early prostate cancer. *N Engl J Med* 2011;**364**:1708–17.

111. Hegde JV, Demanes DJ, Veruttipong D, Raince J, Park SJ, Raman SS, *et al.* Pretreatment 3T multiparametric MRI staging predicts for biochemical failure in high-risk prostate cancer treated with combination high-dose-rate brachytherapy and external beam radiotherapy. *Brachytherapy* 2017;**16**:1106–12.

112. Gnanapragasam VJ, Lophatananon A, Wright KA, Muir KR, Gavin A, Greenberg DC. Improving clinical risk stratification at diagnosis in primary prostate cancer: a prognostic modelling study. *PLOS Med* 2016;**13**:e1002063.

113. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, *et al.* Survival with newly diagnosed metastatic prostate cancer in the 'docetaxel era': data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *Eur Urol* 2015;**67**:1028–38.

114. Bryant RJ, Oxley J, Young GJ, Lane JA, Metcalfe C, Davis M, *et al.*; PROTecT Study Group. The PROTecT trial: analysis of the patient cohort, baseline risk stratification and disease progression. *BJU Int* 2020;**125**:506–14.

115. Yang Y, Abel L, Buchanan J, Fanshawe T, Shinkins B. Use of decision modelling in economic evaluations of diagnostic tests: an appraisal and review of Health Technology Assessments in the UK. *PharmacoEcon Open* 2019;**3**:281–91.

116. 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*. London: NICE; 2022.

117. 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-naïve men. *Radiology* 2017;**285**:157–66.

118. Hayes JH, Ollendorf DA, Pearson SD, Barry MJ, Kantoff PW, Lee PA, McMahon PM. Observation vs. initial treatment for men with localized, low-risk prostate cancer: a cost-effectiveness analysis. *Ann Intern Med* 2013;**158**:853–60.

119. Cheng LJ, Soon SS, Tan TW, Tan CH, Lim TSK, Tay KJ, *et al.* Cost-effectiveness of MRI targeted biopsy strategies for diagnosing prostate cancer in Singapore. *BMC Health Serv Res* 2021;**21**:909.

120. Hao S, Karlsson A, Heintz E, Elfstrom KM, Nordstrom T, Clements M. Cost-effectiveness of magnetic resonance imaging in prostate cancer screening: a microsimulation study. *Value Health* 2021;**24**:1763–72.

121. Wilson ECF, Wreford A, Tamer P, Leonard K, Brechka H, Gnanapragasam VJ. Economic evaluation of transperineal vs. transrectal devices for local anaesthetic prostate biopsies. *PharmacoEcon* 2021;**5**:737–53.

122. Getaneh AM, Heijnsdijk EA, de Koning HJ. Cost-effectiveness of multiparametric magnetic resonance imaging and MRI-guided biopsy in a population-based prostate cancer screening setting using a micro-simulation model. *Cancer Medicine* 2021;**10**:4046–53.

123. National Institute for Health and Care Excellence. *NG131 Health Economic Model Report: Prostate Cancer Update*. London: NICE; 2019.

124. Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. *BJU Int* 2018;**122**:50–8.

125. Faria R, Soares MO, Spackman E, Ahmed HU, Brown LC, Kaplan R, *et al.* Optimising the diagnosis of prostate cancer in the era of multiparametric magnetic resonance imaging: a cost-effectiveness analysis based on the prostate MR imaging study (PROMIS). *Eur Urol* 2018;**73**:23–30.

126. Brown LC, Ahmed HU, Faria R, El-Shater Bosaily A, Gabe R, Kaplan RS, *et al.* Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study. *Health Technol Assess* 2018;**22**:1–176.

127. Patel S, Rongen JJ, Futterer JJ, Boltyenkov A, Rovers MM. The role of multiparametric magnetic resonance imaging in active surveillance for men with low-risk prostate cancer: a cost-effectiveness modeling study. *Eur Urol Oncol* 2018;**1**:476–83.

128. Sathianathen NJ, Kuntz KM, Alarid-Escudero F, Lawrentschuk NL, Bolton DM, Murphy DG, *et al.* Incorporating biomarkers into the primary prostate biopsy setting: a cost-effectiveness analysis. *J Urol* 2018;**200**:1215–20.

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

130. Venderink W, Govers TM, de Rooij M, Futterer JJ, Sedelaar JPM. Cost-effectiveness comparison of imaging-guided prostate biopsy techniques: systematic transrectal ultrasound, direct in-bore MRI, and image fusion. *AJR: Am J Roentgenol* 2017;**208**:1058–63.

131. Cerantola Y, Dragomir A, Tanguay S, Bladou F, Aprikian A, Kassouf W. Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer. *Urol Oncol* 2016;**34**:119.e1–9.

132. de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy vs. systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. *Eur Urol* 2014;**66**:430–6.

133. Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, *et al.* The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. *Health Technol Assess* 2013;**17**:1–281.

134. Royal College of Surgeons of England. *NPCA Annual Report 2020*. London: Royal College of Surgeons of England; 2021.

135. Bill-Axelson A, Holmberg L, Garmo H, Rider JR, Taari K, Busch C, *et al.* Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;**370**:932–42.

136. Torvinen S, Färkkilä N, Sintonen H, Saarto T, Roine RP, Taari K. Health-related quality of life in prostate cancer. *Acta Oncol* 2013;**52**:1094–101.

137. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18.

138. Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, *et al.*; PROTecT Study Group. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;**375**:1425–37.

139. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: a modelling study. *Palliat Med* 2015;**29**:899–907.

140. Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS: a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;**10**:325–37.

141. Mortezavi A, Marzendorfer O, Donati OF, Rizzi G, Rupp NJ, Wettstein MS, *et al.* Diagnostic accuracy of multiparametric magnetic resonance imaging and fusion guided targeted biopsy evaluated by transperineal template saturation prostate biopsy for the detection and characterization of prostate cancer. *J Urol* 2018;**200**:309–18.

142. Zhou Y, Zhou Z, Li Q, Xu Y, Sun H, Xiao Y, *et al.* Diagnostic accuracy of magnetic resonance-guided prostate biopsy and template-guided transperineal saturation biopsy. *Medicine* 2018;**97**:e12495.

143. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, *et al.* Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol* 2019;**30**:1992–2003.

144. Office for National Statistics. *National Life Tables: UK*. Office for National Statistics; 2021. URL: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables (accessed 29 September 2022).

145. Ankit Rohatgi. *WebPlotDigitizer*. Ankit Rohatgi; 2022. URL: https://automeris.io/WebPlotDigitizer/index.html (accessed 27 October 2022).

146. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan--Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9.

147. Jackson C. flexsurv: a platform for parametric survival modeling in R. *J Stat Softw* 2016;**70**:1–33.

148. Brent R. *Algorithms for Minimization without Derivatives*. Mineloa, NY: Dover Publications; 2022.

149. Wallis CJ. *ESMO 2021: Final Overall Survival Analysis from ARCHES: A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Enzalutamide + ADT in Men with mHSPC*. UroToday.com; 2021. URL: www.urotoday.com/conference-highlights/esmo-2021/esmo-2021-prostate-cancer/132209-esmo-2021-lba25-final-overall-survival-os-analysis-from-arches-a-phase-3-randomized-double-blind-placebo-pbo-controlled-study-of-enzalutamide-enza-androgen-deprivation-therapy-adt-in-men-with-metastatic-hormone-sensitive-prostate-cancer-mhspc.html (accessed 13 October 2022).

150. Chi KN, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, *et al.* Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol* 2021;**39**:2294–303.

151. Parry MG, Cowling TE, Sujenthiran A, Nossiter J, Berry B, Cathcart P, *et al.* Risk stratification for prostate cancer management: value of the Cambridge Prognostic Group classification for assessing treatment allocation. *BMC Med* 2020;**18**:114.

152. 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. Addendum 1*. London: NICE; 2022.

153. Armstrong AJ, Iguchi T, Azad AA, Szmulewitz RZ, Holzbeierlein J, Villers A, *et al.* LBA25 final overall survival (OS) analysis from ARCHES: a phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) + androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC). *Ann Oncol* 2021;**32**:S1300–1.

154. Jones K, Burns A. *Unit Costs of Health and Social Care 2021*. Canterbury: Personal Social Services Research Unit, University of Kent; 2021.

155. Imperial College London. *Imperial Prostate 7: Prostate Assessment Using Comparative Interventions – Fast MRI and Image-Fusion for Cancer (IP7-PACIFIC).* ClinicalTrials.gov. Bethesda, MD: National Library of Medicine; 2022. URL: https://clinicaltrials.gov/ct2/show/NCT05574647 (accessed 30 October 2022).

156. Kruschke JK. *Doing Bayesian Data Analysis: A Tutorial with R and BUGS*. London: Academic Press; 2010.

157. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making* 2003;**23**:341–50.

158. Cash HH, Shore SL, Pavlovich N, Bulang CP, Schostak S, Planken M. E Prostate cancer detection by novice micro-ultrasound users enrolled in a training program. *Soc Int Urol J* 2022;**3**:62–8.

166. Exterkate L, Wegelin O, Barentsz JO, van der Leest MG, Kummer JA, Vreuls W, *et al.* Is there still a need for repeated systematic biopsies in patients with previous negative biopsies in the era of magnetic resonance imaging-targeted biopsies of the prostate? *Eur Urol Oncol* 2020;**3**:216–23.

167. Kalavagunta C, Zhou X, Schmechel SC, Metzger GJ. Registration of in vivo prostate MRI and pseudo-whole mount histology using Local Affine Transformations guided by Internal Structures (LATIS). *J Magn Reson Imaging* 2015;**41**:1104–14.

168. Wegelin O, Exterkate L, van der Leest M, Kelder JC, Ruud Bosch JLH, Barentsz JO, *et al.* Complications and adverse events of three magnetic resonance imaging-based target biopsy techniques in the diagnosis of prostate cancer among men with prior negative biopsies: results from the FUTURE trial, a multicentre randomised controlled trial. *Eur Urol Oncol* 2019;**2**:617–24.

169. Mannaerts CK, Engelbrecht MRW, Postema AW, van Kollenburg RAA, Hoeks CMA, Savci-Heijink CD, *et al.* Detection of clinically significant prostate cancer in biopsy-naïve men: direct comparison of systematic biopsy, multiparametric MRI- and contrast-ultrasound-dispersion imaging-targeted biopsy. *BJU Int* 2020;**126**:481–93.

170. Simmons LAM, Kanthabalan A, Arya M, Briggs T, Barratt D, Charman SC, *et al.* Accuracy of transperineal targeted prostate biopsies, visual estimation and image fusion in men needing repeat biopsy in the PICTURE trial. *J Urol* 2018;**200**:1227–34.

171. Hansen N, Patruno G, Wadhwa K, Gaziev G, Miano R, Barrett T, *et al.* Magnetic resonance and ultrasound image fusion supported transperineal prostate biopsy using the Ginsburg protocol: technique, learning points, and biopsy results. *Eur Urol* 2016;**70**:332–40.

172. Kesch C, Radtke JP, Popeneciu IV, Gasch C, Dieffenbacher SC, Klein T, *et al.* TOP: Prospective evaluation of a volume based, computer assisted method for transperineal optimized prostate biopsy. *Urol Int*. 2017;**99**:149–55.

173. Hansen NL, Caglic I, Berman LH, Kastner C, Doble A, Barrett T. Multiparametric prostate magnetic resonance imaging and cognitively targeted transperineal biopsy in patients with previous abdominoperineal resection and suspicion of prostate cancer. *Urology* 2016;**96**:8–14.

174. Oh J, Tyldesley S, Pai HH, McKenzie MR, Halperin RM, Duncan GG, *et al.* An updated analysis of survival endpoints for ASCENDE-RT, a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2020;**108**:S62.

175. Hedley M. Multi-parametric magnetic resonance imaging before prostate biopsy. *Cancer Nurs Pract* 2017;**16**:21–5.

176. de Vries KC, Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Hyprofractionated vs. conventionally fractionated radiation therapy for patients with intermediate- or high-risk, localized, prostate cancer: 7-year outcomes from the randomized, multicenter, open-label, phase 3 HYPRO trial. *Int J Radiat Oncol Biol Phys* 2020;**106**:108–15.

177. David PD, Clare G, Isabel S, Vincent K, Alison Jane B, Ananya C, *et al.* Eight-year outcomes of a phase III randomized trial of conventional vs. hypofractionated high-dose intensity modulated radiotherapy for prostate cancer (CRUK/06/016): update from the CHHiP Trial. *J Clin Oncol* 2020;**38**:325.

178. Fransson P, Nilsson P, Gunnlaugsson A, Beckman L, Tavelin B, Norman D, *et al.* Ultra-hypofractionated vs. conventionally fractionated radiotherapy for prostate cancer (HYPO-RT-PC): patient-reported quality-of-life outcomes of a randomised, controlled, non-inferiority, phase 3 trial. *Lancet Oncol* 2021;**22**:235–45.

179. Wilt TJ, Vo TN, Langsetmo L, Dahm P, Wheeler T, Aronson WJ, *et al.* Radical prostatectomy or observation for clinically localized prostate cancer: extended follow-up of the prostate cancer intervention vs. observation trial (PIVOT). *Eur Urol* 2020;**77**:713–24.

180. Bill-Axelson A, Holmberg L, Garmo H, Taari K, Busch C, Nordling S, *et al.* Radical prostatectomy or watchful waiting in prostate cancer: 29-year follow-up. *N Engl J Med* 2018;**379**:2319–29.

181. Fizazi K, Carmel A, Joly F, Delva R, Gravis G, Rolland F, *et al.* Updated results of GETUG-12, a phase III trial of docetaxel-based chemotherapy in high-risk localized prostate cancer, with a 12-year follow-up. *Ann Oncol* 2018;**29**:viii271.

182. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, *et al.* Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within Protect study. *BMJ* 2012;**344**:d7894. https://doi.org/10.1136/bmj.d7894

183. Pepe P, Aragona F. Morbidity after transperineal prostate biopsy in 3000 patients undergoing 12 vs 18 vs more than 24 needle cores. *Urology* 2013;**81**:1142–6.

184. Tamhankar AS, El-Taji O, Vasdev N, Foley C, Popert R, Adshead J. P9-7 The clinical and financial implications of a decade of prostate biopsies in the NHS: interrogation of the Hospital Episode Statistics (HES) Data 2008-2019 [BAUS abstracts]. *J Clin Urol* 2020;**13**:62.

185. NHS England. *2018/19 National Cost Collection Data Publication*. NHS England; 2021. URL: www.england.nhs.uk/publication/2018-19-national-cost-collection-data-publication/ (accessed 27 September 2022).

186. NHS England. *2019/20 National Cost Collection Data Publication*. NHS England; 2021. URL: www.england.nhs.uk/publication/2019-20-national-cost-collection-data-publication/ (accessed 27 September 2022).

187. NHS England. *2020/2021 National Cost Collection Data*. NHS England; 2022. URL: www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/#ncc1819 (accessed 27 September 2022).

188. NPCA Organisational Audit 2021. *Table of NHS Provider-Level Results: National Prostate Cancer Audit*. The Royal College of Surgeons of England; 2022. URL: www.npca.org.uk/reports/npca-organisational-audit-2021/ (accessed 29 September 2022).

189. National Institute for Health and Care Excellence. *NICE Impact Prostate Cancer*. London: NICE; 2020.

190. Exchange Rates UK. *US Dollar (USD) to British Pound (GBP) Exchange Rate History: Wednesday 9/03/2022 to Saturday 3/09/2022*. Exchange Rates UK; 2022. URL: www.exchangerates.org.uk/USD-GBP-exchange-rate-history.html (accessed 5 September 2022).

191. *Drugs and Pharmaceutical Electronic Market Information Tool (eMIT)*. Deparment of Health and Social Care; 2021. URL: www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (accessed 29 September 2022).

192. British National Formulary (BNF). *BMJ Group and the Royal Pharmaceutical Society of Great Britain*; 2022. URL: https://bnf.nice.org.uk/ (accessed 27 September 2022).

Appendix 1 Software fusion technologies' principal features

TABLE 23 Summary of SF technologies features

Software system	Manufacturer	Hardware system	Fixation for biopsies	Elastic or rigid estimation	Was there a submission for the DAR?
ARTEMIS	InnoMedicus ARTEMIS	ARTEMIS	Stabilised, freehand unknown, semi-robotic arm	Both	No
BioJet	Healthcare Supply Solutions Ltd	Third-party ultrasounds	Stabilised, freehand (without tracking movement)	Both	No
BiopSee	Medcom	MedSta or third-party ultrasounds	Stabilised, freehand	Both	Yes
bkFusion	BK Medical UK Ltd and MIM Software Inc.	BK3000 or BK5000	Stabilised, freehand	Rigid	Yes
Fusion Bx 2.0	Focal Healthcare	Third-party ultrasounds	Stabilised, freehand, robotic arm	Both	Yes
FusionVu	Exact Imaging	ExactVu	Stabilised, freehand	Rigid	Yes
iSR'obot™ MonaLisa	Biobot iSR'obot	iSR'obot™ Mona Lisa	Stabilised, freehand unknown, robotic arm	Elastic	No
KOELIS Trinity	KOELIS and Kebomed	TRINITY ultrasound system	Stabilised, freehand	Elastic	Yes
UroNav Fusion Biopsy System	Phillips	Third- party ultrasounds	Stabilised, freehand	Unknown	No

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 the EAG report, the company had not registered with NICE, and therefore did not provide information on this technology's compatibility with a picture archiving and communication system (PACS), image measurement capabilities and ability to produce archivable cartograms.

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.

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

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 are stored locally and can be connected to a PACS for import and export of images.

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 comprise a magnetic field generator and sensor 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.

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. 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.

FusionVu (Exact Imaging)

The ExactVu device includes a micro-ultrasound (high-resolution ultrasound at > 20MHz) and a FusionVu feature that enables SF 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 in the case that a PACS is not available.

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 co-ordinates are recorded of each biopsy sample. At the time of writing the EAG report, the company had not registered with NICE, and therefore did not provide information on the tracking of patient movement, whether freehand biopsies can be done, PACS compatibility and image measurement capabilities of this system.

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 elastic 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.

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. UroNav uses both rigid and elastic registration methods to create and maintain 3D registration of MR/US images and compensate for patient movement. 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 the EAG report, the company had not registered with NICE, and therefore did not submit 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.

Appendix 2 Literature search strategies

Database search strategies

MEDLINE ALL

(includes: Epub Ahead of Print, In-process and Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

Via Ovid http://ovidsp.ovid.com/

Date range: 1946 to 13 May, 2022

Date searched: 16 May 2022

Records retrieved: 3129

MEDLINE ALL was searched again on 2 August 2022. 3218 studies were retrieved.

1 exp Prostatic Neoplasms/ (142378)
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$)).ti,ab. (165600)
4 (PCa or sPCa or csPCa or PrCa).ti,ab. (52571)
5 (((atypical adj3 proliferation) or ASAP) and prostat$).mp. (292).
6 or/1-5 (224791)
7 Magnetic Resonance Imaging/ (453356)
8 Multiparametric Magnetic Resonance Imaging/ (961)
9 (magnetic resonance or MRI or MR imag$ or MR scan$).ti,ab. (560471)
10 (mpMRI or mp-MRI or mpMR imag$ 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$).ti,ab. (2060)
11 or/7-10 (721668)
12 Image Interpretation, Computer-Assisted/ (47627)
13 (fusion$ or fuse$ or fusing$).ti,ab. (299284)
14 cognitive$.ti,ab. (424900)
15 (visual$ adj3 (estimat$ or direct$ or align$ or guid$ or influenc$)).ti,ab. (28436)
16 registration$.ti,ab. (161125)
17 (elastic or rigid or nonrigid).ti,ab. (138219)
18 Software/ (120348)
19 (software or hardware).ti,ab. (224399)
20 or/12-19 (1355053)
21 Prostate/ (39209)
22 (prostate$ or prostatic).ti,ab. (234214)
23 21 or 22 (238231)
24 Biopsy/ (185156)
25 Image-Guided Biopsy/ (5020)
26 Endoscopic Ultrasound-Guided Fine Needle Aspiration/ (3254)
27 Biopsy, Fine-Needle/ (14970)
28 Biopsy, Large-Core Needle/ (2307)
29 Biopsy, Needle/ (49647)

30 (biopsy or biopsie$ or rebiopsy or rebiopsie$).ti,ab. (427177)
31 or/24-30 (548867)
32 23 and 31 (26179)
33 6 and 11 and 20 and 32 (1621)
34 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (biopsy or biopsie$)).ti,ab. (860)
35 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops$)).ti,ab. (160)
36 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (ultrasound$ or ultrasonic$ or ultrasonograph$ or TRUS or transperineal$ or transrectal$)).ti,ab. (773)
37 or/34-36 (1626)
38 6 and 37 (662)
39 (target$ adj4 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (3800)
40 (focal adj2 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (636)
41 39 or 40 (4405)
42 6 and 41 (1842)
43 (target$ adj4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).ti,ab. (4003)
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 (4534)
46 6 and 32 and 45 (1125)
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$)).ti,ab. (11942)
48 6 and 32 and 47 (951)
49 ((MRI stratified or magnetic resonance imaging stratified) adj3 pathway$)).ti,ab. (3)
50 33 or 38 or 42 or 46 or 48 or 49 (3265)
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. (96)
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. (189)
59 (COG-TB or TB-COG or CBx).ti,ab. (530)
60 TRUS-TB.ti,ab. (3)
61 ('MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB').ti,ab. (306)
62 or/51-61 (1105)
63 6 and 62 (437)
64 50 or 63 (3292)
65 (fusion$ adj3 (software or hardware or computer$ or device$ or system$ or technolog$ or machine$ or platform$)).ti,ab. (5680)
66 6 and 65 (294)
67 64 or 66 (3331)
68 KOELIS.ti,ab. (23)
69 Fusion Bx.ti,ab. (1)
70 BioJet.ti,ab. (28)
71 (Trinity or PROMAP).ti,ab. (1329)
72 Fusion MR.ti,ab. (8)
73 (bkFusion or bk Fusion or BK3000 or BK 3000 or BK5000 or BK 5000 or Predictive Fusion).ti,ab. (7)
74 or/70-73 (1371)

75 6 and 74 (20)
76 68 or 69 or 75 (38)
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. (12)
81 DynaCAD.ti,ab. (9)
82 (ARTEMIS or ProFuse).ti,ab. (4760)
83 Mona Lisa.ti,ab. (106)
84 or/81-83 (4874)
85 6 and 84 (54)
86 or/77-80 (34)
87 85 or 86 (81)
88 67 or 76 or 87 (3362)
89 exp animals/not humans.sh. (5007245)
90 88 not 89 (3357)
91 limit 90 to yr='2008 -Current' (3129)

Key

/ = subject heading (MeSH heading)
sh = subject heading (MeSH heading)
exp = exploded subject heading (MeSH heading)
$ = truncation
ti,ab = terms in title or abstract fields
mp = multi-purpose field search – terms in title, original title, abstract, name of substance word, or subject heading word
adj3 = terms within three words of each other (any order)

Cochrane Controlled Register of Trials (CENTRAL)

Via Wiley http://onlinelibrary.wiley.com/

Issue: Issue 4 of 12, April 2022

Date searched: 16 May 2022

Records retrieved: 425

CENTRAL was searched again on 2 August 2022. 434 studies were retrieved.

#1 MeSH descriptor: [Prostatic Neoplasms] explode all trees 6115
#2 MeSH descriptor: [Prostatic Intraepithelial Neoplasia] this term only 47
#3 ((prostate* or prostatic or intraprostatic) near/4 (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,kw 15719
#4 (PCa or sPCa or csPCa or PrCa):ti,ab,kw 5554
#5 ((atypical near/3 proliferation) or ASAP) and prostat*)):ti,ab,kw 21
#6 #1 or #2 or #3 or #4 or #5 20099
#7 MeSH descriptor: [Magnetic Resonance Imaging] this term only 7831
#8 MeSH descriptor: [Multiparametric Magnetic Resonance Imaging] this term only 11
#9 ('magnetic resonance' or MRI or (MR next imag*) or (MR next scan*)):ti,ab,kw 41256

#10 (mpMRI or mp-MRI or (mpMR next imag*) or (mpMR next scan*) or (mp-MR next imag*) or mp-MR scan* or bpMRI or bp-MRI or (bpMR next imag*) or (bpMR next scan*) or bp-MR imag* or bp-MR scan*):ti,ab,kw 260
#11 #7 or #8 or #9 or #10 41264
#12 MeSH descriptor: [Image Interpretation, Computer-Assisted] this term only 875
#13 (fusion* or fuse* or fusing*):ti,ab,kw 8635
#14 cognitive*:ti,ab,kw 80126
#15 (visual* near/3 (estimat* or direct* or align* or guid* or influenc*)):ti,ab,kw 2089
#16 registration*:ti,ab,kw 66768
#17 (elastic or rigid or nonrigid):ti,ab,kw 6102
#18 MeSH descriptor: [Software] this term only 1008
#19 (software or hardware):ti,ab,kw 26282
#20 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 180581
#21 MeSH descriptor: [Prostate] this term only 975
#22 (prostate* or prostatic):ti,ab,kw 23298
#23 #21 or #22 23298
#24 MeSH descriptor: [Biopsy] this term only 3365
#25 MeSH descriptor: [Image-Guided Biopsy] this term only 119
#26 MeSH descriptor: [Endoscopic Ultrasound-Guided Fine Needle Aspiration] this term only 156
#27 MeSH descriptor: [Biopsy, Needle] explode all trees 1270
#28 (biopsy or biopsie* or rebiopsy or rebiopsie*):ti,ab,kw 32970
#29 #24 or #25 or #26 or #27 or #28 33007
#30 #23 and #29 2832
#31 #6 and #11 and #20 and #30 211
#32 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) near/6 (prior or previous* or preced* or before* or earlier or first or initial*) near/6 (biopsy or biopsie*)):ti,ab,kw 95
#33 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) near/6 prebiops*):ti,ab,kw 34
#34 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) near/6 (prior or previous* or preced* or before* or earlier or first or initial*) near/6 (ultrasound* or ultrasonic* or ultrasonograph* or TRUS or transperineal* or transrectal*)):ti,ab,kw 84
#35 (target* near/4 (biopsy or biopsie* or rebiopsy or rebiopsie*)):ti,ab,kw 573
#36 (focal near/2 (biopsy or biopsie* or rebiopsy or rebiopsie*)):ti,ab,kw 22
#37 #32 or #33 or #34 or #35 or #36 715
#38 #6 and #37 324
#39 (target* near/4 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)):ti,ab,kw 453
#40 (focal near/2 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)):ti,ab,kw 38
#41 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) near/3 (guid* or influenc* or direct* or align*)):ti,ab,kw 923
#42 #39 or #40 or #41 1299
#43 #6 and #30 and #42 279
#44 (('MRI stratified' or 'magnetic resonance imaging stratified') near/3 pathway*):ti,ab,kw 0
#45 #31 or #38 or #43 or #44 430
#46 (MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB'):ti,ab,kw 136
#47 #6 and #46 82
#48 #45 or #47 431
#49 (fusion* near/3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*)):ti,ab,kw 267

#50 #6 and #49 57
#51 #48 or #50 434
#52 (KOELIS or 'Fusion Bx' or BioJet):ti,ab,kw 18
#53 (Trinity or PROMAP or 'Fusion MR' or bkFusion or 'bk Fusion' or BK3000 or 'BK 3000' or BK5000 or 'BK 5000' or 'Predictive Fusion'):ti,ab,kw 161
#54 #6 and #53 3
#55 #52 or #54 19
#56 (BiopSee or UroNav or 'iSR'obot' or iSRobot or 'iSR obot' or UroFusion or UroBiopsy or FusionVu* or ExactVu*):ti,ab,kw 19
#57 (DynaCAD or ARTEMIS or ProFuse or 'Mona Lisa'):ti,ab,kw 283
#58 #6 and #57 9
#59 #56 or #58 27
#60 #51 or #55 or #59 with Publication Year from 2008 to 2022, in Trials 425
#61 #51 or #55 or #59 in Cochrane Reviews, Cochrane Protocols 1

Key

MeSH descriptor = subject heading (MeSH heading)
* = truncation
ti,ab,kw = terms in title, abstract or keyword fields
near/3 = terms within three words of each other (any order)
next = terms are next to each other

Cochrane Database of Systematic Reviews (CDSR)

Via Wiley http://onlinelibrary.wiley.com/

Issue: Issue 5 of 12, May 2022

Date searched: 16 May 2022

Records retrieved: 1

See above under CENTRAL for search strategy.

Cumulative Index to Nursing and Allied Health (CINAHL Plus)

Via Ebsco http://onlinelibrary.wiley.com/

Date range: Inception to 20220516

Date searched: 16 May 2022

Records retrieved: 916

S1 (MH 'Prostatic Neoplasms+') 34,206
S2 TI ((prostate* or prostatic or intraprostatic) N4 (cancer* or neoplas* or tumour* or tumor* or malignan* or metasta* or carcinoma* or adenocarcinoma* or lesion* or nodul* or sarcoma* or lymphoma*)) OR AB ((prostate* or prostatic or intraprostatic) N4 (cancer* or neoplas* or tumour* or tumor* or malignan* or metasta* or carcinoma* or adenocarcinoma* or lesion* or nodul* or sarcoma* or lymphoma*)) 35,654

S3 TI ((PCa or sPCa or csPCa or PrCa)) OR AB ((PCa or sPCa or csPCa or PrCa)) 7320
S4 TI (((atypical N3 proliferation) or ASAP) and prostat*) OR AB (((atypical N3 proliferation) or ASAP) and prostat*) 29
S5 S1 OR S2 OR S3 OR S4 48,489
S6 (MH 'Magnetic Resonance Imaging') 136,332
S7 TI (('magnetic resonance' or MRI or (MR N1 imag*) or (MR N1 scan*))) OR AB (('magnetic resonance' or MRI or (MR N1 imag*) or (MR N1 scan*))) 123,908
S8 TI (((mpMRI or mp-MRI or (mpMR N1 imag*) or (mpMR N1 scan*) or (mp-MR N1 imag*) or (mp-MR N1 scan*) or bpMRI or bp-MRI or (bpMR N1 imag*) or (bpMR N1 scan*) or (bp-MR N1 imag*) or (bp-MR N1 scan*))) OR AB (((mpMRI or mp-MRI or (mpMR N1 imag*) or (mpMR N1 scan*) or (mp-MR N1 imag*) or (mp-MR N1 scan*) or bpMRI or bp-MRI or (bpMR N1 imag*) or (bpMR N1 scan*) or (bp-MR N1 imag*) or (bp-MR N1 scan*))) 631
S9 S6 OR S7 OR S8 181,020
S10 (MH 'Image Interpretation, Computer Assisted') 9454
S11 TI (fusion* or fuse* or fusing*) OR AB (fusion* or fuse* or fusing*) 26,160
S12 TI cognitive* OR AB cognitive* 154,740
S13 TI (visual* N3 (estimat* or direct* or align* or guid* or influenc*)) OR AB (visual* N3 (estimat* or direct* or align* or guid* or influenc*)) 4578
S14 TI registration* OR AB registration* 64,987
S15 TI (elastic or rigid or nonrigid) OR AB (elastic or rigid or nonrigid) 12,473
S16 (MH 'Software') 31,273
S17 TI (software or hardware) OR AB (software or hardware) 59,300
S18 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 341,260
S19 (MH 'Prostate') 3816
S20 TI (prostate* or prostatic) OR AB (prostate* or prostatic) 45,719
S21 S19 OR S20 46,101
S22 (MH 'Biopsy') 35,975
S23 (MH 'Biopsy, Needle') 11,989
S24 TI (biopsy or biopsie* or rebiopsy or rebiopsie*) OR AB (biopsy or biopsie* or rebiopsy or rebiopsie*) 59,743
S25 S22 OR S23 OR S24 84,744
S26 S21 AND S25 4603
S27 S5 AND S9 AND S18 AND S26 463
S28 TI ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 (prior or previous* or preced* or before* or earlier or first or initial*) N6 (biopsy or biopsie*)) OR AB ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 (prior or previous* or preced* or before* or earlier or first or initial*) N6 (biopsy or biopsie*)) 254
S29 TI ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 prebiops*) OR AB ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 prebiops*) 45
S30 TI ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 (prior or previous* or preced* or before* or earlier or first or initial*) N6 (ultrasound* or ultrasonic* or ultrasonograph* or TRUS or transperineal* or transrectal*)) OR AB ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N6 (prior or previous* or preced* or before* or earlier or first or initial*) N6 (ultrasound* or ultrasonic* or ultrasonograph* or TRUS or transperineal* or transrectal*)) 289
S31 TI (target* N4 (biopsy or biopsie* or rebiopsy or rebiopsie*)) OR AB (target* N4 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 961
S32 TI (focal N2 (biopsy or biopsie* or rebiopsy or rebiopsie*)) OR AB (focal N2 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 136
S33 S28 OR S29 OR S30 OR S31 OR S32 1512
S34 S5 AND S33 591

S35 TI (target* N4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)) OR AB (target* N4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)) 880
S36 TI (focal N2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)) OR AB (focal N2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)) 257
S37 TI ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N3 (guid* or influenc* or direct* or align*)) OR AB ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) N3 (guid* or influenc* or direct* or align*)) 3420
S38 S35 OR S36 OR S37 4296
S39 S5 AND S26 AND S38 533
S40 TI (('MRI stratified' or 'magnetic resonance imaging stratified') N3 pathway*) OR AB (('MRI stratified' or 'magnetic resonance imaging stratified') N3 pathway*) 2
S41 S27 OR S34 OR S39 OR S40 909
S42 TI (MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB') OR AB (MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB') 185
S43 S5 AND S42 126
S44 S41 OR S43 915
S45 TI (fusion* N3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*)) OR AB (fusion* N3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*)) 832
S46 S5 AND S45 86
S47 S44 OR S46 922
S48 TI (KOELIS or 'Fusion Bx' or BioJet) OR AB (KOELIS or 'Fusion Bx' or BioJet) 17
S49 TI (Trinity or PROMAP or 'Fusion MR' or bkFusion or 'bk Fusion' or BK3000 or 'BK 3000' or BK5000 or 'BK 5000' or 'Predictive Fusion') OR AB (Trinity or PROMAP or 'Fusion MR' or bkFusion or 'bk Fusion' or BK3000 or 'BK 3000' or BK5000 or 'BK 5000' or 'Predictive Fusion') 482
S50 S5 AND S49 2
S51 S48 OR S50 18
S52 TI (BiopSee or UroNav or 'iSR'obot' or iSRobot or 'iSR obot' or UroFusion or UroBiopsy or FusionVu* or ExactVu*) OR AB (BiopSee or UroNav or 'iSR'obot' or iSRobot or 'iSR obot' or UroFusion or UroBiopsy or FusionVu* or ExactVu*) 11
S53 TI (DynaCAD or ARTEMIS or ProFuse or 'Mona Lisa') AND AB (DynaCAD or ARTEMIS or ProFuse or 'Mona Lisa') 32
S54 S5 AND S53 0
S55 S52 OR S54 11
S56 S47 OR S51 OR S55 925
S57 S47 OR S51 OR S55 Limiters – Published Date: 20080101-20221231 916

Key

MH = CINAHL subject heading
+ = exploded CINAHL subject heading
* = truncation
TI = terms in the title
AB = terms in the abstract
N3 = terms within three words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)

Via http://onlinelibrary.wiley.com/

Date range: Inception – 31 March 2015

Date searched: 16 May 2022

Records retrieved: 7

1 MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES 709
2 MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia 2
3 ((prostate* or prostatic or intraprostatic) NEAR4 (cancer* or neoplas* or tumour* or tumor* or malignan* or metasta* or carcinoma* or adenocarcinoma* or lesion* or nodul* or sarcoma* or lymphoma*)) 891
4 (PCa or sPCa or csPCa or PrCa) 44
5 ((atypical NEAR3 proliferation) or ASAP) AND (prostat*) 1
6 #1 OR #2 OR #3 OR #4 OR #5 935
7 MeSH DESCRIPTOR Magnetic Resonance Imaging 693
8 MeSH DESCRIPTOR Multiparametric Magnetic Resonance Imaging 0
9 ('magnetic resonance' or MRI or MR imag* or MR scan*) 1337
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*) 2
11 #7 OR #8 OR #9 OR #10 1337
12 MeSH DESCRIPTOR Image Interpretation, Computer-Assisted 27
13 (fusion* or fuse* or fusing* or cognitive or registration* or elastic or rigid or nonrigid) 3376
14 (visual* NEAR3 (estimat* or direct* or align* or guid* or influenc*)) 23
15 MeSH DESCRIPTOR Software 76
16 (software or hardware) 812
17 #12 OR #13 OR #14 OR #15 OR #16 4163
18 MeSH DESCRIPTOR Prostate 82
19 (prostate* or prostatic) 1283
20 #18 OR #19 1283
21 MeSH DESCRIPTOR Biopsy 248
22 MeSH DESCRIPTOR Image-Guided Biopsy 11
23 MeSH DESCRIPTOR Endoscopic Ultrasound-Guided Fine Needle Aspiration 19
24 MeSH DESCRIPTOR Biopsy, Fine-Needle 83
25 MeSH DESCRIPTOR Biopsy, Large-Core Needle 8
26 MeSH DESCRIPTOR Biopsy, Needle 164
27 (biopsy or biopsie* or rebiopsy or rebiopsie*) 1457
28 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 1473
29 #20 AND #28 137
30 #6 AND #11 AND #17 AND #29 4
31 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR6 (biopsy or biopsie*)) 39
32 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR6 prebiops*) 0
33 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR6 (ultrasound* or ultrasonic* or ultrasonograph* or TRUS or transperineal* or transrectal*)) 121
34 (target* NEAR4 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 10
35 (focal NEAR2 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 0
36 #31 OR #32 OR #33 OR #34 OR #35 155
37 #6 AND #36 10

38 (target* NEAR4 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)) 3
39 (focal* NEAR2 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)) 1
40 ((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR3 (guid* or influenc* or direct* or align*)) 65
41 #38 OR #39 OR #40 67
42 #6 AND #29 AND #41 5
43 (('MRI stratified' or 'magnetic resonance imaging stratified') NEAR3 pathway*) 0
44 (MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB') 1
45 (fusion* NEAR3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*)) 34
46 #44 OR #45 35
47 #6 AND #46 2
48 #30 OR #37 OR #42 OR #43 OR #47 11
49 (Trinity or PROMAP or 'Fusion MR' or bkFusion or 'bk Fusion' or BK3000 or 'BK 3000' or BK5000 or 'BK 5000' or 'Predictive Fusion') 2
50 (DynaCAD or ARTEMIS or ProFuse or 'Mona Lisa') 8
51 #49 OR #50 10
52 #6 AND #51 0
53 (KOELIS or 'Fusion Bx' or BioJet or BiopSee or UroNav or 'iSR'obot' or iSRobot or 'iSR obot' or UroFusion or UroBiopsy or FusionVu* or ExactVu*) 0
54 #48 OR #52 OR #53 11

Key

MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
NEAR3 = terms within three words of each other (order specified)

EconLit

Via Ovid http://ovidsp.ovid.com/

Date range: 1886 to 5 May, 2022

Date searched: 16 May 2022

Records retrieved: 0

1 ((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$)).mp. (114)
2 (PCa or sPCa or csPCa or PrCa).mp. (541)
3 (((atypical adj3 proliferation) or ASAP) and prostat$).mp. (0)
4 or/1-3 (651)
5 (magnetic resonance or MRI or MR imag$ or MR scan$).mp. (188)
6 (mpMRI or mp-MRI or mpMR imag$ 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$).mp. (0)
7 5 or 6 (188)

8 (fusion$ or fuse$ or fusing$).mp. (643)
9 cognitive$.mp. (17030)
10 (visual$ adj3 (estimat$ or direct$ or align$ or guid$ or influenc$)).mp. (75)
11 registration$.mp. (1925)
12 (elastic or rigid or nonrigid).mp. (4352)
13 (software or hardware).mp. (15832)
14 or/8-13 (39541)
15 (prostate$ or prostatic).mp. (141)
16 (biopsy or biopsie$ or rebiopsy or rebiopsie$).mp. (17)
17 15 and 16 (4)
18 4 and 7 and 14 and 17 (0)
19 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (biopsy or biopsie$)).mp. (0)
20 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops$).mp. (0)
21 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (ultrasound$ or ultrasonic$ or ultrasonograph$ or TRUS or transperineal$ or transrectal$)).mp. (0)
22 (target$ adj4 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).mp. (0)
23 (focal adj2 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).mp. (0)
24 (target$ adj4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).mp. (2)
25 4 and 24 (0)
26 (focal adj2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).mp. (0)
27 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj3 (guid$ or influenc$ or direct$ or align$)).mp. (9)
28 4 and 27 (0)
29 ((MRI stratified or magnetic resonance imaging stratified) adj3 pathway$).mp. (0)
30 (MRGB or MR-GB or MRIGB or MRI-GB).mp. (0)
31 (MRIFB or MRI-FB).mp. (0)
32 (MRFTB or MRF-TB).mp. (0)
33 (MRFTB or MRF-TB).mp. (0)
34 (MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx).mp. (0)
35 FBx.mp. (0)
36 (FUSTB or FUS-TB or TB-FUS).mp. (0)
37 Fusion TB.mp. (0)
38 (MRI-TRUS or MRI-TRUSB or MRI-TPB).mp. (0)
39 (COG-TB or TB-COG or CBx).mp. (1)
40 4 and 39 (0)
41 TRUS-TB.mp. (0)
42 ('MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB').mp. (0)
43 (fusion$ adj3 (software or hardware or computer$ or device$ or system$ or technolog$ or machine$ or platform$)).mp. (26)
44 4 and 43 (0)
45 (KOELIS or Fusion Bx).mp. (0)
46 (BioJet or Trinity or PROMAP or Fusion MR or bkFusion or bk Fusion or BK3000 or BK 3000 or BK5000 or BK 5000 or Predictive Fusion).mp. (356)
47 4 and 46 (0)
48 (BiopSee or UroNav or 'iSR'obot' or iSRobot or iSR obot or UroFusion or UroBiopsy or FusionVu$ or ExactVu$).mp. (0)
49 (DynaCAD or ARTEMIS or ProFuse or Mona Lisa).mp. (24)
50 4 and 49 (0)
51 18 or 19 or 20 or 21 or 22 or 23 or 25 or 26 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 40 or 41 or 42 or 44 or 45 or 47 or 48 or 50 (0)

Key

$ = truncation
mp = multi-purpose field search – terms in title, original title, abstract, name of substance word, or subject heading word
adj3 = terms within three words of each other (any order)

EMBASE

Via Ovid http://onlinelibrary.wiley.com/

Date range: 1974 to 13 May 2022

Date searched: 16 May 2022

Records retrieved: 6221

Embase was searched again on 2 August 2022. After conference abstracts were removed, 3318 studies were retrieved.

1 exp prostate tumor/ (271321)
2 ((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$)).ti,ab. (244110)
3 (PCa or sPCa or csPCa or PrCa).ti,ab. (77312)
4 (((atypical adj3 proliferation) or ASAP) and prostat$).mp. (644)
5 or/1-4 (351675)
6 nuclear magnetic resonance imaging/ (903701)
7 multiparametric magnetic resonance imaging/ (6477)
8 (magnetic resonance or MRI or MR imag$ or MR scan$).ti,ab. (819806)
9 (mpMRI or mp-MRI or mpMR imag$ 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$).ti,ab. (4373)
10 or/6-9 (1163227)
11 computer assisted diagnosis/ (41296)
12 (fusion$ or fuse$ or fusing$).ti,ab. (361890)
13 cognitive$.ti,ab. (585952)
14 (visual$ adj3 (estimat$ or direct$ or align$ or guid$ or influenc$)).ti,ab. (35918)
15 registration$.ti,ab. (163670)
16 (elastic or rigid or nonrigid).ti,ab. (152621)
17 software/ or imaging software/ or nuclear magnetic resonance scanner software/ or ultrasound imaging system software/ (139562)
18 (software or hardware).ti,ab. (363110)
19 or/11-18 (1695591)
20 exp prostate/ (54557)
21 (prostate$ or prostatic).ti,ab. (336120)
22 20 or 21 (339264)
23 biopsy/ (174400)
24 image guided biopsy/ (6935)
25 endoscopic ultrasound guided fine needle biopsy/ (5968)
26 exp needle biopsy/ (79356)
27 biopsy technique/ (7739)
28 tumor biopsy/ (43525)

29 (biopsy or biopsie$ or rebiopsy or rebiopsie$).ti,ab. (685526)
30 or/23-29 (782015)
31 22 and 30 (43352)
32 prostate biopsy/ or exp transperineal biopsy/ or exp transrectal biopsy/ (24654)
33 31 or 32 (48987)
34 5 and 10 and 19 and 33 (3137)
35 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (biopsy or biopsie$)).ti,ab. (1707)
36 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops$).ti,ab. (248)
37 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (ultrasound$ or ultrasonic$ or ultrasonograph$ or TRUS or transperineal$ or transrectal$)).ti,ab. (1370)
38 or/35-37 (2954)
39 5 and 38 (1359)
40 (target$ adj4 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (7633)
41 (focal adj2 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).ti,ab. (1195)
42 40 or 41 (8750)
43 5 and 40 (3525)
44 (target$ adj4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).ti,ab. (6907)
45 (focal adj2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).ti,ab. (959)
46 44 or 45 (7838)
47 5 and 31 and 46 (2297)
48 mri guided biopsy/ (246)
49 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj3 (guid$ or influenc$ or direct$ or align$)).ti,ab. (18601)
50 48 or 49 (18743)
51 5 and 31 and 50 (1937)
52 ((MRI stratified or magnetic resonance imaging stratified) adj3 pathway$).ti,ab. (3)
53 magnetic resonance imaging ultrasound fusion biopsy/ (128)
54 image guided noninferiority targeted biopsy/ (1)
55 cognitive biopsy/ (4)
56 software based targeted biopsy/ (1)
57 visually directed targeted biopsy/ (1)
58 ultrasound fusion targeted biopsy/ (3)
59 or/52-58 (140)
60 34 or 39 or 43 or 47 or 51 or 59 (6166)
61 (MRGB or MR-GB or MRIGB or MRI-GB).ti,ab. (132)
62 (MRIFB or MRI-FB).ti,ab. (8)
63 (MRFTB or MRF-TB).ti,ab. (36)
64 (MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx).ti,ab. (168)
65 FBx.ti,ab. (226)
66 (FUSTB or FUS-TB or TB-FUS).ti,ab. (11)
67 Fusion TB.ti,ab. (29)
68 (MRI-TRUS or MRI-TRUSB or MRI-TPB).ti,ab. (485)
69 (COG-TB or TB-COG or CBx).ti,ab. (829)
70 TRUS-TB.ti,ab. (8)
71 ('MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB').ti,ab. (777)
72 or/61-71 (2124)
73 5 and 72 (1009)
74 60 or 73 (6215)

75 (fusion$ adj3 (software or hardware or computer$ or device$ or system$ or technolog$ or machine$ or platform$)).ti,ab. (7446)
76 5 and 75 (707)
77 magnetic resonance imaging-ultrasound fusion-guided prostate biopsy device/ (245)
78 74 or 76 or 77 (6346)
79 KOELIS.ti,ab,dv. (180)
80 Fusion Bx.ti,ab,dv. (16)
81 BioJet.ti,ab,dv. (105)
82 (Trinity or PROMAP).ti,ab,dv. (2121)
83 Fusion MR.ti,ab,dv. (13)
84 (bkFusion or bk Fusion or BK3000 or BK 3000 or BK5000 or BK 5000 or Predictive Fusion).ti,ab,dv. (60)
85 or/81-84 (2295)
86 5 and 85 (148)
87 79 or 80 or 86 (307)
88 BiopSee .ti,ab,dv. (52)
89 UroNav.ti,ab,dv. (163)
90 ('iSR'obot' or iSRobot or iSR obot or UroFusion or UroBiopsy).ti,ab,dv. (31)
91 (FusionVu$ or ExactVu$).ti,ab,dv. (84)
92 DynaCAD.ti,ab,dv. (73)
93 (ARTEMIS or ProFuse).ti,ab,dv. (6586)
94 Mona Lisa.ti,ab,dv. (162)
95 or/92-94 (6817)
96 5 and 95 (247)
97 88 or 89 or 90 or 91 or 96 (506)
98 78 or 87 or 97 (6483)
99 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6457016)
100 98 not 99 (6455)
101 limit 100 to yr='2008 -Current' (6221)

Key

/ = subject heading (Emtree heading)
exp = exploded subject heading (Emtree heading)
$ = truncation
ti,ab = terms in title or abstract fields
mp = multi-purpose field search – terms in title, original title, abstract, name of substance word, or subject heading word
dv = terms in the device trade name field
adj3 = terms within three words of each other (any order)

Health Management and Information Consortium (HMIC)

Via Ovid http://onlinelibrary.wiley.com/

Date range: 1979 to March 2022

Date searched: 16 May 2022

Records retrieved: 0

1 ((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$)).mp. (736)
2 (PCa or sPCa or csPCa or PrCa).mp. (74)
3 (((atypical adj3 proliferation) or ASAP) and prostat$).mp. (0)
4 or/1-3 (792)
5 (magnetic resonance or MRI or MR imag$ or MR scan$).mp. (483)
6 (mpMRI or mp-MRI or mpMR imag$ 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$).mp. (0)
7 5 or 6 (483)
8 (fusion$ or fuse$ or fusing$).mp. (94)
9 cognitive$.mp. (2602)
10 (visual$ adj3 (estimat$ or direct$ or align$ or guid$ or influenc$)).mp. (23)
11 registration$.mp. (4038)
12 (elastic or rigid or nonrigid).mp. (258)
13 (software or hardware).mp. (1828)
14 or/8-13 (8757)
15 (prostate$ or prostatic).mp. (914)
16 (biopsy or biopsie$ or rebiopsy or rebiopsie$).mp. (303)
17 15 and 16 (36)
18 4 and 7 and 14 and 17 (0)
19 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (biopsy or biopsie$)).mp. (0)
20 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops$).mp. (0)
21 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 (prior or previous$ or preced$ or before$ or earlier or first or initial$) adj6 (ultrasound$ or ultrasonic$ or ultrasonograph$ or TRUS or transperineal$ or transrectal$)).mp. (0)
22 (target$ adj4 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).mp. (0)
23 (focal adj2 (biopsy or biopsie$ or rebiopsy or rebiopsie$)).mp. (0)
24 (target$ adj4 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).mp. (1)
25 4 and 24 (0)
26 (focal adj2 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI)).mp. (0)
27 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj3 (guid$ or influenc$ or direct$ or align$)).mp. (22)
28 4 and 27 (0)
29 ((MRI stratified or magnetic resonance imaging stratified) adj3 pathway$).mp. (0)
30 (MRGB or MR-GB or MRIGB or MRI-GB).mp. (0)
31 (MRIFB or MRI-FB).mp. (0)
32 (MRFTB or MRF-TB).mp. (0)
33 (MRFTB or MRF-TB).mp. (0)
34 (MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx).mp. (0)
35 FBx.mp. (0)
36 (FUSTB or FUS-TB or TB-FUS).mp. (0)
37 Fusion TB.mp. (0)
38 (MRI-TRUS or MRI-TRUSB or MRI-TPB).mp. (0)
39 (COG-TB or TB-COG or CBx).mp. (0)
40 TRUS-TB.mp. (0)
41 ('MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB').mp. (0)
42 (fusion$ adj3 (software or hardware or computer$ or device$ or system$ or technolog$ or machine$ or platform$)).mp. (1)
43 4 and 42 (0)
44 (KOELIS or Fusion Bx or BioJet).mp. (0)

45 (Trinity or PROMAP or Fusion MR or bkFusion or bk Fusion or BK3000 or BK 3000 or BK5000 or BK 5000 or Predictive Fusion).mp. (12)
46 4 and 45 (0)
47 (BiopSee or UroNav or 'iSR'obot' or iSRobot or iSR obot or UroFusion or UroBiopsy or FusionVu$ or ExactVu$).mp. (0)
48 (DynaCAD or ARTEMIS or ProFuse or Mona Lisa).mp. (12)
49 4 and 48 (0)
50 18 or 19 or 20 or 21 or 22 or 23 or 25 or 26 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 43 or 44 or 46 or 47 or 49 (0)

Key

$ = truncation
mp = multi-purpose field search – terms in title, original title, abstract, name of substance word, or subject heading word
adj3 = terms within three words of each other (any order)

Health Technology Assessment (HTA) database

Via www.crd.york.ac.uk/CRDWeb/

Date range: Inception – 31 March 2018

Date searched: 16 May 2022

Records retrieved: 2

See under DARE for search strategy used.

International Health Technology Assessment (INAHTA) database

Via http://onlinelibrary.wiley.com/

Date searched: 16 May 2022

Records retrieved: 38

1. ((((biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[Title] OR (biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[abs] OR (biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[Keywords]) OR ('Biopsy, Needle'[mh]) OR ('Biopsy, Large-Core Needle'[mh]) OR ('Biopsy, Fine-Needle'[mh]) OR ('Endoscopic Ultrasound-Guided Fine Needle Aspiration'[mh]) OR ('Image-Guided Biopsy'[mh]) OR ('Biopsy'[mh])) AND (((prostate* OR prostatic)[Title] OR (prostate* OR prostatic)[abs] OR (prostate* OR prostatic)[Keywords]) OR ('Prostate'[mh]))) AND (((software OR hardware)[Title] OR (software OR hardware)[abs] OR (software OR hardware)[Keywords]) OR ('Software'[mh]) OR ((visual* AND (estimat* OR direct* OR align* OR guid* OR influenc*))[Title] OR (visual* AND (estimat* OR direct* OR align* OR guid* OR influenc*))[abs] OR (visual* AND (estimat* OR direct* OR align* OR guid* OR influenc*))[Keywords]) OR ((fusion* OR fuse* OR fusing* OR cognitive OR registration* OR elastic OR rigid OR nonrigid)[Title] OR (fusion* OR fuse* OR fusing* OR cognitive OR registration* OR elastic OR rigid OR nonrigid)[abs] OR (fusion* OR fuse* OR fusing* OR cognitive OR registration* OR elastic OR rigid OR nonrigid)[Keywords]) OR ('*1mage 1nterpretation*, Computer-Assisted'[mh])) AND (((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*)[Title] OR (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*)[abs] OR (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*)[Keywords]) OR (('magnetic resonance' OR MRI OR MR imag* OR MR scan*)[Title] OR ('magnetic resonance' OR MRI OR MR imag* OR MR scan*)[abs] OR ('magnetic resonance' OR MRI OR MR imag* OR MR scan*)[Keywords]) OR ('Multiparametric Magnetic Resonance Imaging'[mh]) OR ('Magnetic Resonance Imaging'[mh])) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe])) 4 hits

2. ((((target* OR focal) AND (biopsy OR biopsie* OR rebiopsy OR rebiopsie*))[Title] OR ((target* OR focal) AND (biopsy OR biopsie* OR rebiopsy OR rebiopsie*))[abs] OR ((target* OR focal) AND (biopsy OR biopsie* OR rebiopsy OR rebiopsie*))[Keywords]) OR (((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (ultrasound* OR ultrasonic* OR ultrasonograph* OR TRUS OR transperineal* OR transrectal*))[Title] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (ultrasound* OR ultrasonic* OR ultrasonograph* OR TRUS OR transperineal* OR transrectal*))[abs] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (ultrasound* OR ultrasonic* OR ultrasonograph* OR TRUS OR transperineal* OR transrectal*))[Keywords]) OR ((((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND prebiops*)[Title] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND prebiops*)[abs] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND prebiops*)[Keywords])) OR (((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND biops*)[Title] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND biops*)[abs] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND biops*)[Keywords])) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe])) 9 hits
3. ((((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (guid* OR influenc* OR direct* OR align*))[Title] OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (guid* OR influenc* OR direct* OR align*))[abs]

OR ((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (guid* OR influenc* OR direct* OR align*))[Keywords]) OR (((target* OR focal) AND (MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI))[Title] OR ((target* OR focal) AND (MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI))[abs] OR ((target* OR focal) AND (MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI))[Keywords])) AND ((((biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[Title] OR (biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[abs] OR (biopsy OR biopsie* OR rebiopsy OR rebiopsie*)[Keywords]) OR ('Biopsy, Needle'[mh]) OR ('Biopsy, Large-Core Needle'[mh]) OR ('Biopsy, Fine-Needle'[mh]) OR ('Endoscopic Ultrasound-Guided Fine Needle Aspiration'[mh]) OR ('Image-Guided Biopsy'[mh]) OR ('Biopsy'[mh])) AND (((prostate* OR prostatic)[Title] OR (prostate* OR prostatic)[abs] OR (prostate* OR prostatic)[Keywords]) OR ('Prostate'[mh]))) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe])) 5 hits

4. ((MRGB OR MR-GB OR MRIGB OR MRI-GB OR MRIFB OR MRI-FB OR MRFTB OR MRF-TB OR MRFTB OR MRF-TB OR MRTB OR MR-TB OR MRITB OR MRI-TB OR MRTBx OR MR-TBx OR MRITBx OR MRI-TBx OR FBx OR FUSTB OR FUS-TB OR TB-FUS OR 'Fusion TB' OR MRI-TRUS OR MRI-TRUSB OR MRI-TPB OR COG-TB OR TB-COG OR CBx OR TRUS-TB OR 'MRI/TRUS' OR 'mpMRI/TRUS' OR 'MR/US' OR 'MRI/TRUS-TB')[Title] OR (MRGB OR MR-GB OR MRIGB OR MRI-GB OR MRIFB OR MRI-FB OR MRFTB OR MRF-TB OR MRFTB OR MRF-TB OR MRTB OR MR-TB OR MRITB OR MRI-TB OR MRTBx OR MR-TBx OR MRITBx OR MRI-TBx OR FBx OR FUSTB OR FUS-TB OR TB-FUS OR 'Fusion TB' OR MRI-TRUS OR MRI-TRUSB OR MRI-TPB OR COG-TB OR TB-COG OR CBx OR TRUS-TB OR 'MRI/TRUS' OR 'mpMRI/TRUS' OR 'MR/US' OR 'MRI/TRUS-TB')[abs] OR (MRGB OR MR-GB OR MRIGB OR MRI-GB OR MRIFB OR MRI-FB OR MRFTB OR MRF-TB OR MRFTB OR MRF-TB OR MRTB OR MR-TB OR MRITB OR MRI-TB OR MRTBx OR MR-TBx OR MRITBx OR MRI-TBx OR FBx OR FUSTB OR FUS-TB OR TB-FUS OR 'Fusion TB' OR MRI-TRUS OR MRI-TRUSB OR MRI-TPB OR COG-TB OR TB-COG OR CBx OR TRUS-TB OR 'MRI/TRUS' OR 'mpMRI/TRUS' OR 'MR/US' OR 'MRI/TRUS-TB')[Keywords]) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe])) 14 hits
5. ((Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa')[Title] OR (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR

ProFuse OR 'Mona Lisa')[abs] OR (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa')[Keywords]) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe]))

6. ((fusion* AND (software OR hardware OR computer* OR device* OR system* OR technolog* OR machine* OR platform*))[Title] OR (fusion* AND (software OR hardware OR computer* OR device* OR system* OR technolog* OR machine* OR platform*))[abs] OR (fusion* AND (software OR hardware OR computer* OR device* OR system* OR technolog* OR machine* OR platform*))[Keywords]) AND (((ASAP AND prostat*)[Title] OR (ASAP AND prostat*)[abs] OR (ASAP AND prostat*)[Keywords]) OR ((atypical AND proliferation AND prostat*)[Title] OR (atypical AND proliferation AND prostat*)[abs] OR (atypical AND proliferation AND prostat*)[Keywords]) OR ((PCa OR sPCa OR csPCa OR PrCa)[Title] OR (PCa OR sPCa OR csPCa OR PrCa)[abs] OR (PCa OR sPCa OR csPCa OR PrCa)[Keywords]) OR (((cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Title] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[abs] OR (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)[Keywords]) AND (((prostate* OR prostatic OR intraprostatic))[Title] OR ((prostate* OR prostatic OR intraprostatic))[abs] OR ((prostate* OR prostatic OR intraprostatic))[Keywords])) OR ('Prostatic Intraepithelial Neoplasia'[mh]) OR ('Prostatic Neoplasms'[mhe])) 2 hits

key

[abs] = abstract
[mh] = subject heading (MeSH heading)
[mhe] = exploded subject heading (MeSH heading)
* = truncation

Latin American and Caribbean Health Sciences Literature (LILACS)

Via https://pesquisa.bvsalud.org/portal/advanced/?lang=en

Date searched: 16 May 2022

Records retrieved: 98

1. Search of title, abstract, subject heading fields: (prostat$) AND (cancer$ OR neoplas$ OR tumour$ OR tumor$ OR malignan$ OR metasta$ OR carcinoma$ OR adenocarcinoma$ OR lesion$ OR nodul$ OR sarcoma$ OR lymphoma$) AND ('magnetic resonance' OR MRI OR MR imag$ OR MR

scan$ OR 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$) AND (fusion$ OR fuse$ OR fusing$ OR cognitive$ OR visual$ OR registration$ OR elastic OR rigid OR nonrigid OR software OR hardware OR target$ OR focal OR guid$ OR influenc$ OR direct$ OR align$) AND (biopsy OR biopsie$ OR rebiopsy OR rebiopsie$ OR prebiopsy$)

Limit: 2008–2022
35 hits

2. Search of title, abstract, subject heading fields: (prostat$) AND (cancer$ OR neoplas$ OR tumour$ OR tumor$ OR malignan$ OR metasta$ OR carcinoma$ OR adenocarcinoma$ OR lesion$ OR nodul$ OR sarcoma$ OR lymphoma$) AND (MRI OR MR OR magnetic resonance OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) AND (ultrasound$ OR ultrasonic$ OR ultrasonograph$ OR TRUS OR transperineal$ OR transrectal$)

Limit: 200–2022
53 hits

3. Search of title, abstract, subject heading fields: (prostat$) AND (cancer$ OR neoplas$ OR tumour$ OR tumor$ OR malignan$ OR metasta$ OR carcinoma$ OR adenocarcinoma$ OR lesion$ OR nodul$ OR sarcoma$ OR lymphoma$) AND (MRGB OR MR-GB OR MRIGB OR MRI-GB OR MRIFB OR MRI-FB OR MRFTB OR MRF-TB OR MRFTB OR MRF-TB OR MRTB OR MR-TB OR MRITB OR MRI-TB OR MRTBx OR MR-TBx OR MRITBx OR MRI-TBx OR FBx OR FUSTB OR FUS-TB OR TB-FUS OR 'Fusion TB' OR MRI-TRUS OR MRI-TRUSB OR MRI-TPB OR COG-TB OR TB-COG OR CBx OR TRUS-TB OR 'MRI/TRUS' OR 'mpMRI/TRUS' OR 'MR/US' OR 'MRI/TRUS-TB')

Limit: 2008–2022
9 hits

4. Search of title, abstract, subject heading fields: (KOELIS OR 'Fusion Bx' OR BioJet OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu$ OR ExactVu$)

Limit: 2008–2022
0 hits

5. Search of title, abstract, subject heading fields: (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa') AND (prostat$)

Limit: 2008–2022
1 hit

NHS Economic Evaluations Database (NHS EED)

Via www.crd.york.ac.uk/CRDWeb/

Date range: Inception – 31 March 2015

Date searched: 16 May 2022

Records retrieved: 2

See under DARE for search strategy used.

Science Citation Index

Va Web of Science, Clarivate Analytics https://clarivate.com/

Date range: 1900 – present

Date searched: 16 May 2022

Records retrieved: 3616

The Science Citation Index and the Conference Proceedings Citation Index-Science were both searched using the strategy below. Numbers of records retrieved are therefore the total number from searching both databases.

The Science Citation Index only was searched again on 2 August 2022. An amount of 3561 studies were retrieved.

48 #45 OR #41 OR #37 3616
47 #45 or #41 or #37 3857
46 #45 OR #41 OR #37 3857
45 #42 OR #44 69
44 #43 AND #4 42
43 TS = (DynaCAD or ARTEMIS or ProFuse or 'Mona Lisa') 5737
42 TS = (BiopSee or UroNav or 'iSR'obot' or iSRobot or 'iSR obot' or UroFusion or UroBiopsy or FusionVu* or ExactVu*) 34
41 #40 OR #38 41
40 #39 AND #4 19
39 TS = (BioJet or Trinity or PROMAP or 'Fusion MR' or bkFusion or 'bk Fusion' or BK3000 or 'BK 3000' or BK5000 or 'BK 5000' or 'Predictive Fusion') 2748
38 TS = (KOELIS or 'Fusion Bx') 25
37 #36 OR #34 OR #32 3825
36 #35 AND #4 471
35 TS = (fusion* NEAR/3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*)) 24,330
34 #33 AND #4 451
33 TS = (MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB') 1351
32 #31 OR #30 OR #25 OR #18 3620
31 TS=(('MRI stratified' or 'magnetic resonance imaging stratified') NEAR/3 pathway*) 3
30 #29 AND #17 AND #4 2,016
29 #26 OR #27 OR #28 22800
28 TS=((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR/3 (guid* or influenc* or direct* or align*)) 17,122
27 TS = (focal NEAR/2 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)) 1243

26 TS = (target* NEAR/4 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI)) 5682
25 #24 AND #4 2567
24 #23 OR #22 OR #21 OR #20 OR #19 6484
23 TS = (focal NEAR/2 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 666
22 TS = (target* NEAR/4 (biopsy or biopsie* or rebiopsy or rebiopsie*)) 4437
21 TS=((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR/6 (prior or previous* or preced* or before* or earlier or first or initial*) NEAR/6 (ultrasound* or ultrasonic* or ultrasonograph* or TRUS or transperineal* or transrectal*)) 858
20 TS=((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR/6 prebiops*) 179
19 TS=((MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) NEAR/6 (prior or previous* or preced* or before* or earlier or first or initial*) NEAR/6 (biopsy or biopsie*)) 963
18 #17 AND #14 AND #7 AND #4 1832
17 #15 AND #16 28,427
16 TS = (biopsy or biopsie* or rebiopsy or rebiopsie*) 379,853
15 TS = (prostate* or prostatic) 336,855
14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 2,737,360
13 TS = (software or hardware) 906,626
12 TS = (elastic or rigid or nonrigid) 624,588
11 TS = (registration*) 134,030
10 TS = (visual* NEAR/3 (estimat* or direct* or align* or guid* or influenc*)) 43,631
9 TS = cognitive* 514,118
8 TS = (fusion* or fuse* or fusing*) 589,649
7 #5 OR #6 757,071
6 TS = (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*') 2175
5 TS=('magnetic resonance' or MRI or 'MR imag*' or 'MR scan*') 756,868
4 #1 OR #2 OR #3 332,891
3 TS=(((atypical NEAR/3 proliferation) or ASAP) and prostat*) 317
2 TS = (PCa or sPCa or csPCa or PrCa) 101,467
1 TS=((prostate* or prostatic or intraprostatic) NEAR/4 (cancer* or neoplas* or tumour* or tumor* or malignan* or metasta* or carcinoma* or adenocarcinoma* or lesion* or nodul* or sarcoma* or lymphoma*)) 246,739

Key

TS = topic tag; searches in title, abstract, author keywords and keywords plus fields
* = truncation
NEAR/3 = terms within three words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov
https://clinicaltrials.gov/ct2/

Date searched: 23 May 2022

Records retrieved: 572

Targeted search screen

1. 87 Studies found for: (prostate OR prostatic OR intraprostatic) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) [condition] | (biopsy OR biopsied OR rebiopsy OR rebiopsied) AND (MRI OR MR OR 'magnetic resonance' OR biparametric OR multiparametric OR bpMRI OR mpMRI OR bp-MRI OR mp-MRI)[title]
2. 238 Studies found for: (prostate OR prostatic OR intraprostatic) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) [condition] | (biopsy OR biopsied OR rebiopsy OR rebiopsied) AND (MRI OR MR OR 'magnetic resonance' OR biparametric OR multiparametric OR bpMRI OR mpMRI OR bp-MRI OR mp-MRI) [intervention]
3. 53 Studies found for: (prostate OR prostatic OR intraprostatic) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) [condition] | (biopsy OR biopsied OR rebiopsy OR rebiopsied) AND (targeted) [title]
4. 129 Studies found for: (prostate OR prostatic OR intraprostatic) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) [condition] | (biopsy OR biopsied OR rebiopsy OR rebiopsied) AND (targeted) [intervention]

Main search screen

5. 21 Studies found for: KOELIS OR 'Fusion Bx' OR BioJet OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu OR ExactVu [other terms]
6. 44 Studies found for: Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa' [other terms] | (prostate OR prostatic OR intraprostatic) [condition]

Conference proceedings citation index – Science (CPCI-Science)

Via Web of Science, Clarivate Analytics https://clarivate.com/

Date range: 1990–present (CPCI-Science)

Date searched: 16 May 2022

See above under Science Citation Index for search strategy used. The number of records retrieved from CPCI-Science is not available as both Science Citation Index and CPCI-Science were searched together retrieving 3616 records in total from both databases.

EU Clinical Trials Register

via https://www.clinicaltrialsregister.eu/ctr-search/search

Search date: 15 June 2022

Records retrieved: 86

1. 68 result(s) found for: (prostate OR prostatic OR intraprostatic) AND (biopsy OR rebiopsy OR re-biopsy) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) AND (MRI OR MR OR 'magnetic resonance' OR biparametric OR multiparametric OR bpMRI OR mpMRI OR bp-MRI OR mp-MRI) date range: 2015-01-01 to 2022-06-15

2. 18 result(s) found for: (prostate OR prostatic OR intraprostatic) AND (biopsy OR rebiopsy OR re-biopsy) AND (neoplasm OR cancer OR tumour OR tumor OR lesion OR nodule OR adenocarcinoma) AND targeted date range: 2015-01-01 to 2022-06-15
3. 0 result(s) found for: (KOELIS OR 'Fusion Bx' OR BioJet OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu OR ExactVu) date range: 2015-01-01 to 2022-06-15
4. 0 result(s) found for: (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa') AND (prostate OR prostatic OR intraprostatic) date range: 2015-01-01 to 2022-06-15

Open Access Theses and Dissertations (OATD)

Via https://oatd.org/

Date searched: 16 May 2022

Records retrieved: 74

3 search queries used:

Query 1

(Prostat* AND biops*) AND (fusion* OR cognitive* OR software) AND (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*) AND ('magnetic resonance' OR MRI OR biparametric OR multiparametric)

50 hits

Query 2

(cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*) AND (prostat*) AND (BioJet OR Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa')

23 hits

Query 3

KOELIS OR 'Fusion Bx' OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu* OR ExactVu*

1 hit

Key

* = truncation

ProQuest Dissertations and Theses A&I

Via https://www.proquest.com

Date searched: 16 May 2022

Records retrieved: 207

1. ((TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) OR TI,AB,SU,IF(((atypical NEAR/3 proliferation) OR ASAP) AND prostat*)) AND (TI,AB,SU,IF('magnetic resonance' OR MRI OR MR imag* OR MR scan*) OR TI,AB,SU,IF(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*)) AND (TI,AB,SU,IF(prostate* OR prostatic) AND TI,AB,SU,IF(biopsy OR biopsie* OR rebiopsy OR rebiopsie*)) AND (TI,AB,SU,IF(fusion* OR fuse* OR fusing* OR cognitive* OR registration* OR elastic OR rigid OR nonrigid OR software OR hardware) OR TI,AB,SU,IF(visual* NEAR/3 (estimat* OR direct* OR align* OR guid* OR influenc*))) limit: 2008-01-01 to 2022-05-16 33 Hits
2. (TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) AND TI,AB,SU,IF((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) NEAR/6 (biopsy OR biopsie* OR prebiops* OR ultrasound* OR ultrasonic* OR ultrasonograph* OR TRUS OR transperineal* OR transrectal*)) limit: 2008-01-01 to 2022-05-16 67 hits
3. (TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) AND (TI,AB,SU,IF((target* OR focal) NEAR/4 (biopsy OR biopsie* OR rebiopsy OR rebiopsie*)) OR TI,AB,SU,IF((target* OR focal) NEAR/4 (MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI))) limit: 2008-01-01 to 2022-05-16 53 hits
4. ((TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) OR TI,AB,SU,IF(((atypical NEAR/3 proliferation) OR ASAP) AND prostat*)) AND (TI,AB,SU,IF(prostate* OR prostatic) AND TI,AB,SU,IF(biopsy OR biopsie* OR rebiopsy OR rebiopsie*)) AND TI,AB,SU,IF((MRI OR MR OR 'magnetic resonance' OR mpMRI OR mp-MRI OR bpMRI OR bp-MRI) NEAR/3 (guid* OR influenc* OR direct* OR align*)) limit: 2008-01-01 to 2022-05-16 20 hits
5. ((TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) OR TI,AB,SU,IF(((atypical NEAR/3 proliferation) OR ASAP) AND prostat*)) AND TI,AB,SU,IF(MRGB OR MR-GB OR MRIGB OR MRI-GB OR MRIFB OR MRI-FB OR MRFTB OR MRF-TB OR MRFTB OR MRF-TB OR MRTB OR MR-TB OR MRITB OR MRI-TB OR MRTBx OR MR-TBx OR MRITBx OR MRI-TBx OR FBx OR FUSTB OR FUS-TB OR TB-FUS OR 'Fusion TB' OR MRI-TRUS OR MRI-TRUSB OR MRI-TPB OR COG-TB OR TB-COG OR CBx OR TRUS-TB OR 'MRI/TRUS' OR 'mpMRI/TRUS' OR 'MR/US' OR 'MRI/TRUS-TB') limit: 2008-01-01 to 2022-05-16 6 hits
6. ((TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) OR TI,AB,SU,IF(((atypical NEAR/3 proliferation) OR ASAP) AND prostat*)) AND TI,AB,SU,IF(fusion* NEAR/3 (software OR hardware OR computer* OR device* OR system* OR technolog* OR machine* OR platform*)) limit: 2008-01-01 to 2022-05-16 26 hits

7. TI,AB,SU,IF(KOELIS OR 'Fusion Bx' OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu* OR ExactVu*) 0 hits
8. ((TI,AB,SU,IF((prostate* OR prostatic OR intraprostatic) NEAR/4 (cancer* OR neoplas* OR tumour* OR tumor* OR malignan* OR metasta* OR carcinoma* OR adenocarcinoma* OR lesion* OR nodul* OR sarcoma* OR lymphoma*)) OR TI,AB,SU,IF(PCa OR sPCa OR csPCa OR PrCa)) OR TI,AB,SU,IF(((atypical NEAR/3 proliferation) OR ASAP) AND prostat*)) AND TI,AB,SU,IF(BioJet OR Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion') limit: 2008-01-01 to 2022-05-16 2 hits

Key

TI,AB,SU,IF = search of title, abstract, subject heading and keyword fields
* = truncation
NEAR/3 = terms within three words of each other (any order)

PROSPERO

Via https://www.crd.york.ac.uk/prospero/

Date searched: 23 May 2022

Records retrieved: 78

#1 MeSH DESCRIPTOR Prostatic Intraepithelial Neoplasia 0
#2 MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES 406
#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*) 1351
#4 ((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 740
#5 ((prostate* or prostatic or intraprostatic)):TI 1080
#6 PCa or sPCa or csPCa or PrCa 335
#7 #1 OR #2 OR #4 OR #6 951
#8 #1 OR #2 OR #3 OR #6 1509
#9 #5 OR #2 OR #1 1092
#10 MeSH DESCRIPTOR Magnetic Resonance Imaging 458
#11 MeSH DESCRIPTOR Multiparametric Magnetic Resonance Imaging 6
#12 'magnetic resonance' or MRI or MR imag* or MR scan* 5234
#13 ('magnetic resonance' or MRI or MR imag* or MR scan*):TI 773
#14 ((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 8
#15 (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*) 59
#16 #10 OR #11 OR #12 OR #15 5259
#17 #10 OR #11 OR #13 OR #14 887
#18 MeSH DESCRIPTOR Image Interpretation, Computer-Assisted 4
#19 MeSH DESCRIPTOR Software 31
#20 fusion* or fuse* or fusing* or cognitive or registration* or elastic or rigid or nonrigid 17958
#21 visual* adj3 (estimat* or direct* or align* or guid* or influenc*) 274
#22 software or hardware 48745

#23 #18 OR #19 OR #20 OR #21 OR #22 60890
#24 MeSH DESCRIPTOR Prostate 102
#25 prostate* or prostatic 1862
#26 (prostate* or prostatic):TI 1080
#27 #24 OR #25 1881
#28 #24 OR #26 1102
#29 (MeSH DESCRIPTOR Biopsy):TI 0
#30 (MeSH DESCRIPTOR Image-Guided Biopsy EXPLODE ALL TREES):TI 0
#31 (MeSH DESCRIPTOR Biopsy, Needle EXPLODE ALL TREES):TI 0
#32 MeSH DESCRIPTOR Biopsy, Needle EXPLODE ALL TREES 50
#33 MeSH DESCRIPTOR Biopsy, Needle EXPLODE ALL TREES 50
#34 MeSH DESCRIPTOR Biopsy 103
#35 MeSH DESCRIPTOR Image-Guided Biopsy EXPLODE ALL TREES 27
#36 biopsy or biopsie* or rebiopsy or rebiopsie* 2655
#37 (biopsy or biopsie* or rebiopsy or rebiopsie*):TI 251
#38 #32 OR #34 OR #35 OR #36 2678
#39 #32 OR #34 OR #35 OR #37 295
#40 #8 AND #16 AND #23 AND #27 AND #38 54
#41 ((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 1
#42 ((MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops*):TI 0
#43 ((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 0
#44 (target* adj4 (biopsy or biopsie* or rebiopsy or rebiopsie*)):TI 15
#45 (focal* adj2 (biopsy or biopsie* or rebiopsy or rebiopsie*)):TI 1
#46 (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*) 9
#47 (MRI or MR or magnetic resonance or mpMRI or mp-MRI or bpMRI or bp-MRI) adj6 prebiops* 0
#48 (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*) 0
#49 target* adj4 (biopsy or biopsie* or rebiopsy or rebiopsie*) 48
#50 focal* adj2 (biopsy or biopsie* or rebiopsy or rebiopsie*) 1
#51 #46 OR #47 OR #48 OR #49 OR #50 55
#52 #8 AND #51 44
#53 #52 OR #40 66
#54 target* adj4 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) 22
#55 focal* adj2 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) 2
#56 (MRI or MR or 'magnetic resonance' or mpMRI or mp-MRI or bpMRI or bp-MRI) adj3 (guid* or influenc* or direct* or align*) 139
#57 #54 OR #55 OR #56 154
#58 #8 AND #27 AND #38 AND #57 38
#59 #53 OR #58 76
#60 MRGB or MR-GB or MRIGB or MRI-GB or MRIFB or MRI-FB or MRFTB or MRF-TB or MRFTB or MRF-TB or MRTB or MR-TB or MRITB or MRI-TB or MRTBx or MR-TBx or MRITBx or MRI-TBx or FBx or FUSTB or FUS-TB or TB-FUS or 'Fusion TB' or MRI-TRUS or MRI-TRUSB or MRI-TPB or COG-TB or TB-COG or CBx or TRUS-TB or 'MRI/TRUS' or 'mpMRI/TRUS' or 'MR/US' or 'MRI/TRUS-TB' 17
#61 fusion* adj3 (software or hardware or computer* or device* or system* or technolog* or machine* or platform*) 75
#62 #60 OR #61 91
#63 #8 AND #62 16

#64 #63 OR #59 76
#65 KOELIS OR 'Fusion Bx' OR BioJet OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu* OR ExactVu* 7
#66 Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa' 489
#67 #66 AND #8 4
#68 #64 OR #65 OR #67 78

Key

MeSH DESCRIPTOR = subject heading (MeSH heading)

* = truncation

adj3 = terms within 3 words of each other (order specified)

WHO International Clinical Trials Registry Platform (ICTRP)

https://trialsearch.who.int/AdvSearch.aspx

Date searched: 23 May 2022

Records retrieved: 378

Advanced search screen. Recruitment status set to ALL

1. Title field: (biops* OR rebiops* OR re-biops*) AND (MRI OR MR OR 'magnetic resonance' OR bi-parametric OR multiparametric OR bpMRI OR mpMRI OR bp-MRI OR mp-MRI)

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
117 hits

2. Intervention field: (biops* OR rebiops* OR re-biops*) AND (MRI OR MR OR 'magnetic resonance' OR biparametric OR multiparametric OR bpMRI OR mpMRI OR bp-MRI OR mp-MRI)

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
106 hits

3. Title field: (biops* OR rebiops* OR re-biops*) AND target*

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
68 hits

4. Intervention field: (biops* OR rebiops* OR re-biops*) AND target*

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
64 hits

5. Title field: (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa')

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
4 hits

6. Intervention field: (Trinity OR PROMAP OR 'Fusion MR' OR bkFusion OR 'bk Fusion' OR BK3000 OR 'BK 3000' OR BK5000 OR 'BK 5000' OR 'Predictive Fusion' OR DynaCAD OR ARTEMIS OR ProFuse OR 'Mona Lisa')

Condition field: (prostate* OR prostatic OR intraprostatic) AND (neoplas* OR cancer* OR tumour* OR tumor* OR lesion* OR nodul* OR adenocarcinoma*)
3 hits

Basic search screen

7. KOELIS OR 'Fusion Bx' OR BioJet OR BiopSee OR UroNav OR 'iSR'obot' OR iSRobot OR 'iSR obot' OR UroFusion OR UroBiopsy OR FusionVu* OR ExactVu*

16 hits

Key

* = truncation

Guideline website searches

Simple searches were carried out on the guideline websites listed below and any results were browsed for relevance. Relevant guidelines identified were checked against the endNote library of results and added to the library if they had not already been found through previous searches.

ECRI guidelines trust

https://guidelines.ecri.org/

Date searched: 23 May 2022

1. prostate or prostatic – 39 results browsed – 9 relevant

GIN international guideline library

https://guidelines.ebmportal.com/

Date searched: 23 May 2022

1. prostate cancer – 36 results browsed – 8 relevant

National Institute of Health and Care Excellence (NICE)

https://www.nice.org.uk/

Date searched: 23 May 2022

1. Browsed 43 items on the prostate cancer guidance page https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer

- 4 relevant

Trip database

https://www.tripdatabase.com/

Date searched: 23 May 2022

Two further guidelines found through searching the Trip database.

1. Prostate cancer AND MRI OR 'magnetic resonance' OR biparametric OR multiparametric – 5 guideline results – browsed for relevance – 4 relevant – all in EndNote library already.
2. Prostate cancer AND fusion OR cognitive OR software – 0 guideline results
3. Prostate cancer AND imag* – 6 guideline results – browsed for relevance – 3 relevant – all in EndNote library already.
4. Prostate cancer AND diagnos* – 10 guideline results – browsed for relevance – 8 relevant – 6 in EndNote library already.

Appendix 3 Multinomial network meta-analysis model

A multinomial logistic regression model was used where the odds of being categorised in each of the different categories in *Table 2* compared to the reference category (no PCa) are allowed to vary by biopsy type.[74,75,156,157] This model is conceptually equivalent to R-1 binomial logistic regressions comparing category $r > 1$ with category 1 (no PCa), for each different biopsy type compared to the reference, cognitive biopsy.

Define

i – study index
k – study arm index
r – category index
R – number of categories

Data from the N studies are modelled with a multinomial likelihood with probability vector $qikr$

$$y_{ik,1:R} \sim \text{Multinomial}\left(q_{ik,1:R}, M_{ik}\right)$$

$yik,_1:R$ – vector of observed events in arm k of study i
Mik – number of patients in arm k of study i

Category probabilities for arm k of study i are defined as

$$q_{ik,r} = \frac{\phi_{ikr}}{\sum_{s=1}^{R} \phi_{iks}}$$

Log-odds ratio for category r relative to category 1, for arm k in study i:

$$\eta_{ikr} = \log\left(\frac{q_{ikr}}{q_{ik1}}\right) = a_{ir} + \delta_{ikr} \tag{1}$$

with air representing the baseline log-odds for being classified in category r, instead of category 1, in study i and $\delta_{ikr} = d_{t_{i1}t_{ik},r} = d_{1t_{ik},r} - d_{1t_{i1},r}$ representing the additional effect for being classified in category r, instead of category 1, using the intervention in arm k, compared to the intervention in arm 1.

We set

$d_{1r} = 0$, for all r
$d_{k1} = 0$, for all k
$a_{i1} = 0$, for all i

Note that

$$q_{ik1} = \frac{\phi_{ik1}}{\sum_{s=1}^{R} \phi_{iks}} = \frac{1}{\sum_{s=1}^{R} \phi_{iks}}$$

Hence

$$\begin{aligned}\phi_{ikr} &= q_{ikr} \times \textstyle\sum_{s=1}^{R} \phi_{iks} \\ &= q_{ikr} \times \frac{1}{q_{ik1}} = \frac{q_{ikr}}{q_{ik1}} \\ &= \exp(\eta_{ikr}) = \exp(a_{ir} + \delta_{ikr})\end{aligned}$$

We model ϕ_{ikr}, the odds ratio for category *r* relative to category 1, for arm *k* in study *i* as

$$\log(\phi_{ikr}) = a_{ir} + \delta_{ikr} \tag{2}$$

Calculating absolute probabilities

To calculate the absolute probabilities of being classified in category *r* using **intervention** *k*, *Tkr* we note:

$$\begin{aligned}T_{kr} &= \frac{\phi_{kr}}{\sum_{s=1}^{R} \phi_{ks}} \\ T_{k1} &= \frac{1}{\sum_{s=1}^{R} \phi_{ks}}\end{aligned} \tag{3}$$

Using equation (2), and defining *Ar* as the log-odds of being classified in category *r* using the reference intervention, we have

$$\begin{aligned}&\log(\phi_{k1}) = A_1 + d_{k1} = 0 \\ &\phi_{k1} = 1\end{aligned} \tag{4}$$

and using equation (1) we have

$$\begin{aligned}&\log\left(\frac{T_{kr}}{T_{k1}}\right) = A_r + d_{kr} \\ &\log(T_{kr}) = \log(T_{k1}) + A_r + d_{kr} \\ &T_{kr} = \exp(\log(T_{k1}) + A_r + d_{kr})\end{aligned}$$

External data inform Tk_1 which are used to calculate *Ar* and calculate all the other probabilities

Using equations (3) and (4), we have

$$\log(\phi_{kr}) = A_r + d_{kr}$$

$$T_{k1} = \frac{1}{1 + \phi_{k2} + \ldots + \phi_{kR}}$$

TABLE 24 Data for multinomial synthesis model

Study	Biopsy type			Number of patients			Category 1, No cancer			Category 2, ISUP grade 1			Category 3, ISUP grade 2			Category 4, ISUP grade 3			Category 5, ISUP grades 4–5		
	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
PAIREDCAP (2019)[88]	CF	SB	ARTEMIS	248	248	248	94	52	71	38	46	43	52	87	70	39	37	40	25	26	24
Izadpanahi (2021)[82]	CF + SB	ARTEMIS + SB	NA	100	99	NA	69	55	NA	19	25	NA	6	13	NA	5	3	NA	1	3	NA
Wajswol (2020)[87]	SB	UroNav	UroNav + SB	169	169	169	53	49	36	116	120	133	NA	NA	NA	NA	NA	NA	NA	NA	NA
Thangarasu (2021)[79]	CF	SB	CF + SB	75	75	75	41	35	32	34	40	43	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kulis (2020)[86]	CF	SB	CF + SB	63	63	63	30	33	25	33	30	38	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cornud (2018)[93]	CF	Urostation	NA	88	88	NA	57	48	NA	31	40	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
FUTURE (2019)[31]	CF	BiopSee	NA	78	79	NA	44	40	NA	8	12	NA	26	27	NA	NA	NA	NA	NA	NA	NA
PROFUS (2014)[97]	CF	ARTEMIS	NA	125	125	NA	85	80	NA	16	16	NA	24	29	NA	NA	NA	NA	NA	NA	NA
Albisinni (2018)[94]	SB	Urostation	Urostation + SB	74	74	74	41	39	32	12	10	13	21	25	29	NA	NA	NA	NA	NA	NA
Fourcade (2018)[92]	SB	Urostation	Urostation + SB	191	191	191	103	106	85	36	25	34	52	60	72	NA	NA	NA	NA	NA	NA
Gomez-Ortiz (2022)[99]	CF	SB	CF + SB	111	111	111	69	81	65	19	9	20	23	21	26	NA	NA	NA	NA	NA	NA
Rabah (2021)[84]	ARTEMIS	BioJet	NA	165	142	NA	117	78	NA	27	18	NA	21	46	NA	NA	NA	NA	NA	NA	NA
Alberts (2018)[80]	SB	Urostation	Urostation + SB	48	48	48	23	20	16	11	11	13	10	13	13	4	4	6	NA	NA	NA
Filson (2016)[96]	SB	ARTEMIS	ARTEMIS + SB	538	538	538	294	310	252	114	68	100	74	81	92	56	79	94	NA	NA	NA

NA, not available/not applicable; SB, systematic biopsy.
a Study only included in analyses with individual device effects as it compares two SF devices.

Note
Studies are ordered by reported ISUP grade breakdown. Studies not reporting all ISUP breakdown, report data on the total number of patients classified at that ISUP grade or higher.

WinBUGS code for multinomial model

Code

```
model{
for (i in 1:ns){ # studies reporting all categories 1,2,3,4,5
  for (k in 1:na[i]) {
    y[i,k,1:nc] ~ dmulti(q[i,k,1:nc], M[i,k])
    for (r in 1:nc) {
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
      # predicted number events
      yhat[i,k,r] <-  q[i,k,r] * M[i,k]
      # Deviance contribution
      dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
    dev[i,k] <- sum(dv[i,k,]) # deviance contribution of each arm
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:nc) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
#relative effects of treatment 1 compared to itself are zero, for all categories
for (r in 2:nc) {d[1,r] <- 0}
for (k in 1:nt){
  # giving phi[i,k,1] = 1, logOR of  going from cat 1 to cat 1 for all treats
  d[k,1] <- 0
  for (r in 2:nc) {
    # vague priors for relative treatment effects: log-odds ratios
    d[k,r] ~ dnorm(0, 0.0001)
   }
 }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE A
for (i in (ns+1):(ns+nsA)){ # studies reporting categories 1,2-5
  for (k in 1:na[i]) {
    y[i,k,1] ~ dbin(q[i,k,1], M[i,k])
    # first category the same
    q[i,k,1] <- phi[i,k,1]/sum(phi[i,k,1:ncA])
    log(phi[i,k,1]) <- a[i,1] + d[t[i,k],1] - d[t[i,1],1]
     yhat[i,k,1] <-  q[i,k,1] * M[i,k]
     # Deviance contribution
     dev[i,k] <- 2 * (y[i,k,1] * (log(y[i,k,1])-log(yhat[i,k,1])) +  (M[i,k]-
y[i,k,1]) * (log(M[i,k]-y[i,k,1]) - log(M[i,k]-yhat[i,k,1])))
# last category is collapsed, type A
    q[i,k,2] <- 1- q[i,k,1]
    log(phi[i,k,2]) <- a[i,2] + dA[t[i,k],2] - dA[t[i,1],2]
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  a[i,2] ~ dnorm(0, 0.0001)
  a[i,1] <- 0
 # summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na[i]])
 }
dA[1,2] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dA[k,2] ~ dnorm(0, 0.0001)
   }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE B
for (i in (ns+nsA+1):(ns+nsA+nsB)){ # studies reporting categories 1,2,3-5
  for (k in 1:na[i]) {
    y[i,k,1:ncB] ~ dmulti(q[i,k,1:ncB], M[i,k])
```

```
    for (r in 1:(ncB-1)) {  # first 2 categories the same
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,1:ncB])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
      # predicted number events
      yhat[i,k,r] <-  q[i,k,r] * M[i,k]
      # Deviance contribution
      dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
# last category is collapsed, type B
    q[i,k,3] <- 1- sum(q[i,k,1:(ncB-1)])
    log(phi[i,k,3]) <- a[i,3] + dB[t[i,k],3] - dB[t[i,1],3]
   # predicted number events
   yhat[i,k,3] <-  q[i,k,3] * M[i,k]
   # Deviance contribution
    dv[i,k,3] <- 2*y[i,k,3]*(log(y[i,k,3]/yhat[i,k,3]))
    dev[i,k] <- sum(dv[i,k,1:ncB]) # deviance contribution of each arm
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:ncB) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
dB[1,ncB] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dB[k,ncB] ~ dnorm(0, 0.0001)
   }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE C
for (i in (ns+nsA+nsB+1):(ns+nsA+nsB+nsC)){ # studies reporting categories 1,2,3,4-
5
  for (k in 1:na[i]) {
    y[i,k,1:ncC] ~ dmulti(q[i,k,1:ncC], M[i,k])
    for (r in 1:(ncC-1)) {  # first 3 categories the same
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,1:ncC])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
      # predicted number events
      yhat[i,k,r] <-  q[i,k,r] * M[i,k]
      # Deviance contribution
      dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
# last category is collapsed, type C
    q[i,k,4] <- 1- sum(q[i,k,1:(ncC-1)])
    log(phi[i,k,4]) <- a[i,4] + dC[t[i,k],4] - dC[t[i,1],4]
   # predicted number events
   yhat[i,k,4] <-  q[i,k,4] * M[i,k]
   # Deviance contribution
   dv[i,k,4] <- 2*y[i,k,4]*(log(y[i,k,4]/yhat[i,k,4]))
   dev[i,k] <- sum(dv[i,k,1:ncC]) # deviance contribution of each arm
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:ncC) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
  # summed residual deviance contribution for this trial
  resdev[i] <- sum(dev[i,1:na[i]])
 }
dC[1,ncC] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dC[k,ncC] ~ dnorm(0, 0.0001)
   }
totresdev <- sum(resdev[])        # Total Residual Deviance
# pairwise ORs and LORs for all possible pair-wise comparisons
```

```
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  {
      for (r in 1:nc) {
        or[c,k,r] <- exp(d[k,r] - d[c,r])
        lor[c,k,r] <- (d[k,r]-d[c,r])
         }
     }
 }
# calculate absolute probabilities from relative effects (no uncertainty in
baseline)
# baseline intervention = 3 (software) or 5 (software + SB)
for (r in 1:nc){
  T[3,r] <- b1[r]  # baseline probabilities for software biopsy (from data)
  T[5,r] <- b2[r]  # baseline probabilities for software + SB (from data)
  # log-odds of being classified in category r using intervention 3=software
  A.T[r] <- log(T[3,r]/T[3,1])
  # log-odds of being classified in category r using intervention 5=software +SB
  B.T[r] <- log(T[5,r]/T[5,1])
 }
for (k in 1:2){                    # fully connected only T[2,] to T[3,]
  for (r in 1:nc){
    phi.T[k,r]  <- exp(A.T[r] - lor[k,3,r])
    T[k,r] <- phi.T[k,r]/(sum(phi.T[k,]))
   }
 }
for (r in 1:nc){
  phi.T[4,r]  <- exp(B.T[r] - lor[4,5,r])
  T[4,r] <- phi.T[4,r]/(sum(phi.T[4,]))
 }
}
```

Data

```
# ns = number of studies
# nt = number of treatments
# nc = number of categories
# nsX = number of studies of type X
# ncX = number of categories in studies type X

# T1=cog
# T2=SB
# T3=fus
# T4=cog+SB
# T5=fus+SB

list(ns=2, nt=5, nc=5, nsA=4, ncA=2, nsB=5, ncB=3, nsC=2, ncC=4,
#b1=c(0.379032,0.153226,0.209677,0.157258,0.100806),  # PAIREDCAP baseline probs - cognitive
#b1=c(0.286290,0.173387,0.282258,0.161290,0.096774),  # PAIREDCAP baseline probs - software (Artemis)
#b1=c(0.468864,0.164835,0.197802,0.105311,0.063187),  # Filson (naive only) baseline probs - software
(Artemis)
b1=c(0.686792,0.086792,0.101887,0.077830,0.046698),  # Filson (prior neg) baseline probs - software
(Artemis)
#b2=c(0.355311,0.219780,0.223443,0.118321,0.083144)  # Filson (naive only) baseline probs - software + SB
(Artemis) [split by SB proportion in PAIREDCAP]
b2=c(0.584906,0.150943,0.116981,0.086433,0.060737)  # Filson (prior neg) baseline probs - software + SB
(Artemis) [split by SB proportion in PAIREDCAP]
#b2=c(0.355311,0.219780,0.223443,0.125916,0.075549)  # Filson (naive only) baseline probs - software + SB
(Artemis) [split by Artemis proportion in PAIREDCAP]
)
```

na[]	t[,1]	t[,2]	t[,3]	M[,1]	M[,2]	M[,3]	y[,1,1]	y[,2,1]	y[,3,1]	y[,1,2]	y[,2,2]	
	y[,3,2]	y[,1,3]	y[,2,3]	y[,3,3]	y[,1,4]	y[,2,4]	y[,3,4]	y[,1,5]	y[,2,5]	y[,3,5]	#	study
ID	Study type											
3	1	2	3	248	248	248	94	52	71	38	46	43
	52	87	70	39	37	40	25	26	24	#	PAIREDCAP	
	all											
2	4	5	NA	100	99	NA	69	55	NA	19	25	NA
	6	13	NA	5	3	NA	1	3	NA	#	Izadpanahi	
	all											
3	2	3	5	169	169	169	53	49	36	116	120	133
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Wajswol 2020	
	A											
3	1	2	4	75	75	75	41	35	32	34	40	43
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Thangarasu	
2021	A											
3	1	2	4	63	63	63	30	33	25	33	30	38
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Kulis 2020	
	A											
2	1	3	NA	88	88	NA	57	48	NA	31	40	NA
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Cornud	A
2	1	3	NA	78	79	NA	44	40	NA	8	12	NA
	26	27	NA	NA	NA	NA	NA	NA	NA	#	FUTURE	B
2	1	3	NA	125	125	NA	85	80	NA	16	16	NA
	24	29	NA	NA	NA	NA	NA	NA	NA	#	PROFUS	B
3	2	3	5	74	74	74	41	39	32	12	10	13
	21	25	29	NA	NA	NA	NA	NA	NA	#	Albisinni 2018	
	B											
3	2	3	5	191	191	191	103	106	85	36	25	34
	52	60	72	NA	NA	NA	NA	NA	NA	#	Fourcade 2018	
	B											
3	1	2	4	111	111	111	69	81	65	19	9	20
	23	21	26	NA	NA	NA	NA	NA	NA	#	Gomez-Ortiz	
2022	B											
3	2	3	5	48	48	48	23	20	16	11	11	13
	10	13	13	4	4	6	NA	NA	NA	#	Alberts 2018	
(all men)	C											
3	2	3	5	538	538	538	294	310	252	114	68	100
	74	81	92	56	79	94	NA	NA	NA	#	Filson 2016	
	C											
END												

Initial values

#chain 1

```
list( a = structure(.Data = c(  NA,0,0,0,0,          NA,0,0,0,0,          NA,0,NA,NA,NA,          NA,0,NA,NA,NA,
NA,0,NA,NA,NA,          NA,0,NA,NA,NA,          NA,0,0,NA,NA,          NA,0,0,NA,NA,          NA,0,0,NA,NA,
NA,0,0,NA,NA,          NA,0,0,NA,NA,          NA,0,0,0,NA,          NA,0,0,0,NA),
.Dim = c(13,5)),
d = structure(.Data = c( NA,NA,NA,NA,NA,          NA,0,0,0,0,          NA,0,0,0,0,          NA,0,0,0,0,
NA,0,0,0,0),
.Dim = c(5,5)),
dA = structure(.Data = c(NA,NA,          NA,0,          NA,0,          NA,0,          NA,0),
.Dim = c(5,2)),
dB = structure(.Data = c(NA,NA,NA,          NA,NA,0,          NA,NA,0,          NA,NA,0,          NA,NA,0),
.Dim = c(5,3)),
dC = structure(.Data = c(NA,NA,NA,NA,          NA,NA,NA,0,          NA,NA,NA,0,          NA,NA,NA,0,
NA,NA,NA,0),
.Dim = c(5,4))
)
```

#chain 2

```
list( a = structure(.Data = c(  NA,2,-.5,1,-1,          NA,2,3,1,2,          NA,-2,NA,NA,NA,          NA,-2,NA,NA,NA,
NA,-2,NA,NA,NA,          NA,-2,NA,NA,NA,          NA,-2,1,NA,NA,          NA,1,-2,NA,NA,          NA,-2,1,NA,NA,
NA,-2,1,NA,NA,          NA,-2,1,NA,NA,          NA,.7,-2,-1,NA,          NA,1,-2,2,NA),
.Dim = c(13,5)),
d = structure(.Data = c( NA,NA,NA,NA,NA,          NA,-1,-2,1,2,          NA,.5,-2,-1,1,          NA,2,-2,.5,-2,
NA,1,2,1,-2),
.Dim = c(5,5)),
dA = structure(.Data = c(NA,NA,          NA,-2,          NA,2,          NA,1,          NA,2),
```

```
.Dim = c(5,2)),
dB = structure(.Data = c(NA,NA,NA,          NA,NA,1,          NA,NA,-1,          NA,NA,-2,          NA,NA,-1),
.Dim = c(5,3)),
dC = structure(.Data = c(NA,NA,NA,NA,          NA,NA,NA,2,          NA,NA,NA,.7,          NA,NA,NA,-.5,
NA,NA,NA,-2),
.Dim = c(5,4))
)
```

Appendix 4 Characteristics of studies included in the systematic review of clinical evidence

TABLE 25 Study characteristics of studies included in the systematic review

Study	Country	Design	*N*	Population investigated	MRI type	MRI magnet strength (T)	SF technology	Comparison	Biopsy route	*N* of cores per lesion (targeted biopsy)[a]	Number of ROI targeted	*N* of cores (SB)	Anaesthesia	Definition of CSPCa	Definition of PCa
SF vs. cognitive fusion: prospective															
Cornud (2018)[93]	France	Prospective, within-patient	88	BN, RB	mpMRI	1.5	Urostation Touch (KOELIS)	SF vs. CF[b]	TR	2	NR	NR	NR	NA	Gleason 3 + 3
Delongchamps (2013)[98]	France	Consecutive series, between patient	SF: 82 CF: 54	BN	mpMRI	1.5	Urostation Touch (KOELIS)[c]	SF vs. CF vs. SB	TR	≥2	NR	10–12	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
FUTURE (2019)[31,166]	The Netherlands	RCT, between patient	SF: 79, CF: 78	RB	mpMRI	3	BiopSee (MedCom)	SF vs. CF	SF: TP, CF: TR	Median (IQR). SF: 4 (3–5), CF: 3 (3–4)	All	NA	General/ spinal	Gleason ≥ 3 + 4	NR
Hansen (2018)[95]	UK, Germany, Australia	Prospective, between patient	SF: 395 CF: 176	BN	mpMRI	1.5 or 3	BiopSee (Medcom)	SF vs. CF vs. SB	TP	At least 2	All ROI	18–24[d]	General	Gleason ≥ 3 + 4	Gleason 3 + 3
Izadpanahi (2021)[82]	Iran	RCT, between patient	SF: 99 CF: 100	BN	mpMRI	3	ARTEMIS (InnoMedicus ARTEMIS)	SF vs. CF, ± SB	TR	SF: 1–2 CF: 1-2	2	4	Local	Gleason ≥ 3 + 4, or 3 + 3 with ≥ 4 mm core length	GS 3 + 3 with < 4 mm core length
PAIREDCAP (2019)[88]	USA	Prospective, within-patient	248	BN	mpMRI	3	ARTEMIS (InnoMedicus ARTEMIS)	SF vs. CF vs. SB	TR	SF: 3 CF: 3	1	12	Local	Gleason ≥ 3 + 4	Gleason ≥ 3 + 3
PROFUS (2014)[97]	USA	Prospective, within patient	101 (BN, RB)	BN, RB, AS	mpMRI	3	ARTEMIS (InnoMedicus ARTEMIS)	SF vs. CF	TR	SF: 2 CF: 2	2	12[d]	Local	Gleason ≥ 3 + 4	Gleason 3 + 3
Stabile (2018)[89]	Italy	Prospective, between patient	SF: 157 CF: 87	BN, RB	mpMRI	1.5	BioJet	SF + SB vs. CF + SB	SF: TP/TR CF: TR	Median (range) SF: 3 (2–3); CF: 2 (2–5)	All ROI	12	NR	Gleason ≥ 3 + 4	NR

Study	Country	Design	*N*	Population investigated	MRI type	MRI magnet strength (T)	SF technology	Comparison	Biopsy route	*N* of cores per lesion (targeted biopsy)[a]	Number of ROI targeted	*N* of cores (SB)	Anaesthesia	Definition of CSPCa	Definition of PCa
SF vs. CF: retrospective															
Kaufmann (2018)[91,101]	Germany, Italy	Retrospective, between patient	SF: 191 CF: 87	BN, RB	mpMRI	3	iSR'obot Mona Lisa (Biobot Surgical)	SF vs. CF	SF: TP CF: TR	4	1	14[d]	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Liang (2020)[85]	China	Retrospective, between patient	SF: 92 CF: 71	BN	bpMRI	3	Predictive Fusion Software (BK)	SF vs. CF	TP	4	All ROI	NA	Local	Gleason ≥ 3 + 4	Gleason 3 + 3
Lockhart (2022)[100]	Australia	Retrospective, between patient	SF: 131 CF: 224	BN	mpMRI	3	MIM Fusion Software (with BK 3000 US)	SF + SB vs. CF + SB	TP	NR[e]	NR	NR	NR	Gleason ≥ 3 + 4	NR
Monda (2018)[90]	USA	Retrospective; before and after study	SF: 348 CF: 162	BN, RB (+ve/−ve)	mpMRI	3	UroNav (Invivo Corporation)	SF vs. CF vs. SB	TR	NR	NR	12	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Software fusion vs. software fusion															
Ferriero (2022)[81]	Italy	Prospective cohort, between patient	Urostation: 103 BioJet: 232	BN	mpMRI	NR	Urostation (KOELIS) BioJet (Healthcare Supply Solutions Ltd)	SF vs. SF	Urostation: TR; BioJet: NR	Median (IQR) **Unmatched** Urostation: 4 (4–6) BioJet: 6 (5–6) **Matched** Urostation: 4 (4–6) BioJet: 6 (4–6)	NR	NA	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Rabah (2021)[84]	Saudi Arabia	RCT, between patient	Artermis: 165 BioJet: 142	BN, RB[f]	mpMRI	NR	ARTEMIS (InnoMedicus ARTEMIS) BioJet (Healthcare Supply Solutions Ltd)	SF vs. SF vs. SB	ARTEMIS: TR BioJet: TP	2–4	All ROI	12	ARTEMIS: Local BioJet: General	NR	NR

continued

TABLE 25 Study characteristics of studies included in the systematic review (*continued*)

Study	Country	Design	*N*	Population investigated	MRI type	MRI magnet strength (T)	SF technology	Comparison	Biopsy route	*N* of cores per lesion (targeted biopsy)[a]	Number of ROI targeted	*N* of cores (SB)	Anaesthesia	Definition of CSPCa	Definition of PCa
Sokolakis (2021)[83]	Germany	Prospective, between patient	BioJet: 20 Urnoav: 20 KOELIS Trinity: 20	BN, RB	mpMRI	3	BioJet (Healthcare Supply), UroNav (Phillips), KOELIS Trinity	SF vs. SF	TR	2–3	All ROI	12[d]	Local	NR	Gleason 3 + 3
SF vs. systematic biopsy vs. SF and systematic biopsy															
Alberts (2018)[80]	The Netherlands	Prospective, within patient	48[g]	BN, RB	mpMRI	NR	Urostation (KOELIS)	SF vs. SB vs. SF + SB	TR	2	All ROIs	12	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Albisinni (2018)[94]	Belgium	Prospective, within-patient	74	RB	mpMRI	3	Urostation (KOELIS)	SF vs. SB vs. SF + SB	TR	2–4	1	12–14	NR	Gleason ≥ 3 + 4 and/or cancer core length ≥ 6 mm (UCL)	NR
Filson (2016)[96]	USA	Prospective, within-patient	538 (PI-RADS ≥ 3, excl AS)	BN, RB, AS (NR)	mpMRI	3	ARTEMIS (InnoMedicus ARTEMIS)	SF vs. SB vs. SF + SB	NR	1	NR	12	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Fourcade (2018)[92]	France	Prospective, within-patient	191	BN, RB	mpMRI	3	Urostation (KOELIS)	SF vs. SB vs. SF + SB	TR	2–4	All ROI	12	NR	NR	NR
Wajswol (2020)[87]	USA	Prospective, within-patient	169 (PI-RADS ≥ 3)	BN, RB	mpMRI	3	UroNav (Phillips)	SF vs. SB vs. SF + SB	TP	4–6	All ROI	12	Local	Gleason ≥ 3 + 4	NR
CF vs. systematic biopsy vs. CF and systematic b632iopsy															
Gomez-Ortiz (2022)[99]	Mexico	Prospective, within-patient	111	RB	NR	1.5	N/A	CB vs. SB vs. CB + SB	TR	2–4	All ROI	12	NR	Gleason ≥ 3 + 4	Gleason 3 + 3
Kulis (2020)[86]	Croatia	Prospective, within-patient	63	RB	mpMRI	3	N/A	CB vs. SB vs. CB + SB	NR	6	Up to 2	12	Local[h]	Gleason ≥ 3 + 4	GS ≤ 6
Thangarasu (2021)[79]	India	Prospective, within-patient	75	BN	mpMRI	3	N/A	CB vs. SB vs. CB + SB	TR	2	All ROI	12	Local[h]	Gleason ≥ 3 + 4	NR

AS, active surveillance; BN, biopsy naive; CSPCa, clinically significant prostate cancer; IQR, interquartile range; ROI, region of interest; RB, repeat biopsy; SB, systematic biopsy.
a All targeted biopsy methods, unless otherwise specified.
b SB performed at operator's discretion (N patients NR).
c Also compared with Esaote SF.
d SB performed but results were NR and did not inform detection comparisons between targeted biopsies.
e SF + SB: mean 21 (range 12–33), CF + SB: 26 (9–54).
f Did not report whether a subset of AS patients were also included.
g Subset who received TB and SB.
h 'Periprostatic block'.

TABLE 26 Summary of characteristics of studies of SF included in the systematic review

			Biopsy route			Anaesthesia			Image registration		
Device	**Author**	***N***	**TR**	**TP**	**NR**	**Local**	**General**	**NR**	**Rigid**	**Elastic**	**NR**
ARTEMIS (InnoMedicus)	Filson, 2016	538			X			X			X
	Izadpanahi, 2021	99	X			X				X	
	PAIRED CAP, 2019	248	X			X					X
	PROFUS, 2014	101	X			X				X	
	Rabah, 2021	165	X			X					X
	TOTAL	1151	**4**	**0**	**1**	**4**	**0**	**1**	**0**	**2**	3
BiopSee (Medcom)	FUTURE, 2019	79		X			X		X		
	Hansen, 2018	395		X			X				X
	TOTAL	**474**	**0**	**2**	**0**	**0**	**2**	**0**	**1**	**0**	**1**
BK	Liang, 2020	92		X		X			X		
	Lockhart, 2022	131		X				X	X		
	TOTAL	223	**0**	**2**	**0**	**1**	**0**	**1**	**2**	**0**	**0**
KOELIS (earlier versions)	Alberts, 2018	48	X					X		X	
	Albisinni, 2018	74	X					X		X	
	Cornud, 2018	88	X					X		X	
	Delongchamps, 2013	82	X					X		X	
	Ferriero, 2022	103			X			X		X	
	Fourcade, 2018	191	X					X		X	
	TOTAL	**586**	**5**	**0**	**1**	**0**	**0**	**6**	**0**	**6**	**0**
BioJet	Ferriero, 2022	232			X			X	X		
	Rabah, 2021	142		X			X				X
	Sokolakis 2021	20	X			X			X		
	Stabile, 2018	157	X	X				X			X
	TOTAL	**551**	**2**	**2**	**1**	**1**	**1**	**2**	**2**	**0**	**2**

continued

TABLE 26 Study characteristics of studies included in the systematic review (*continued*)

			Biopsy route			Anaesthesia			Image registration		
Device	**Author**	***N***	**TR**	**TP**	**NR**	**Local**	**General**	**NR**	**Rigid**	**Elastic**	**NR**
iSR'obot Mona Lisa	Kaufmann, 2018	191		X				X		X	
	TOTAL	**191**	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**1**	**0**
UroNav	Monda, 2018	348	X					X		X	
	Sokolakis, 2021	20	X			X			X		
	Wajswol, 2020	169		X		X			X	X	
	TOTAL	**537**	**2**	**1**	**0**	**2**	**0**	**1**	**2**	**2**	**0**
KOELIS Trinity	Sokolakis, 2021	20	X			X				X	
	TOTAL	**20**	**1**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**0**

TR, transrectal; TP, transperineal.

TABLE 27 Study and population characteristics of studies included in the systematic review

Study	*N*	Population investigated	Recruitment criteria	Age (years)	PSA (ng/ml)	PI-RADS version	PI-RADS score			Lesion location
							3	4	5	
SF vs. CF										
Cornud (2018)[93]	88	BN, RB	PI-RADS ≥ 3[a]	Med (IQR) 63 (60–69)	Med (IQR) 8.2 (6.0–10.9)	NR	NR			NR
Delongchamps (2013)[167b]	mpMRI + ve SF: 82 CF: 54	BN	PSA ≥ 4 ng/ml, and/or suspicious DRE	Mean (SD)[c] SF: 64.5 (7.9) CF: 62.7 (7.4)	Mean (SD)[c] SF: 8.3 (4.1) CF: 9 (3.9)	NR	NR			NR
FUTURE (2019)[31]	SF: 79 CF: 78	RB	Repeat SB (< 4 years), PSA ≥ 4 (ng/ml) and/or suspicious DRE	Mean (SD) SF: 64.6 (6.9) CF: 66.5 (6.3)	Mean (SD) SF: 11.6 (9.0) CF: 11.0 (7.1)	v2	SF: 23 CF: 21	SF: 34 CF: 32	SF: 22 CF: 25	SF: 35 Post, 37 Ant CF: 46 Post, 25 Ant
Hansen (2018)[95]	PI-RADS ≥ 3 SF: 395 CF: 176	BN	PSA ≤ 30 ng/mL, ≤79 years	Median (IQR)[+] Centre 1 (SF): 64 (57–69) Centre 2 (SF): 65 (60–70) Centre 3 (CF): 65 (60–70)	Median (IQR)[+] Centre 1 (SF): 6.6 (4.6–9.0) Centre 2 (SF): 6.9 (5.2–9.1) Centre 3 (CF): 5.9 (4.6–8.0)	v1-2	Centre 1 (SF): 34, Centre 2 (SF): 91, Centre 3 (CF): 28	Centre 1 (SF): 99, Centre 2 (SF): 171, Centre 3 (CF): 148		NR
Izadpanahi (2019)[82]	SF: 99; CF: 100	BN	PSA 2-10 ng/dL, PI-RADS ≥ 3	Mean (SD) SF: 61.9 (7.4) CF: 61.9 (7.4)	Mean (SD) SF: 6.1 (1.3) CF: 5.9 (1.3)	v2	NR			NR
PAIREDCAP (2019)[31]	248	BN	Elevated PSA (serum PSA < 25 ng/mL) or abnormal DRE	Mean (SD) 65.5 (7.7)	Med (IQR) 6.2 (4.6–8.20)	v2	56	91	101	Ant: 93
PROFUS (2014)[97]	125 (101 BN, RB)	BN, RB, AS	NR	NR (range) 65 (56.3–71.0)	NR (range)	v2	NR			Post: 140 Ant: 32

continued

TABLE 27 Study and population characteristics of studies included in the systematic review (*continued*)

Study	*N*	Population investigated	Recruitment criteria	Age (years)	PSA (ng/ml)	PI-RADS version	PI-RADS score			Lesion location
							3	4	5	
Stabile (2018)[89]	SF: 157 CF: 87	BN, RB	NR	Median (IQR) SF: 67 (61–73) CF: 62 (58–70)	Median (IQR) SF: 7.3 (5.2–10.5) CF: 6 (4–9)	NR	SF: 59, CF: 35	SF: 98 CF: 52		NR
SF vs. CF – Retrospective										
Kaufman (2018)[91,101]	SF: 191 CF: 87	BN, RB	Rising and/or persistently elevated PSA	Median (IQR): 69.0 (63.0–74.0)	Median (IQR): 8.0 (5.87–12.0)	v2	NR			NR
Liang (2020)[85]	SF: 92 CF: 71	BN	PSA level of ≤ 20 ng/mL	Mean (SD) SF: 69.17 (9.18) CF: 67.59 (8.45)	Median (IQR) SF: 8.03 (0.66–19.78) CF: 7.66 (0.67–18.81)	v2	NR			NR
Lockhart (2022)[100]	Total: 355 (SF: 131, CF: 224); BN only: 283 (SF: 97; CF: 186)	BN, AS	NR	Mean (range) SF: 65 (41–80) CF: 66.6 (44–85)	Mean SF: 5.8 CF: 7.64	NR	NR			NR
Monda (2018)[90]	SF: 348 CF: 162	BN, RB (+ve/−ve)	NR	Mean (SD) SF: 65.0 (7.2) CF: 63.9 (7.8)	Mean (SD) 7.8 (7.8) 7.9 (7.8)	v2	NR			NR
SF vs. SF										
Ferriero (2022)[81]	Unmatched Urostation: 103 BioJet: 232 Matched: Urostation: 83 BioJet: 83	BN	PI-RADS ≥ 3	Median (IQR) Unmatched Urostation: 67 (59, 72) BioJet: 60 (65, 75) Matched Urostation: 69 (60, 72) BioJet: 65 (61, 71)	Median (IQR) Unmatched Urostation: 7 (4.9, 10.3) BioJet: 6.5 (5, 5.95) Matched Urostation: 7 (4.9, 10.3) BioJet: 6.6 (5, 10)	NR	Unmatched: Urostation: 21 BioJet: 52. Matched: Urostation: 50 BioJet: 19.	Unmatched: Urostation: 55 BioJet: 108 Matched: Urostation: 26 BioJet: 43	Unmatched: Urostation:27 BioJet: 51 Matched: Urostation: 15 BioJet: 21	NR

Study	N	Population investigated	Recruitment criteria	Age (years)	PSA (ng/ml)	PI-RADS version	PI-RADS score			Lesion location
							3	4	5	
Rabah (2021)[84]	Artermis: 165 BioJet: 142	BN, RB	PI-RADS ≥ 3, and PSA ≥ 3.5 ng/ml or abnormal DRE	Mean (SD) ARTEMIS: 65.1 (7.8) BioJet: 65 (8.5)	Mean (SD) ARTEMIS: 14.2 (5) BioJet: 13.7 (25.9)	v2	ARTEMIS: 35 BioJet: 30	ARTEMIS: 19 BioJet: 25	ARTEMIS: 16 BioJet: 20	NR
Sokolakis (2021)[83]	BioJet: 20 Urnoav: 20 KOELIS Trinity: 20	BN, RB	PI-RADS ≥ 3	Median (IQR) BioJet: 66 (61, 67) UroNav: 64 (61, 74) Trinity: 64 (62, 67)	Median (IQR) BioJet: 8 (6,9) UroNav: 6 (5,8) Trinity: 7 (5,8)	v2	BioJet: 4 UroNav: 6 Trinity: 6	BioJet: 12 UroNav: 7 Trinity: 9	BioJet: 4 UroNav: 7 Trinity: 5	NR
SF vs. systematic biopsy vs. SF and systematic biopsy										
Alberts (2018)[80]	48 (who received TB and SB)	BN, RB	PI-RADS ≥ 3, and PSA ≥ 3.5 ng/ml	Median (IQR)[c] 73.1 (72.4–73.8)	Median (IQR)[c] 4.2 (3.4–5.8)	NR	NR			NR
Albisinni (2018)[91]	74	RB	NR	Median (IQR) 65 (62–69)	Median (IQR) 9.27 (6.84–13.4)	v2	NR			NR
Filson (2016)[96]	538 (PI-RADS ≥ 3, excl AS)	BN, RB, AS (NR)	Elevated PSA or abnormal DRE	Median (IQR) BN: 64.4 (58.5–69.4) RB: 65.7 (59.3–70.2)	Median (IQR) BN: 5.8 (4.4–8.1) RB: 7.6 (5.0–11.5)	v2	BN: 129 RB:148	BN: 109 RB: 87	BN: 35 RB: 30	Anterior: BN: 148 RB: 100
Fourcade (2018)[92]	191	BN, RB	PSA > 4ng/mL and abnormal DRE	Median (range) 66 (47–80)	Mean (range) 9 (0.7–48)	v2	NR			
Wajswol (2020)[87]	169 (PI-RADS ≥ 3)	BN, RB	PI-RADS ≥ 2 (visible lesion), PSA > 2.5ng/mL	Median (range) 67.5 (44–89)	Median (range) 8.25 (1.4–103.8)	v2	26	76	67	NR

continued

TABLE 27 Study and population characteristics of studies included in the systematic review (*continued*)

Study	*N*	Population investigated	Recruitment criteria	Age (years)	PSA (ng/ml)	PI-RADS version	PI-RADS score			Lesion location
							3	4	5	
CF vs. systematic biopsy vs. CF and systematic biopsy										
Gomez-Ortiz (2022)[99]	111	RB	PI-RADS ≥ 3	Mean (SD) 66.27 (6.85)	Median (IQR) 9.9 (1.21–26)	2	NR			NR
Kulis (2020)[86]	63	RB	PI-RADS ≥ 3, PSA > 4 ng/mL	Median (range) 67 (57–84)	Median (range) 10.70 (4.86–64.00)	v2	12	35	16	Central: 42 Peripheral: 9 Apical: 9 Anterior: 3
Thangarasu (2021)[79]	75	BN	PI-RADS ≥ 3, serum PSA > 4 and ≤ 20 ng/mL, suspected ≤ T2 stage on rectal examination	Mean (SD) 66.31 (7.9)	Median (NR) 10.6 (4.5–20)	v2	42	23	10	NR

AS, active surveillance; BN, biopsy naivenaïve; RB, repeat biopsy.
a PI-RADS version 1.
b Also compared with Esaote SF.
c Not specific to the population of interest.

Appendix 5 Quality assessment

TABLE 28 Operator experience in studies included in the systematic review

Study	Operator experience
Cornud (2018)[93]	> 10 years in MRI and elastic SF
Delongchamps (2013)[98]	'Experienced uroradiologist'
FUTURE (2019)[31,166]	'Performed by five urologists and expert-trained PhD candidates having at least 6 mo of experience, including 3 mo of experience under expert supervision'
Hansen (2018)[95]	SF (Centre 1): several years' experience of TP biopsy. SF (Centre 2): Supervised Residents. CF: 1/5 urologists
Izadpanahi (2021)[82]	'Experience of performing at least 2000 targeted prostate biopsies'
PAIREDCAP (2019)[88]	'Experienced'
PROFUS (2014)[97]	NR
Stabile (2018)[89]	Urologists had performed at least 200 prostate biopsies but were naive for TB techniques.
Kaufman (2018)[91,101]	NR
Liang (2020)[85]	Experienced urologist with more than 1 year experience
Lockhart (2022)[100]	Experienced radiologist
Monda (2018)[90]	NR
Rabah (2021)[84]	NR
Ferriero (2022)[81]	9 years experience
Sokolakis (2021)[83]	4 operators with no prior experience on mpMRI/TRUS fusion PB, 2 trainees who accomplished 40 TRUS-guided biopsies; and two senior urologists who had done over 250 TRUS-guided biopsies
Alberts (2018)[80]	NR
Albisinni (2018)[94]	Single operator who performs > 100 TBs each year with 20 + years experience
Filson (2016)[96]	NR
Fourcade (2018)[92]	NR
Wajswol (2020)[87]	NR
Gomez-Ortiz (2022)[99]	NR
Kulis (2020)[86]	NR
Thangarasu (2021)[79]	NR

TABLE 29 Risk of bias and applicability assessment with rationale

Study	Tests	Reference std or tests to estimate total positive rates	Risk of bias (QUADAS-C)					Applicability concerns (QUADAS-2)			
			P	I	R	FT	Comments	P	I	R	Comments
Alberts (2018)[80]	SF (KOELIS Urostation) SB	SF + SB	✓	✓	✗	✓	SF performed after SB within the same examination, by the same operator; no blinding.	✓	?	✓	Equivalence of Urostation (out of scope) with KOELIS Trinity (in scope) is uncertain. Anaesthesia method NR.
Albisinni (2018)[94]	SF (KOELIS Urostation) SB	SF + SB	✓	✓	✗	✓	SF performed after SB within the same examination, by the same operator; no blinding.	✗	?	✓	All patients had one prior negative TRUS. Equivalence of Urostation (out of scope) with KOELIS Trinity (in scope) is uncertain. Anaesthesia method NR.
Cornud (2018)[93]	SB CF	SF + CF ± SB	✓	✗	✓	✗	Although SF and CF were conducted by a separate operator, both were conducted within the same session and tracks from the first method (CF) may have been visible to the SF operator. 12 out of 100 patients were not considered for analysis because of missing data (n = 6) or difficulties in extracting the information from the Digital Imaging and Communications in Medicine archives of the biopsy procedure (n = 6).	?	✓ ?	?	47% referred following a prior negative SB. Urostation (TR) is not within scope. Equivalence with KOELIS Trinity (in scope) is uncertain. Reference standard informed by both index tests + SB in unknown number of patients.
Delongchamps (2013)[98]	SF (Urostation Touch, KOELIS) CF	SF + SB CF + SB	✗	✓	✗	✓	Consecutive series, unpaired, no matching. Targeted biopsies performed after SB within the same examination, by the same operator; no blinding. Different reference standards were used in relative comparisons (CF + SB vs. SF + SB).	✓	? ✓	✓	Applicability of KOELIS Urostation to KOELIS Trinity is uncertain. Anaesthesia method NR.
Elkhoury (2019)[88] (PAIREDCAP)	SF (ARTEMIS) CF	SF + CF + SB	✓	✗	✓	✓	SB, followed by CF, then SF by same operator in the same session. SB operator blinded to MRI report, but no blinding of SF operator to CF tracks.	✓	✓	✓	

Study	Tests	Reference std or tests to estimate total positive rates	Risk of bias (QUADAS-C)					Applicability concerns (QUADAS-2)			
			P	I	R	FT	Comments	P	I	R	Comments
Ferriero (2022)[81]	SF (Urostation, KOELIS) SF (BioJet)	SF (Urostation, KOELIS) SF (BioJet)	✗	✗	✗	✓	Significant differences in characteristics of two study cohorts (including age, positive DRE and *n* of target cores), although attempts were made to adjust with propensity score matching (PSM). After adjustment, significant differences remained in median *n* of target cores [4 (IQR 4–6) for Urostation, vs 6 (4–6) for BioJet]. *N* following PSM reduced from 103 to 83 (Urostation) and 211 to 83 (BioJet). Unclear if anaesthesia and biopsy routes differed between the two index tests. Different reference standard between study arms, only informed by one of two index tests.	✓	?	✗	Applicability of Urostation to KOELIS Trinity is unknown. Anaesthesia type unclear. Biopsy positivity rates were not informed by SB, but only by SF biopsies.
Filson (2016)[96]	SF (ARTEMIS) SB	SF + SB	✓	✓	✗	✓	SB performed after SF within the same examination, by the same operator; no blinding.	✓	?	✓	Biopsy route and anaesthesia method NR.
Fourcade (2018)[92]	SF (KOELIS Urostation) SB	SF + SB	✓	✓	✗	✓	No blinding; biopsy method order NR.	?	?	✓	Half of the patients had a prior negative biopsy. Biopsy route and anaesthesia method NR. Applicability of Urostation to KOELIS Trinity is unknown.
FUTURE[31]	SF (BiopSee) CF	SF CF	✝	✗	✗	✓	RCT, no reporting of allocation concealment; higher proportion of posterior lesions in cog (59%) vs. SF arm (44%). Different routes and anaesthesia methods between arms (TP and GA for SF, s. TR and LA for CF) No SB; test positivity informed by index test, which by design differed between the two arms.	✗	✗ ✓	✗	Only includes individuals with prior negative SB. SF conducted under GA. Positivity rate was only informed by targeted biopsy (index test).
Gomez-Ortiz (2022)[99]	CF SB	CF + SB	✓	✓	✗	✓	SB performed after CF within the same examination, by the same operator; no blinding.	✗	?	✓	All patients had prior negative biopsy. Anaesthesia method NR.
Hansen (2018)[95]	SF (BiopSee) CF	SF + SB CF + SB	✗	✓	✗	✗	Allocation to SF or CF according to study centre. Participant allocation not randomised, no matching. Different reference standards used between centres (CF + SB in 1 centre, SF + SB in 2 centres). Significant number of participants in centre III were excluded from the analysis due to process errors.	✓	✗	✗	All index test and reference standard biopsies performed under GA.

continued

TABLE 29 Risk of bias and applicability assessment with rationale (*continued*)

Study	Tests	Reference std or tests to estimate total positive rates	Risk of bias (QUADAS-C)					Applicability concerns (QUADAS-2)			
			P	I	R	FT	Comments	P	I	R	Comments
Izadpanahi (2021)[82]	SF (ARTEMIS) + SB CF + SB	SF + SB CF + SB	✓	✓	✗	✓	Different reference standard test between arms.	✓	✓	✓	
Kaufmann (2018)[101]	SF (iSR'obot Mona Lisa) CF	SF CF	✗	✗	✗	✓	Assignment to SF (TP, GA) or CF (TR, LA) based on patient preference, and statistically significant differences between arms in PSA density, median lesion size and cancer positive rate, though nearest-neighbour matching was performed. SF conducted transperineally under GA, CF transrectally under LA. Different reference standards used between study arms (SF + SB or CF + SB).	? ✓	✗	✗	Large proportion of prior negative biopsy patients (40%). Positive DRE excluded. SF conducted under GA. Cancer rate was only informed by targeted biopsy (index test).
Kulis (2020)[86]	CF SB	CF + SB	✓	✓	✗	✓	SB performed after CF within the same examination, by the same operator; no blinding.	✗	✓	✓	All patients had prior negative TRUS.
Liang (2020)[85]	SF (BK) CF	SF CF	?	✓	✗	✓	No random allocation; criteria for assignment to SF and CF NR; no significant differences in characteristics between SF and CF arms. No systematic biopsy; cancer rates only informed by targeted biopsy, which by design differed between the study arms (either SF or CF).	✓	✓	✗	Positivity rate was only informed by targeted biopsy (index test).
Lockhart (2022)[100]	SF (BK/MIM) CF	SF + SB CF + SB	✗	✓	✗	✓	Retrospective, criteria for assignment to FS and CF NR; significant differences in characteristics between the two study arms, including mean PSA, AS, median ISUP, mean *n* of cores per case, CSPCa rates. No blinding; biopsy method order NR. Different reference standard used between arms (SF + SB, vs. CF + SB).	✓	?	✓	Biopsy route and anaesthesia method NR.
Monda (2018)[90]	SF (UroNav) CF	SF + SB CF + SB	✗	✓	✗	✓	Assignment to SF and CF determined by time of introduction of SF to practice. Significant difference in percentage of biopsy naive (SF: 36%; CF: 27%). Targeted and SB performed in same session, order NR, no blinding reported. Different reference standards between study arms due to design (SF + SB, or CF + SB).	✗	?	✓	Only 36% of SF and 27% of CF were biopsy naive; 18% and 21% were on AS respectively. Biopsy route and anaesthesia method NR.

Study	Tests	Reference std or tests to estimate total positive rates	Risk of bias (QUADAS-C)					Applicability concerns (QUADAS-2)			
			P	I	R	FT	Comments	P	I	R	Comments
PROFUS[97]	SF (ARTEMIS) CF	SF + CF	✓	✗	?	✓	Although CF was blinded to the SF targets and conducted by a separate operator, the risk that biopsy tracks from SF biopsy may have influenced the placement of CF cores cannot be excluded. Results for SF + SB and CF + SB, or comparisons between each targeted method with SF + CF + SB NR.	✓	✓	✗	Results for SF + SB and CF + SB, or comparisons between each targeted method with SF + CF + SB NR.
Rabah (2021)[84]	SF (BioJet) SF (ARTEMIS)	SF (BioJet) SF (ARTEMIS)	?	✗	✗	✓	Insufficient details on random allocation method and allocation concealment; unclear why a larger number of patients was randomised to TRUSBx (n = 165) than TPBx (n = 142); no baseline imbalances reported, although no data on lesions location reported. GA was peformed for the TPBx arm only; N of biopsies taken was higher in TRUSBx arm (n = 403) compared with TPBx (n = 338). Positive rates only informed by one index test in each arm. Each arm had a different software fusion method, route and anaesthesia type.	✓	✗ ✓	✗	All BioJet biopsies performed under GA. Positive rates only informed by one index test in each arm. SB (12 core) were conducted for all patients but not included as part of ref std.
Sokolakis (2021)[83]	SF (BioJet) SF (UroNav) SF (KOELIS Trinity)	SF (BioJet) SF (UroNav) SF (KOELIS Trinity)	✗	✓	✗	✓	No randomisation, consecutive series. Small sample size in each arm; no statistically significant differences in reported characteristics, though difference in % with previous biopsy (0 in Trinity arm, vs. 40% in UroNav and 22% in BioJet arm. Different test for positive rate estimates for each cohort; SB was not incorporated to the results.	✓	✓	✗	Positivity rate was only informed by targeted biopsy (index test).
Stabile (2018)[89]	SF (BioJet) CF	SF + SB CF + SB	✗	✗	✗	✓	Unpaired, unmatched design; choice of TB method (including route) at operator's discretion; statistically significant difference in age, PSA, median n of targets per lesion, and previous biopsy between SF and cog fusion cohorts ($p < 0.05$). Median target cores per MRI was higher in the SF cohort [3, IQR (2–3)] than the cognitive biopsy cohort [2 (2–5)] ($p < 0.001$), which may favour the fusion biopsy group. Different reference standards between arms (SB + cog vs. SB + SF) and no blinding of SB operator.	?	✗	✓	46% prior negative biopsy. All three urologists were naive to targeted biopsy techniques. Evidence of significant learning curve provided for all targeted biopsy approaches. Anaesthesia method NR.
Thangarasu (2021)[79]	CF SB	CF + SB	✓	✓	✗	✓	SB performed after CF within the same examination, by the same operator; no blinding.	✓	✓	✓	
Wasjwol 202087	SF **(UroNav)** **SB**	SF **+ SB**	✓	✓	✗	✓	**SB performed after** SF **within the same examination, by the same operator; no blinding.**	**?**	✓	✓	**49% had prior negative biopsy.**

FT, flow and timing; GA, general anaesthesia; I, index test; LA, local anaesthesia; P, patient selection; R, reference standard/test(s) used to derive overall biopsy positive rates; TP, transperineal; TR, transrectal; SSB, saturation biopsy. ✓ indicates low risk; ✗ indicates high risk; ? indicates unclear risk

Appendix 6 Additional network meta-analysis data and results

Data for additional analyses

TABLE 30 Data for NMA comparing the number of PCas detected

	Intervention			Number of patients			Number of cancers		
Study	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
PAIREDCAP (2019)[88]	CF	SB	ARTEMIS	248	248	248	154	196	177
Izadpanahi (2021)[82]	CF + SB	ARTEMIS + SB	NA	100	99	NA	31	44	NA
Wajswol (2020)[87]	SB	UroNav	UroNav + SB	169	169	169	116	120	133
Thangarasu (2021)[79]	CF	SB	CF + SB	75	75	75	34	40	43
Kulis (2020)[86]	CF	SB	CF + SB	63	63	63	33	30	38
Cornud (2018)[93]	CF	Urostation	NA	88	88	NA	31	40	NA
FUTURE (2019)[31]	CF	BiopSee	NA	78	79	NA	34	39	NA
PROFUS (2014)[97]	CF	ARTEMIS	NA	125	125	NA	40	45	NA
Albisinni (2018)[94]	SB	Urostation	Urostation + SB	74	74	74	33	35	42
Fourcade (2018)[92]	SB	Urostation	Urostation + SB	191	191	191	88	85	106
Gomez-Ortiz (2022)[99]	CF	SB	CF + SB	111	111	111	42	30	46
[a]Rabah (2021)[84]	ARTEMIS	BioJet	NA	165	142	NA	48	64	NA
Alberts (2018)[80]	SB	Urostation	Urostation + SB	48	48	48	25	28	32
Filson (2016)[96]	SB	ARTEMIS	ARTEMIS + SB	538	538	538	244	228	286

SB, systematic biopsy.
a Study only included in analyses with individual device effects as it compares two SF devices.

TABLE 31 Data for NMA comparing the number of CSPCas detected

	Intervention			Number of patients			Number of CS cancers		
Study	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3	Arm 1	Arm 2	Arm 3
PAIREDCAP (2019)[88]	CF	SB	ARTEMIS	248	248	248	116	150	134
Izadpanahi (2021)[82]	CF + SB	ARTEMIS + SB	NA	100	99	NA	12	19	NA
FUTURE (2019)[31]	CF	BiopSee	NA	78	79	NA	26	27	NA
PROFUS (2014)[97]	CF	ARTEMIS	NA	125	125	NA	24	29	NA
Albisinni (2018)[94]	SB	Urostation	Urostation + SB	74	74	74	21	25	42
Fourcade (2018)[92]	SB	Urostation	Urostation + SB	191	191	191	52	60	106
Gomez-Ortiz (2022)[99]	CF	SB	CF + SB	111	111	111	23	21	46
[a]Rabah (2021)[84]	ARTEMIS	BioJet	NA	165	142	NA	21	46	NA
Alberts (2018)[80]	SB	Urostation	Urostation + SB	48	48	48	14	17	19
Filson (2016)[96]	SB	ARTEMIS	ARTEMIS + SB	538	538	538	130	160	186

SB, systematic biopsy.
a Study only included in analyses with individual device effects as it compares two SF devices.

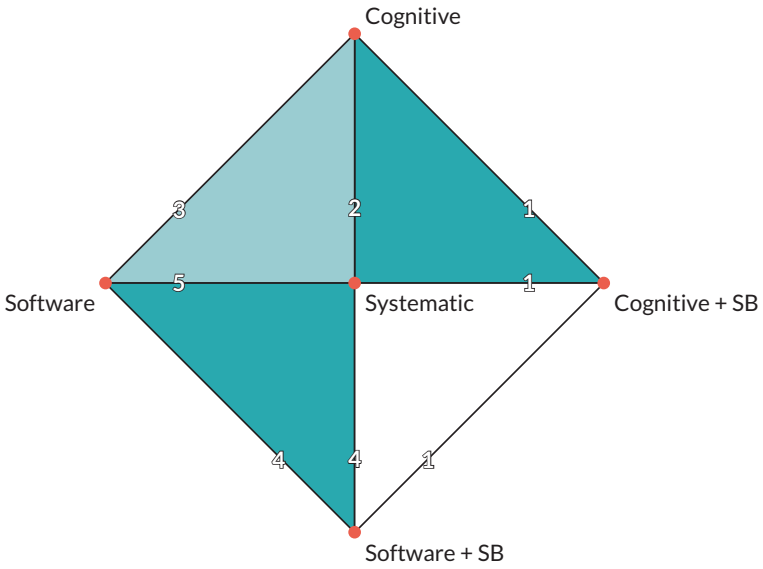


FIGURE 13 Network of biopsy types and devices compared for CSPCa detection, under the assumption of a common effect for different SF devices. Lines represent comparisons made in studies, numbers on the lines show how many studies included that comparison and shaded areas represent multi arm studies. SB, systematic biopsy.

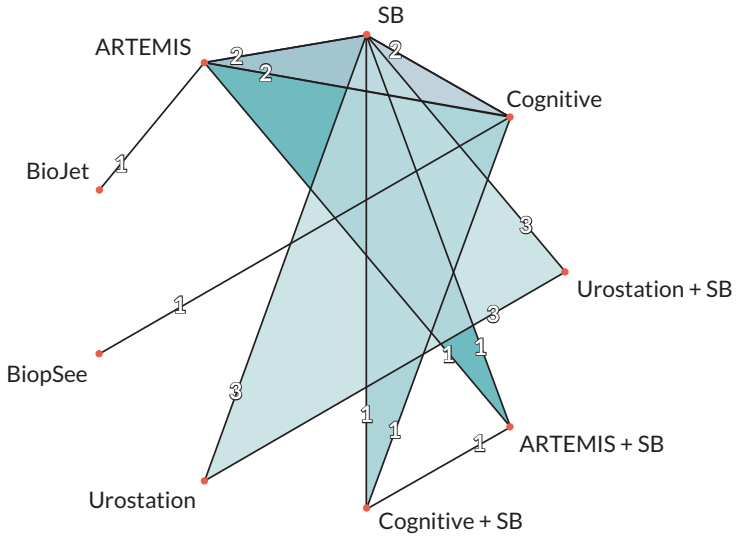


FIGURE 14 Network of biopsy types and devices compared for CSPCa detection. Lines represent comparisons made in studies, numbers on the lines show how many studies included that comparison and shaded areas represent multi arm studies. SB, systematic biopsy.

Results from additional analyses: tables

TABLE 32 Probabilities (median and 95% CrI) of being classified at different ISUP grades for biopsy-naive patients

	ARTEMIS probabilities from Filson *et al.*[96] biopsy-naive data			ARTEMIS + SB probabilities from Filson *et al.*[96] biopsy-naive data	
ISUP	Cognitive	Systematic	Software[a]	Cognitive + SB	Software + SB[a]
NC	0.36 (0.29 to 0.44)	0.25 (0.21 to 0.29)	0.29	0.41 (0.21 to 0.56)	0.36
1	0.20 (0.15 to 0.25)	0.21 (0.17 to 0.26)	0.17	0.21 (0.10 to 0.33)	0.22
2	0.18 (0.13 to 0.25)	0.28 (0.23 to 0.33)	0.28	0.10 (0.03 to 0.23)	0.22
3	0.15 (0.10 to 0.23)	0.15 (0.10 to 0.22)	0.16	0.21 (0.06 to 0.59)	0.12
4-5	0.10 (0.06 to 0.17)	0.10 (0.06 to 0.17)	0.10	0.02 (0.00 to 0.18)	0.08

a Assumed underlying baseline probabilities.

TABLE 33 Model 1b: Odds ratios (median and 95% CrI) of being classified as ISUP grades 1 to 4–5 compared to being categorised as having NC, for the different (single) biopsy methods, compared to CF biopsy; and categorisations using the different biopsy methods combined with systematic biopsy, compared to CF plus systematic biopsy

	Compared to CF biopsy										Compared to CF biopsy plus systematic biopsy			
ISUP	SB		ARTEMIS		BioJet		BiopSee		Urostation		ARTEMIS + SB		Urostation + SB	
NC	REFERENCE										REFERENCE			
1	1.54	(1.06 to 2.24)	1.04	(0.72 to 1.52)	1.04	(0.49 to 2.24)	1.65	(0.61 to 4.73)	1.21	(0.67 to 2.15)	1.17	(0.71 to 1.94)	1.28	(0.65 to 2.53)
2	2.28	(1.50 to 3.47)	1.92	(1.26 to 2.95)	NE	NE	NE	NE	3.03	(1.04 to 8.94)	2.57	(0.94 to 8.13)	3.31	(0.78 to 15.77)
3	1.41	(0.82 to 2.41)	1.31	(0.78 to 2.22)	NE	NE	NE	NE	NE	NE	0.65	(0.12 to 2.90)	NE	NE
4-5	1.54	(0.83 to 2.86)	1.22	(0.65 to 2.29)	NE	NE	NE	NE	NE	NE	4.41	(0.46 to 150.05)	NE	NE

SB: systematic biopsy; NE, not estimable (due to data sparseness).

Note
No results can be obtained for UroNav or UroNav + SB due to lack of detailed ISUP grade reporting.

TABLE 34 Model 1b: Probabilities (median and 95% CrI) of being classified at different ISUP grades for biopsy-naive patients based on the independent effects analysis

	ARTEMIS probabilities from Filson *et al.*[96] biopsy-naive data					ARTEMIS + SB probabilities from Filson *et al.*[96] biopsy-naive data		
ISUP	Cognitive		SB		ARTEMIS[a]	Cognitive + SB		ARTEMIS + SB[a]
NC	0.54	(0.46 to 0.61)	0.41	(0.35 to 0.47)	0.47	0.41	(0.21 to 0.56)	0.36
1	0.18	(0.13 to 0.24)	0.21	(0.17 to 0.26)	0.16	0.21	(0.10 to 0.33)	0.22
2	0.12	(0.08 to 0.16)	0.20	(0.16 to 0.25)	0.20	0.10	(0.03 to 0.23)	0.22
3	0.09	(0.06 to 0.14)	0.10	(0.06 to 0.15)	0.11	0.21	(0.06 to 0.59)	0.12
4-5	0.06	(0.03 to 0.10)	0.07	(0.04 to 0.12)	0.06	0.02	(0.00 to 0.17)	0.08

SB, systematic biopsy.
a Assumed underlying baseline probabilities.

TABLE 35 Probabilities (median and 95% CrI) of being classified at different ISUP grades for patients with a previous negative biopsy based on the independent effects analysis

	ARTEMIS probabilities from Filson *et al.*[96] previous negative-biopsy data					ARTEMIS + SB probabilities from Filson *et al.*[96] previous negative-biopsy data		
ISUP	Cognitive		SB		ARTEMIS[a]	Cognitive + SB		ARTEMIS + SB[a]
NC	0.74	(0.68 to 0.80)	0.63	(0.57 to 0.69)	0.69	0.63	(0.38 to 0.76)	0.58
1	0.09	(0.07 to 0.12)	0.12	(0.09 to 0.15)	0.09	0.14	(0.07 to 0.21)	0.15
2	0.06	(0.04 to 0.08)	0.11	(0.09 to 0.14)	0.10	0.05	(0.02 to 0.12)	0.12
3	0.07	(0.04 to 0.10)	0.08	(0.05 to 0.12)	0.08	0.14	(0.04 to 0.47)	0.09
4-5	0.04	(0.02 to 0.07)	0.05	(0.03 to 0.09)	0.05	0.01	(0.00 to 0.12)	0.06

a Assumed fixed.

TABLE 36 Model fit statistics for the cancer detection NMAs

	Any cancer				CS cancer			
	Model 2a		Model 2b		Model 3a		Model 3b	
Model	ResDev[a]	DIC	ResDev[b]	DIC	ResDev[c]	DIC	ResDev[d]	DIC
NMA random effects	33.56	55.35	36.60	66.13	23.11	42.76	26.51	49.33
NMA fixed effect	37.54	54.57	43.21	67.26	40.29	53.32	34.47	52.65
UME randomeffects	NA	NA	NA	NA	23.30	43.53	25.83	48.49
UME fixedeffect	37.95	56.96	44.35	71.48	NA	NA	NA	NA3

DIC, deviance information criteria, ResDev, residual deviance, UME, unrelated mean effects.
a Compare to 35 data points.
b Compare to 37 data points.
c Compare to 24 data points.
d Compare to 26 data points.

Note
Shaded cells denote preferred model.

TABLE 37 Odds ratios (median and 95% CrI) of cancer detection

		Any cancer (model 2a)				CS cancer (model 3a)	
Device Y compared to X		Fixed-effect NMA		Random-effects NMA		Random-effects NMA	
X	Y	Median	(95% CrI)	Median	(95% CrI)	Median	(95% CrI)
Cognitive	Systematic	1.37	(1.11 to 1.68)	1.32	(0.99 to 1.70)	1.18	(0.72 to 1.89)
Cognitive	Software	1.30	(1.06 to 1.61)	1.29	(1.00 to 1.67)	1.35	(0.86 to 2.10)
Cognitive	Cognitive + SB	1.56	(1.16 to 2.12)	1.54	(1.08 to 2.16)	2.47	(1.20 to 4.98)
Cognitive	Software + SB	2.05	(1.60 to 2.61)	2.03	(1.49 to 2.75)	2.71	(1.56 to 4.71)
Systematic	Software	0.95	(0.82 to 1.11)	0.98	(0.81 to 1.24)	1.15	(0.80 to 1.66)
Systematic	Cognitive + SB	1.15	(0.86 to 1.53)	1.17	(0.84 to 1.66)	2.09	(1.07 to 4.10)
Systematic	Software + SB	1.50	(1.27 to 1.77)	1.54	(1.24 to 1.99)	2.29	(1.56 to 3.52)
Software	Cognitive + SB	1.20	(0.88 to 1.63)	1.19	(0.82 to 1.70)	1.82	(0.90 to 3.64)
Software	Software + SB	1.57	(1.32 to 1.86)	1.57	(1.25 to 1.98)	2.00	(1.34 to 3.07)
Cognitive + SB	Software + SB	1.31	(0.96 to 1.78)	1.32	(0.92 to 1.91)	1.10	(0.56 to 2.22)

SB, systematic biopsy.

TABLE 38 All pairwise odds ratios (median and 95% CrI) of any cancer detection (model 2b)

Device Y compared to X		Fixed-effect NMA		Random-effects NMA	
X	Y	Median	(95% CrI)	Median	(95% CrI)
Cognitive	SB	1.39	(1.11 to 1.73)	1.31	(0.92 to 1.78)
Cognitive	ARTEMIS	1.24	(0.98 to 1.58)	1.20	(0.81 to 1.75)
Cognitive	BioJet	2.49	(1.47 to 4.27)	2.43	(1.08 to 5.24)
Cognitive	BiopSee	1.26	(0.67 to 2.38)	1.26	(0.56 to 2.81)

continued

TABLE 38 All pairwise odds ratios (median and 95% CrI) of any cancer detection (model 2b) (*continued*)

Device Y compared to X		Fixed-effect NMA		Random-effects NMA	
X	**Y**	**Median**	**(95% CrI)**	**Median**	**(95% CrI)**
Cognitive	Urostation	1.45	(1.05 to 2.01)	1.41	(0.88 to 2.22)
Cognitive	UroNav	1.55	(0.93 to 2.62)	1.47	(0.67 to 3.06)
Cognitive	Cognitive + SB	1.56	(1.15 to 2.13)	1.53	(1.01 to 2.30)
Cognitive	ARTEMIS + SB	2.00	(1.51 to 2.65)	2.01	(1.23 to 3.33)
Cognitive	Urostation + SB	2.18	(1.51 to 3.13)	2.10	(1.23 to 3.49)
Cognitive	UroNav + SB	2.35	(1.37 to 4.07)	2.24	(1.00 to 4.77)
SB	ARTEMIS	0.90	(0.74 to 1.09)	0.92	(0.64 to 1.36)
SB	BioJet	1.80	(1.08 to 3.00)	1.85	(0.85 to 4.06)
SB	BiopSee	0.91	(0.47 to 1.78)	0.96	(0.41 to 2.35)
SB	Urostation	1.04	(0.79 to 1.38)	1.08	(0.73 to 1.63)
SB	UroNav	1.12	(0.70 to 1.79)	1.12	(0.57 to 2.23)
SB	Cognitive + SB	1.13	(0.84 to 1.51)	1.17	(0.80 to 1.77)
SB	ARTEMIS + SB	1.44	(1.16 to 1.79)	1.53	(1.01 to 2.52)
SB	Urostation + SB	1.57	(1.15 to 2.13)	1.60	(1.04 to 2.50)
SB	UroNav + SB	1.69	(1.04 to 2.80)	1.71	(0.85 to 3.46)
ARTEMIS	BioJet	2.01	(1.25 to 3.22)	2.01	(1.01 to 3.98)
ARTEMIS	BiopSee	1.02	(0.52 to 2.00)	1.05	(0.43 to 2.58)
ARTEMIS	Urostation	1.17	(0.84 to 1.62)	1.17	(0.69 to 1.97)
ARTEMIS	UroNav	1.25	(0.76 to 2.08)	1.22	(0.55 to 2.63)
ARTEMIS	Cognitive + SB	1.26	(0.91 to 1.74)	1.27	(0.79 to 2.07)
ARTEMIS	ARTEMIS + SB	1.61	(1.29 to 2.01)	1.66	(1.06 to 2.76)
ARTEMIS	Urostation + SB	1.75	(1.22 to 2.50)	1.75	(0.99 to 3.04)
ARTEMIS	UroNav + SB	1.89	(1.12 to 3.24)	1.86	(0.83 to 4.07)
BioJet	BiopSee	0.51	(0.22 to 1.16)	0.52	(0.17 to 1.62)
BioJet	Urostation	0.58	(0.32 to 1.03)	0.58	(0.25 to 1.39)
BioJet	UroNav	0.62	(0.31 to 1.25)	0.61	(0.22 to 1.71)
BioJet	Cognitive + SB	0.63	(0.35 to 1.11)	0.63	(0.28 to 1.48)
BioJet	ARTEMIS + SB	0.80	(0.47 to 1.35)	0.83	(0.37 to 1.97)
BioJet	Urostation + SB	0.87	(0.48 to 1.58)	0.87	(0.36 to 2.12)
BioJet	UroNav + SB	0.94	(0.46 to 1.93)	0.93	(0.32 to 2.62)
BiopSee	Urostation	1.15	(0.56 to 2.32)	1.11	(0.44 to 2.81)
BiopSee	UroNav	1.23	(0.54 to 2.80)	1.16	(0.38 to 3.41)
BiopSee	Cognitive + SB	1.24	(0.61 to 2.49)	1.21	(0.49 to 3.01)
BiopSee	ARTEMIS + SB	1.58	(0.79 to 3.13)	1.59	(0.63 to 4.14)

TABLE 38 All pairwise odds ratios (median and 95% CrI) of any cancer detection (model 2b) (*continued*)

Device Y compared to X		Fixed-effect NMA		Random-effects NMA	
X	Y	Median	(95% CrI)	Median	(95% CrI)
BiopSee	Urostation + SB	1.73	(0.83 to 3.56)	1.66	(0.63 to 4.26)
BiopSee	UroNav + SB	1.86	(0.80 to 4.30)	1.78	(0.57 to 5.26)
Urostation	UroNav	1.07	(0.62 to 1.86)	1.04	(0.47 to 2.28)
Urostation	Cognitive + SB	1.08	(0.73 to 1.60)	1.09	(0.64 to 1.86)
Urostation	ARTEMIS + SB	1.38	(0.97 to 1.95)	1.42	(0.81 to 2.62)
Urostation	Urostation + SB	1.50	(1.10 to 2.05)	1.49	(0.96 to 2.29)
Urostation	UroNav + SB	1.62	(0.92 to 2.88)	1.59	(0.70 to 3.51)
UroNav	Cognitive + SB	1.01	(0.58 to 1.74)	1.04	(0.48 to 2.34)
UroNav	ARTEMIS + SB	1.29	(0.76 to 2.14)	1.36	(0.62 to 3.20)
UroNav	Urostation + SB	1.40	(0.80 to 2.45)	1.42	(0.64 to 3.25)
UroNav	UroNav + SB	1.51	(0.92 to 2.51)	1.52	(0.75 to 3.07)
Cognitive + SB	ARTEMIS + SB	1.28	(0.92 to 1.76)	1.31	(0.81 to 2.20)
Cognitive + SB	Urostation + SB	1.39	(0.92 to 2.11)	1.37	(0.76 to 2.42)
Cognitive + SB	UroNav + SB	1.50	(0.85 to 2.69)	1.46	(0.64 to 3.23)
ARTEMIS + SB	Urostation + SB	1.09	(0.75 to 1.58)	1.05	(0.55 to 1.88)
ARTEMIS + SB	UroNav + SB	1.18	(0.69 to 2.03)	1.12	(0.47 to 2.50)
Urostation + SB	UroNav + SB	1.08	(0.61 to 1.94)	1.07	(0.46 to 2.43)

TABLE 39 All pairwise odds ratios (median and 95% CrI) of CS cancer detection (model 3b)

Device Y compared to X		Random-effects NMA	
X	Y	Median	(95% CrI)
Cognitive	SB	1.30	(0.71 to 2.24)
Cognitive	ARTEMIS	1.44	(0.80 to 2.47)
Cognitive	BioJet	4.79	(1.56 to 14.56)
Cognitive	BiopSee	1.04	(0.38 to 2.85)
Cognitive	Urostation	1.65	(0.72 to 3.64)
Cognitive	Cognitive + SB	2.41	(1.10 to 5.18)
Cognitive	ARTEMIS + SB	2.32	(1.13 to 5.28)
Cognitive	Urostation + SB	3.71	(1.55 to 7.91)
SB	ARTEMIS	1.10	(0.65 to 1.90)
SB	BioJet	3.69	(1.23 to 11.40)
SB	BiopSee	0.80	(0.26 to 2.61)
SB	Urostation	1.27	(0.72 to 2.27)

continued

TABLE 39 All pairwise odds ratios (median and 95% CrI) of CS cancer detection (model 3b) (*continued*)

Device Y compared to X		Random-effects NMA	
X	**Y**	**Median**	**(95% CrI)**
SB	Cognitive + SB	1.86	(0.89 to 3.91)
SB	ARTEMIS + SB	1.78	(0.98 to 3.78)
SB	Urostation + SB	2.85	(1.56 to 4.94)
ARTEMIS	BioJet	3.34	(1.28 to 8.88)
ARTEMIS	BiopSee	0.72	(0.23 to 2.34)
ARTEMIS	Urostation	1.15	(0.52 to 2.53)
ARTEMIS	Cognitive + SB	1.68	(0.75 to 3.75)
ARTEMIS	ARTEMIS + SB	1.62	(0.86 to 3.50)
ARTEMIS	Urostation + SB	2.59	(1.12 to 5.45)
BioJet	BiopSee	0.22	(0.05 to 0.99)
BioJet	Urostation	0.34	(0.10 to 1.18)
BioJet	Cognitive + SB	0.51	(0.14 to 1.77)
BioJet	ARTEMIS + SB	0.48	(0.15 to 1.70)
BioJet	Urostation + SB	0.77	(0.21 to 2.59)
BiopSee	Urostation	1.59	(0.43 to 5.71)
BiopSee	Cognitive + SB	2.32	(0.64 to 8.11)
BiopSee	ARTEMIS + SB	2.24	(0.66 to 8.19)
BiopSee	Urostation + SB	3.56	(0.92 to 12.33)
Urostation	Cognitive + SB	1.47	(0.57 to 3.75)
Urostation	ARTEMIS + SB	1.41	(0.62 to 3.66)
Urostation	Urostation + SB	2.25	(1.23 to 3.86)
Cognitive + SB	ARTEMIS + SB	0.96	(0.47 to 2.23)
Cognitive + SB	Urostation + SB	1.53	(0.58 to 3.80)
ARTEMIS + SB	Urostation + SB	1.60	(0.59 to 3.53)

Results from additional analyses: Figures

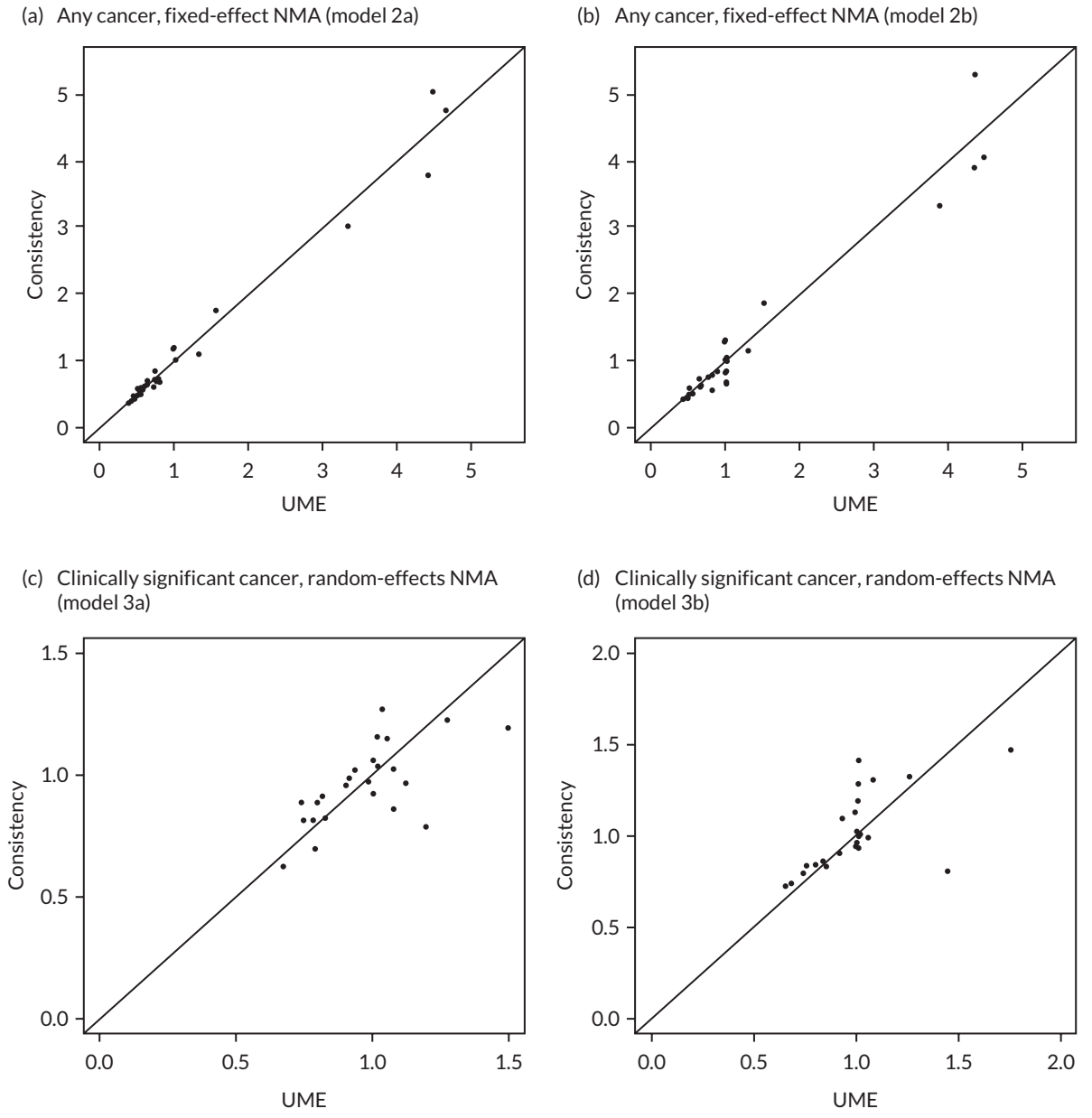


FIGURE 15 Plots of residual deviance contributions for the NMA (consistency) and unrelated mean effects model. UME, unrelated mean effects.

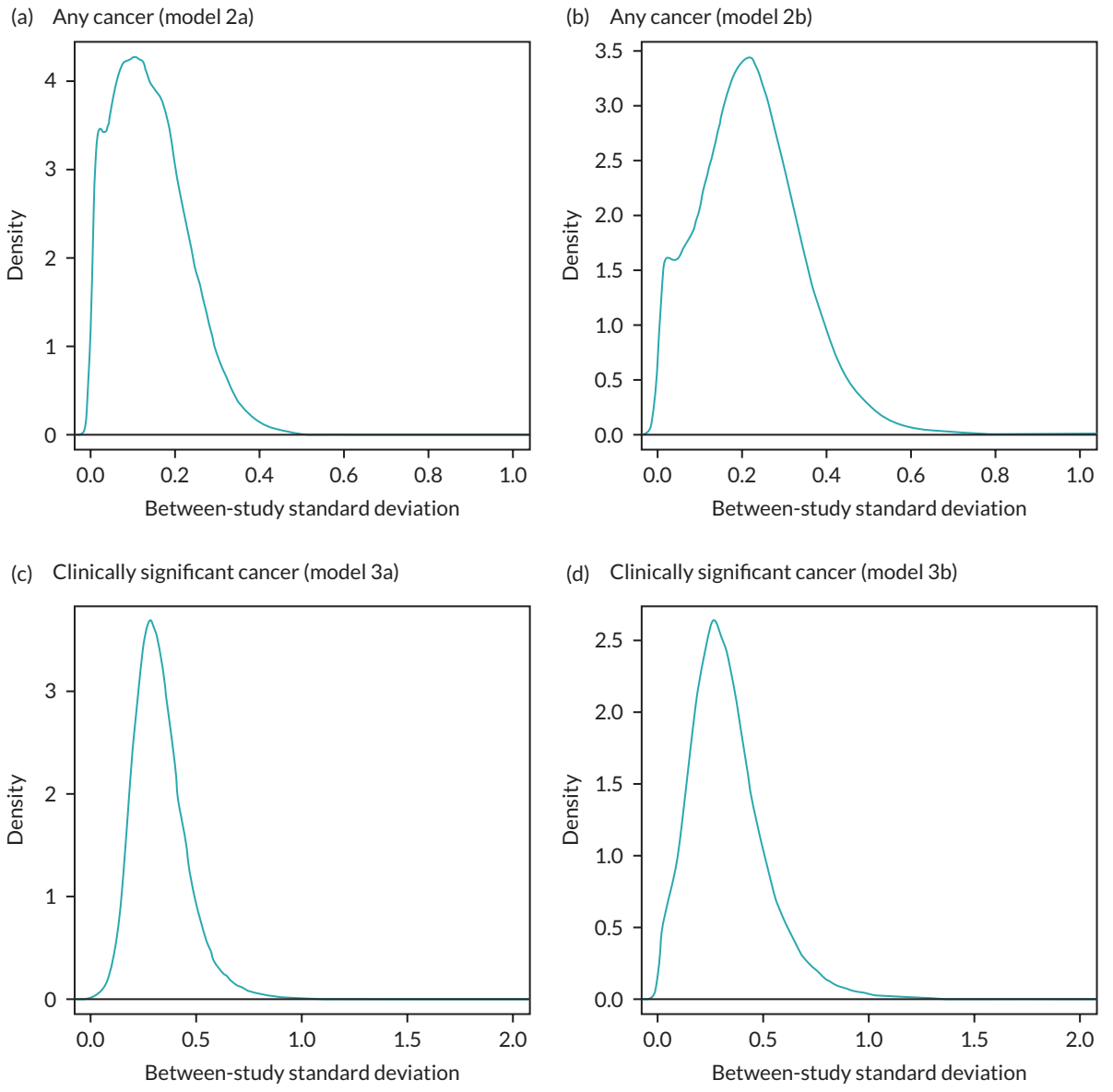


FIGURE 16 Posterior densities of the between-study SD for random-effects models.

Appendix 7 Additional results from studies included in the systematic review

TABLE 40 Software fusion vs. CF, PCa test positive rates (studies not included in the meta-analyses)

	Population	SF technology	Route[a]	Anaesthesia[a]	Sample size	PCa definition	Effect estimates	Statistical significance
Delongchamps (2013)[98]	BN	Urostation Touch (KOELIS)[b]	TR	NR	SF: 82 CF: 54	NR	NR[c]	SF vs. SB: $p = 0.006$[d] CF vs. SB: $p = 0.22$
Hansen (2018)[95]	BN	BiopSee	TP	GA	SF: 395 CF: 176	NR	SF: 53% CF: 38%	NR
Kaufmann (2018)[91]	BN, RB	BioJet	SF: TP CF: TR	NR	SF: 191 CF: 87	GS: 6	SF: 58.1% CF: 43.7%	$p = 0.02$
Liang (2020)[85]	BN	bkFusion[e]	TP	LA	SF: 92 CF: 71	GS: 6	SF: 51.08% CF: 60.56%	$p = 0.228$
Monda (2018)[90]	BN, RB	UroNav	TR	NR	SF: 348 CF: 162	GS: 6	SF: 14.4% CF: 22.8%	NR

BN, biopsy naive; SB, systematic biopsy.
a For both SF and CF approaches unless otherwise specified.
b Also compared to Esaote rigid SF system.
c Probability of detecting cancer undetected by SB against SB as reference was calculated but NR.
d Favours SF.
e Predictive Fusion Software.

TABLE 41 Software fusion vs. CF, CS PCa biopsy-positive rates (studies not included in the meta-analyses)

	Population	SF technology	Route[a]	Anaesthesia	Sample size	CSPCa definition	Effect estimates	*p*-value
Delongchamps (2013)[98]	BN	Urostation Touch (KOELIS)[a]	TR	NR	SF: 82 CF: 54	GS ≥ 3 + 4	SF: 44% CF: 45%	SF vs. SB: $p = 0.01$[b] CF vs. SB: $p = 0.6$
Hansen (2018)[95]	BN	BiopSee	TP	GA	SF: 395 CF: 176	GS ≥ 3 + 4	SF: 56% CF: 70%	NR
Kaufmann (2018)[91]	BN, RB	BioJet	SF: TP CF: TR	NR	SF: 191 CF: 87	GS ≥ 3 + 4	SF: 80.4% CF: 84.6%	$p = 0.55$
Liang (2020)[85]	BN	bkFusion[c]	TP	LA	SF: 92 CF: 71	GS ≥ 3 + 4	SF: 35.87% CF: 39.43%	$p = 0.641$
Monda (2018)[90]	BN, RB	UroNav	TR	NR	SF: 162 CF: 348	GS ≥ 3 + 4	SF: 27.9%, CF: 27.2%	NR

a Also compared to Esaote rigid SF system.
b Favours SF.
c 'Predictive Fusion Software'.

TABLE 42 Software fusion with systematic biopsy vs. CF with systematic biospy, PCa and CSPCa test-positive rates (studies not included in the meta-analyses)

	Population	SF technology	Route	Anaesthesia	Sample size	Outcome	Effect estimates	Statistical significance
Lockhart (2022)[100]	BN	bkFusion[a]	TP	NR	SF + SB: 97 CF + SB: 186	GS ≥ 3 + 4	SF + SB: 53% CF + SB: 66.7%	NR
Stabile (2018)[89]	BN, RB	BioJet	SF: TP or TR CF: TR	NR	SF: 157 CF: 87	PCa (not defined)	SF + SB: 68.2% CF + SB: 58.6%	$p = 0.2$
						CSPCa (GS ≥ 3 + 4)	SF + SB: 58% CF + SB: 44.8%	$p = 0.07$

BN, biopsy naive; RB, repeat biopsy; SB, systematic biopsy.
a MIM fusion software platform with a BK3000 ultrasound.

TABLE 43 Software fusion vs. software fusion, PCa and CSPCa biopsy test positive rates (studies not included in the meta-analyses)

	Population	SF technology	Route[a]	Anaesthesia[a]	Sample size	Outcome	Effect estimates	Statistical significance
Ferriero (2022)[81]	BN, RB	BioJet Urostation	Urostation: TR BioJet: NR	NR	SF: 103 (83)[b] SF: 211 (83)[b]	PCa (NR) Per target	SF(Urostation): 69.8% SF (BioJet): 56.6%	$p = 0.077$
						CSPCa (NR) Per target	SF(Urostation): 50.6% SF (BioJet): 50.6%	$p = 1$
Sokolakis (2021)[83]	BN, RB	BioJet KOELIS Trinity UroNav	TR	LA	BioJet: 20 Trinity: 20 UroNav: 20	PCa	BioJet: 65% Trinity: 70% UroNav: 65%	$p > 0.99$
						CSPCa (GS ≥ 3 + 4)	BioJet: 50% Trinity: 55% UroNav: 50%	$p > 0.99$

BN, biopsy naive; CsPCa, clinically significant prostate cancer; LA, local anaesthetic; RB, repeat biopsy.
a For all SF approaches unless otherwise specified.
b Values in brackets refer to effective sample sizes following propensity score matching.

TABLE 44 Additional test-positive results from studies not included in the meta-analyses (including alternative outcome definitions and by subgroup)

Study	Design	Pop.	Tests	*N*	Outcome (metric)	Summary	Test-positive estimates	Direction of effect/ *p*-value
Delongchamps (2013)[98]	Consecutive series, between-patient	BN	SF (KOELIS –Urostation Touch) vs. SB[a]	82	CSPCa: Gleason ≥ 3 + 4 (*N*)	SF alone detected 35 of the 44 cancers detected by SB as well as 27 undetected by SB, of which 8 had a GS of > 6. All 9 cancers missed by SF but detected by SB had a GS of 6, of which 7 involved < 5 mm of the biopsy core.	SF: 44% CF: 45%	Favours SF vs. SB *p* = 0.01
			CB vs. SB	54	PCa (OR) Definition NR	CF alone detected 37 of the 55 cancers detected by SB as well as 3 undetected by RB, of which 2 had a GS of > 6. Of the 18 cancers missed by SF but detected by RB, 16 had a GS of 6 and 15 involved < 5 mm of the biopsy core. Conditional logistic regression analysis showed that CF was not significantly better at detecting PCa compared to systematic biopsy (OR NR)	NR	No significant difference (*p* = 0.66)
Hansen (2018)[95]	Prospective, between-patient	BN	SF vs. CF; SB vs. SF + CF + SB	SF: 395 CF: 176	PCa (PI-RADS 3)	Favours combination biopsy over targeted biopsy alone. No significant difference between combination biopsy and systematic biopsy	SB: 53% CF + SF: 38% SB + SF + CF: 56%	*p* < 0.001 (TB vs. SB + TB) *P* = 0.063 (SB vs. SB + TB)
					PCa (PI-RADS 4–5)	Favours combination biopsy over systematic biopsy or targeted biopsy alone	SB: 80% CF + SF: 73% SB + SF + CF: 88%	*p* < 0.001 (both)
					CSPCa: Gleason ≥ 3 + 4 (PI-RADS 3)	Favours combination biopsy over targeted biopsy alone. No significant difference between combination biopsy and systematic biopsy	SB: 37% SF + CF: 21% SB + SF + CF: 30%	*p* < 0.001 (TB vs. SB + TB) *p* = 0.125 (SB vs. SB + TB)
					CSPCa: Gleason ≥ 3 + 4 (PI-RADS 4–5)	Favours combination biopsy over systematic biopsy or targeted biopsy alone	SB: 61% CF + SF: 59% SB + SF + CF: 71%	*p* < 0.001 (both)

Study	Design	Pop.	Tests	*N*	Outcome (metric)	Summary	Test-positive estimates	Direction of effect/ *p*-value
Ferriero (2022)[81]	Prospective cohort, between patients	BN + RB	SF (Urostation) vs. SF (BioJet)	Urostation: 103 BioJet: 211	PCa per target (%) Definition NR	No significant differences between the two SF types	SF (Urostation): 69.8%, SF (BioJet): 56.6%	Not significant $p = 0.077$
					CSPCa per (%) Definition NR	No significant differences between the two SF types	SF (Urostation): 50.6%, SF (BioJet): 50.6%	Not significant $p = 1.0$
Sokolakis (2021)[83]	Prospective cohort, between patients	BN + RB	SF (BioJet) vs. SF (Trinity) vs. SF (UroNav)	BioJet: 20 Trinity: 20 UroNav: 20	ISUP 1 (N)	No significant difference between the three software types	BioJet: 2, Trinity: 3, UroNav: 3	No significant difference. $p > 0.99$
					ISUP 2 (N)		BioJet: 4, Trinity: 4, UroNav: 4	
					ISUP 3 (N)		BioJet: 4, Trinity: 3, UroNav: 3	
					ISUP 4 (N)		BioJet: 1, Trinity: 2, UroNav: 2	
					ISUP 5 (N)		BioJet: 1, Trinity: 2, UroNav: 1	
Liang (2020)[85]	Retrospective cohort, between patients	BN	SF (Predictive Fusion Software) vs. CF	SF: 92 CF: 71	ISUP 1 (%)	Similar detection rates (within 5%)	SF = 17%, CF = 21%	Significance NR
					ISUP 2 (%)		SF = 14%, CF = 13%	
					ISUP 3 (%)		SF = 9%, CF = 11%	
					ISUP 4 (%)		SF = 8%, CF = 13%	
					ISUP 5 (%)		SF = 3%, CF = 3%	
Lockhart (2022)[100]	Retrospective cohort, between patients	BN, AS	SF (MIM Fusion Software) vs. CF	SF: 131 CF: 223	ISUP 2	Multinomial logistic regression analysis was performed to explore potential factors affecting CSPCa detection rates. Fusion or cognitive biopsy made no difference to CSPCa detection rates	NR	$p = 0.729$

continued

TABLE 44 Additional test positive results from studies not included in the meta-analyses (including alternative outcome definitions and by subgroup) (*continued*)

Study	Design	Pop.	Tests	*N*	Outcome (metric)	Summary	Test-positive estimates	Direction of effect/ *p*-value
Monda (2018)[90]	Retrospective cohort, between patients	BN + RB	SF (UroNav) vs. CF vs. SB (concurrent)	SF/SB: 162 CF/SB: 348	Gleason 6 (%)	Higher rate of PCa detection with cognitive targeted biopsy	SF: 14.4%, CF: 22.8%	Significance NR
					Gleason 7 (%)	Similar rates of detection	SF: 20.1%, CF: 18.5%	Significance NR
					Gleason 8 (%)	Similar rates of detection	SF: 3.4%, CF: 3.1%	Significance NR
					Gleason 9–10 (%)	Similar rates of detection	SF: 4.3%, CF: 5.6%	Significance NR
					Missed targeted biopsy (%) TB < 7 and SB > 7	Similar rates (within 5%)	SF: 5.5%, CF: 9.9%	Not significant $p = 0.172$
					Equivalent (%) TB and SB ≥ 7 or TB and SB < 7		SF: 85.1%, CF: 82.1%	Not significant $p = 0.172$
					Upstage (%) TB ≥ 7 and SB < 7		SF: 9.5%, CF: 8.0%	Not significant $p = 0.172$

AS, active surveillance; BN, biopsy naive; CsPCa, PI-RADS, Prostate Imaging Reporting and Data System; OR, odds ratio; RB, repeat biopsy; SB, systematic biopsy.
a Also compared to Esaote rigid SF system.

TABLE 45 Test-positive rates of PCa and CSPCa by lesion location (anterior, posterior) in FUTURE

Study	SF technology	Route	Anaesthesia	Lesion location	N of lesions	Outcome (definition)	Test-positive rates	Statistical significance
FUTURE (2019)[31]	BiopSee	SF: TP CF: TR	SF: GA CF: LA	Anterior	SF: 37 CF: 25	PCa (NR)	SF: 62.2% CF: 60.0%	$p > 0.9$
						CSPCa (GS: ≥3 + 4)	SF: 48.6% CF: 44.0%	$p = 0.6$
				Posterior	SF: 35 CF: 46	PCa (NR)	SF: 40.0% CF: 26.1%	$p = 0.12$
						CSPCa (GS: ≥3 + 4)	SF: 20.0% CF: 26.1%	$p = 0.7$

TABLE 46 Test-positive rates for patients undergoing repeat biopsy following prior negative biopsy

Study	Population	SF technology	Route[a]	Anaesthesia[a]	Number of patients	Outcome (definition)	Biopsy positive rates	Statistical significance
FUTURE (2019)[31]	Prior negative SB within median 8 months (IQR 4–23)	BiopSee	SF: TP CF: TR	SF: GA CF: LA	SF: 79 CF: 78	PCa (NR)	SF: 49.4% CF: 43.6%	$p = 0.4$
						CsPCa (GS: ≥3 + 4)	SF: 34.2% CF: 33.3%	$p > 0.9$
PROFUS (2014)[97]	Prior negative biopsy (no further details)	ARTEMIS	TR	LA	SF and CF[b]: 34	PCa (NR)	SF: 29.4% CF: 23.5%	NR
						CsPCa (GS: ≥3 + 4)	SF: 20.6% CF: 14.7%	NR

GA, general anaesthetic; IQR, interquartile range; LA, local anaesthetic; SB, systematic biopsy; TP, transperineal; TR, transrectal.
a For SF and CF approaches unless otherwise specified.
b Within-patient comparison.

TABLE 47 Test-positive rates for biopsy-naive patients

Study	SF technology	Route[a]	Anaesthesia[a]	Number of patients	Outcome (definition)	Test positive rate	Statistical significance
Delongchamps (2013)[98]	Urostation Touch (KOELIS)[b]	TR	NR	SF: 82 CF: 54	PCa (NR)	NR[c]	SF vs. SB: $p = 0.006$ CF vs. SB: $p = 0.22$
					CSPCa (NR)	NR[c]	SF vs. SB: $p = 0.001$ CF vs. SB: $p = 0.6$
Ferriero (2022)[81]	Urostation; BioJet	Urostation: TR; BioJet: NR	NR	Urostation: 103 BioJet: 232 (1:1 PS matched cohort, $n = 83$)	PCa **(**GS 6)	Urostation: 69.8% BioJet: 56.6%	$p = 0.077$
					CSPCa (GS ≥ 7)	Urostation: 50.6% BioJet: 50.6%	$p = 1$
Hansen (2018)[95]	BiopSee	TP	GA	SF: 395 CF: 176	PCa (NR)	SF: 53% CF: 38%	NR
					CSPCa ()	SF: 56% CF: 70%	NR
Izadpanahi (2021)[82]	ARTEMIS	TR	LA	SF: 99 CF: 100	PCa (GS 6 and < 4-mm core length)	SF: 44.4% CF: 31.0%	$p = 0.035$
					CSPCa (GS ≥ 7 or GS 6 and ≥ 4mm core length)	SF: 33.3% CF: 19.0%	$p = 0.016$
Liang (2020)[31,85]	bkFusion[d]	TP	LA	SF: 92 CF: 71	PCa (GS 6)	SF: 51.08% CF: 60.56%	$p = 0.228$
					CSPCa ()	SF: 35.87% CF: 39.43%	$p = 0.641$
Lockhart (2022)[100]	bkFusion^	TP	NR	SF + SB: 97 CF + SB: 186	**CS**PCa (GS ≥ 7)	SF + SB: 53% CF + SB: 66.7%	NR

Study	SF technology	Route[a]	Anaesthesia[a]	Number of patients	Outcome (definition)	Test positive rate	Statistical significance
PAIREDCAP (2019)[88]	ARTEMIS	TR	LA	248	PCa (GS 6)	SF: 17.3% CF: 15.3%	NR
					CSPCa (GS ≥ 7)	SF: 54.0% CF: 46.8%	NR
PROFUS (2014)[97]	ARTEMIS	TR	LA	67	PCa (GS 6)	SF: 35.8% CF: 34.3%	NR
					CSPCa (GS ≥ 7)	SF: 28.4% CF: 26.9%	NR

GA, general anaesthetic; LA, local anaesthetic; SB, systematic biopsy; TR, transrectal; TP, transperineal.
a For SF and CF approaches unless otherwise specified.
b Also compared to Esaote rigid SF system.
c Probability of detecting cancer undetected by SB against SB as reference was calculated but NR.
d 'Predictive Fusion Software'.

TABLE 48 Impact of operator experience on PCa detection

Study	Pop.	SF technology	Route	Anaesthesia	Sample size	Number of targeted biopsies	*N* cores per ROI	Effect estimates	*p*-value
Stabile (2018)[89]	BN, RB	BioJet	SF: TP or TR CF: TR	NR	SF: 157 CF: 87	TR SF: 70 TP SF: 87 TR CF: 87	Med (range) SF: 3 (2–3); CF: 2 (2–5)	Learning curve CSPCa detection by operator experience: OR 1.03, 1.06, and 1.01 for operators 1, 2, and 3, respectively CSPCa biopsy positivity rate at first procedure to 60th procedure: Operator 1 (TR CF): 30–57% Operator 2 (TR SF): 15–78% Operator 3 (TP-SF): 70–83%	$p < 0.04$

BN, biopsy naive; RB, repeat biopsy; ROI, regions of interest; TP, transperineal; TR, transrectal.

TABLE 49 Biopsy positivity rates from studies included in the systematic review

Study	Design	Pop.	Biopsy method			Sample size (participants)	Total n of cores	*N* cores	*N* ROI targeted[a]	Biopsy positivity definition	Effect estimates	*p*-value
			Type	Route	Anaesthesia							
SF vs. CF												
Delongchamps (2013)[98]	Consecutive series, between-patient	BN	SF (Urostation Touch)[b] CF	SF and CF: TR	NR	mpMRI + ve KOELIS: 82 CF: 54	NR	Med (range) SF: 3 (2–5) CF: 4 (3–10)	NR	NR	Median % (IQR) SF: 75% (33–100) CF: 67% (20–86)	$p = 0.003$
FUTURE (2019)[31]	RCT, between patient	RB	SF (BiopSee); CF	SF: TP, CF: TR	NR	157 (SF: 79, CF: 78)	SF: 358 CF: 275	Med (IQR) SF: 4 (3–5) CF: 3 (3–4)	All ROI	NR	Mean % (SD) SF: 31.3% (37.8) CF: 33.3% (42.1)	NR
PAIREDCAP (2019)[88]	Prospective cohort, within patient	BN	SF (ARTEMIS); CF; SB	NR	NR	248	SF: 741 CF: 744	3 cores	Index ROI	NR	SF: 38.1% CF: 33.3% SB: 15.7%[c]	SF vs. CF: NS[c]
Software fusion vs. software fusion												
Rabah (2021)[84]	RCT, between patient	BN, RB	SF (ARTEMIS), SF (BioJet)	ARTEMIS: TR BioJet: TP	ARTEMIS: LA BioJet: GA	307	ARTERMIS: 403 BioJet: 338	2–4 cores	All ROI	NR	BioJet: 43.5% ARTEMIS: 21.1%	$p = 0.0002$

BN, biopsy naive; GA, general anaesthesia; IQR: interquartile range; LA, local anaesthesia; NS: not significant; RB, repeat biopsy; SB: systematic biopsy; ROI, regions of interest; TP, transperineal; TR, transrectal.

a Unless specified, the number of cores sampled, and number of ROIs targeted related to both targeted biopsy methods.

b Also compared to Esaote rigid SF system.

c The biopsy positivity rate was significantly higher for targeted biopsies (SF and CF) compared to systematic biopsy $p = 0.008$.

TABLE 50 Summary of safety outcomes: SF vs. CF

Study	Design	Pop.	Biopsy method			Sample size	*N* cores per ROI[a]	Total *N* of cores	Effect estimates	*p*-value
			Type	Route	Anaesthesia					
FUTURE (2019)[31,168]	RCT, between patient	RB	SF (BiopSee , TP) vs. CF (TR)	SF: TP, CF: TR	SF: GA/spinal anaesthesia CF: LA	SF: 79 CF: 78	Median (IQR) SF: 4 (3–5) CF: 3 (3–4)	SF: 358 CF: 275	SF vs. CF: OR 2.27 (95% CI 1.04 to 5.00) (Grade 1–2) Grade 1 AEs (SF: 65.8%; CF: 74.4%); Grade 2 AEs (SF: 5.1%; CF: 10.3%) Grade 1–2 AEs	$p < 0.05$
									SF (%) / CF (%) Haematuria 50.6 / 74.4 Haematospermia 35.4 / 50.0 Rectal bleeding 2.5 / 5.1 UTI 1.3 / 6.4 Fever 2.5 / 5.1 Urinary retention 3.8 / 5.1 Haematoma 3.8 / – Lower back pain 1.3 / – Atrial fibrillation 1.3 / –	
Liang (2020)[85]	Retrospective, between patients	BN	SF (BK Predictive Software) vs. CF (Both TP)	TP	LA	SF: 92 CF: 71	4	NR	SF: 2 AEs (1 post-biopsy fever, 1 bacteraemia). CF: 2 AEs (2 post-biopsy fever). AE grade NR. No patients developed severe bleeding, dysuria, vasovagal reactions, or other complications that required to be addressed.	NR
Monda (2018)[90]	Retrospective; before and after study	BN, RB (+ve/−ve)	SF: UroNav vs. CF. (Both TR)	NR	NR	SF: 348 CF: 162	NR	NR	% patients with complications: CF: 8.6%; SF: 7.2% AE grade NR.	$p = 0.564$

BN, biopsy naive; GA, general anaesthesia; LA, local anaesthesia; RB, repeat biopsy; ROI, regions of interest; TP, transperineal; TR, transrectal.
a Number of cores and number of ROI targeted relate to both targeted biopsy method unless specified otherwise.

TABLE 51 Summary of safety outcomes: comparisons between SF devices

Study	Design	Pop.	Biopsy method			Sample size	*N* cores per ROI[a]	Total *N* of cores	Effect estimates	*p*-value
			Type	Route	Anaesthesia					
Rabah (2021)[84]	RCT, between patient	BN, RB	SF: ARTEMIS (TR) and BioJet (TP)	ARTEMIS: TR BioJet: TP	ARTEMIS: Local BioJet: General	ARTEMIS:165 BioJet: 142	2–4	Artemis: 403 BioJet: 338	Haematuria: 2 ARTEMIS 1 BioJet Urinary retention 7 ARTEMIS 8 BioJet Rectal bleeding 6 ARTEMIS AE grade NR	$p = 0.6$ $p = 0.56$
Sokolakis (2021)[83]	Prospective cohort, between patient	BN, RB	SF: BioJet vs. KOELIS vs. UroNav (All TR)	TR	Local	BioJet: 20 KOELIS: 20 UroNav: 20	2–3	NR	No severe peri- or post operative AEs. Transient AEs common (haematuria, haematospermia and haematochezia)	NR

BN, biopsy naive; RB, repeat biopsy; ROI, regions of interest; TP, transperineal; TR, transrectal.
a Number of cores and number of ROI targeted relate to both targeted biopsy method unless specified otherwise.

TABLE 52 Summary of usability

Study	Design	Pop.	Biopsy methods			Sample size	*N* cores per ROI[a]	Total *N* of cores	Effect estimates
			Type	Route	Anaes-thesia				
Sokolakis (2021)[83]	Prospective, between patient	BN, RB	SF: BioJet, KOELIS, UroNav	TR (all)	LA (all)	BioJet: 20 KOELIS: 20 UroNav: 20	2–3	NR	System Usability Scale [Median (IQR)] Total BioJet: 65 (63.8, 68.1); KOELIS: 38.8 (37.5,45); UroNav: 72.5 (63.8, 80.6) Junior Urologists BioJet: 65 (65, 65); KOELIS: 38.8 (38.1, 39.4); UroNav: 62.5 (61.2, 63.8) Senior urologists BioJet: 68.8 (64.4, 73.1); KOELIS: 48.8 (43.1, 54.4); UroNav: 81.2 (80.6, 81.9) *p*-values NR

BN, biopsy naive; GA, general anaesthesia; LA, local anaesthesia; RB, repeat biopsy; ROI, regions of interest; TR, transrectal.
a Number of cores and number of ROI targeted relate to both targeted biopsy method unless specified otherwise.

Appendix 8 Studies informing model parametrisation and structure

TABLE 53 Study characteristics from targeted review of prevalence, distribution of test results and test accuracy

Study	Study design	Sample size	Population	Biopsy test 1	Biopsy test 2
Mannaerts (2020)[169]	Prospective, Within patient	142	Naive	SF (ARTEMIS)	SB
PAIREDCAP (2019)[88]	Prospective, Within patient	248	Naive	SF (ARTEMIS)	CF
Izadpanahi (2021)[82]	RCT, Between patient	199	Naive	SF (ARTEMIS) + SB	CF + SB
Filson (2016)[96]	Prospective, Within-patient	538[a,b] (273 naive)	Naive, repeat or active surveillance[c]	SF (ARTEMIS)	SB
Alberts (2018)[80]	Prospective, Within-patient	48	Naive, repeat[c]	SF (UroStation)	SB
Mortezavi (2018)[141]	Retrospective	291[b]	Naive, repeat or active surveillance	SF (BiopSee)	TTMB
Zhou (2018)[142]	Prospective, Between patient	153	NR	SF (Hitachi) or CF	TTMB
Simmons (2018)[170]	Prospective, Within patient	200	Repeat	SF (SmartTarget) or CF	TTMB
Hansen (2016)[171]	Retrospective	289[a,b]	Naive, repeat or active surveillance[c]	SF (BiopSee)	TTMB
Kesch (2017)[172]	Prospective, Within-patient	172	Naive, repeat or active surveillance	MRI targeted (both software and cognitive)	TTMB

SB, systematic biopsy.
a Excluding patients currently on active surveillance.
b MRI + ve lesion (PI-RADS ≥ 3).
c Despite included in the study, results by previous biopsy experience were separable.

Prevalence

We were unable to identify any population-level evidence on the prevalence of PCa by ISUP grade. From the 10 studies identified in our targeted review, 5 studies compared MRI-targeted biopsy compared to a template-guided biopsy (template mapping or saturation biopsy (see *Table 54*, *Appendix 8*).[141,142,170–172] The template-guided biopsy does not present perfect accuracy, as the test's accuracy depends on the intensity of cores taken and core (see *Reference standard*). Therefore, to approximate prevalence, and given the assumption of negligible false-positive results to biopsy, we used a 'composite' reference standard combining the template-guided biopsy with the other biopsy method investigated in each study. The results from the five studies included are shown in *Table 54*, *Appendix 8*.

The results show considerable variation between studies with, for example, the prevalence of NC varying between 7.5% and 34% across studies and the prevalence of ISUP grade 4 or 5 cancer from

TABLE 54 Prevalence estimates based on Gleason grade from studies identified in targeted review, using a composite reference standard (PI-RADS ≥ 3)

	Hansen *et al.*[171] Proportion (*N*)			Zhou (2018)[142] Proportion (*N*)	Simmons *et al.*[170] Proportion (*N*)	Mortezavi *et al.*[141] Proportion (N)	Kesch *et al.*[172] Proportion (N)
ISUP	BN	RB	AS				
0	0.306 (26)	0.461 (94)	0.101 (9)	0.340 (52)	0.075 (15)	0.237 (69)	0.276 (35)
1	0.235 (20)	0.181 (37)	0.393 (35)	0.163 (25)	0.210 (42)	0.12 (35)	0.173 (22)
2	0.212 (18)	0.191 (39)	0.270 (24)	0.190 (29)	0.675 (135)	0.285 (83)	0.378 (48)
3	0.129 (11)	0.083 (17)	0.157 (14)	0.131 (20)		0.155 (45)	0.079 (10)
4 or 5	0.118 (10)	0.083 (17)	0.079 (7)	0.176 (27)	0.04 (8)	0.203 (59)	0.094 (12)
N	85	204	89	153	200	291	127

AS, active surveillance; BN, biopsy naive; RB, repeat biopsy following prior negative biopsy.

4% to 20%. The reasons for this heterogeneity are unclear, and may arise from the significant clinical diversity across studies, including in participants (settings of care), diagnostic tests (and in the protocols for their implementation) and outcomes, and/or from the methodological diversity across studies, including variability in study design and risk of bias. The results from Hansen *et al.*[171] suggest that the position of patients in the pathway may be a significant source of heterogeneity.

Distribution of test results obtained with cognitive fusion or software fusion biopsy

The 10 studies identified in the targeted review were potentially relevant to inform the distribution of test results obtained with CF or SF biopsy. Four studies were initially excluded because their population was not considered representative of the NHS.[80,141,170,172] Mortezavi *et al.*[107] and Kesch *et al.*[111] included patients under active surveillance. Simmons *et al.*[109] only included patients with a repeat biopsy, and patients in Alberts *et al.*[80] were selected from a population-wide screening programme.

The distribution of test results obtained from a targeted biopsy for the remaining five studies are presented in *Table 55*, *Appendix 8*. There is considerable heterogeneity in the proportion of patients identified in each Gleason grade group (GG) across the studies.

Therefore, to ensure that the distribution of Gleason grades is representative to the NHS population, the remaining six studies' eligibility criteria were compared to determine which was most representative to NHS practice. According to the NICE guideline NG131 and the PCa diagnostic pathway, patients are referred if their prostate-specific antigen levels are above the age-specific reference range (which, for men aged 50–69 is a PSA level of >3.0 ng/ml) or if their prostate feels malignant (hard, or lumpy) on DRE.[10,17] Furthermore, this DAR is focused on patients with mpMRI visible lesions (PI-RADS 3+), who are biopsy naive, or are undergoing a repeat biopsy (after a negative result). *Table 56*, *Appendix 8* summarises the study eligibility criteria and participant characteristics, and the decisions for inclusion/exclusion.

Two studies[82,142] were not deemed to be appropriate for use in this analysis. Izadpanahi *et al.*[82] limited their population to patients with a PSA > 10 ng/mL; and the population in Zhou *et al.*[142] had a considerably higher baseline PSA compared to the other studies. In addition, the settings of these studies (Iran and China) may not be reflective of NHS practice.

TABLE 55 Distribution of test results for potentially included studies identified from the targeted review (biopsy-naive population only)

	Mannaerts[169]	PAIREDCAP[88]		Izadpanahi[82]		Zhou[142]	Hansen (RB)[171]	Filson (BN)[96]		Filson (RB)[96]	
ISUP	SF (ARTEMIS)	CF	SF (ARTEMIS)	CF + SB	SF + SB	Mixed CF/SF	SF (BiopSee)	SF (ARTEMIS)	SF + S	SF	SF + SB
0	0.140 (7)	0.379 (94)	0.286 (71)	0.690 (69)	0.556 (55)	0.503 (77)	0.642 (131)	0.469 (128)	0.355 (97)	0.687 (182)	0.585 (155)
1	0.040 (2)	0.153 (38)	0.173 (43)	0.190 (19)	0.253 (25)	0.105 (16)	0.103 (21)	0.165 (45)	0.220 (60)	0.087 (23)	0.151 (40)
2	0.380 (19)	0.21 (52)	0.282 (70)	0.060 (6)	0.131 (13)	0.118 (18)	0.167 (34)	0.198 (54)	0.223 (61)	0.102 (27)	0.117 (31)
3	0.280 (14)	0.157 (39)	0.161 (40)	0.050 (5)	0.03 (3)	0.111 (17)	0.088 (18)	0.168 (46)	0.201 (55)	0.125 (33)	0.147 (39)
4/5	0.160 (8)	0.101 (25)	0.097 (24)	0.010 (1)	0.03 (3)	0.163 (25)	0.118 (10)				
N	50	248	248	100	99	153	204	273	273	265	265

BN, biopsy naive; SB, systematic biopsy; RB, repeat biopsy.

Note
Results presented as proportion (*N*).

TABLE 56 Population eligibility criteria for studies that are considered for use to inform the distribution of test results

Study	Country	PSA 3level		DRE exam	Naive/ repeat	Considerations for inclusion or exclusion
		Eligibility criteria	Included patients			
Mannaerts (2020)[169]	The Netherlands	≥ 3.0 – 20 ng/mL	Median (IQR) 6.2 (4.7–8.0)	Suspicious DRE	100% BN	Similar referral pathway: appropriate PSA cut-off and suspicious DRE
PAIREDCAP (2019)[88]	USA	< 25 ng/mL	Median (IQR) 6.2 (4.6–8.2)	Suspicious DRE	100% BN	Similar referral pathway: appropriate PSA cut-off and suspicious DRE
Filson (2016)[96]	USA	'Elevated PSA'	Median (IQR) Naive: 5.8 (4.4–8.1) Repeat: 7.6 (5.0–11.5)	Suspicious DRE	33% BN 32% RB 35% AS	Unclear PSA cut-off, but similar PSA of included patients. Less granularity in Gleason grades (only data on Grade 3+).
Hansen (2016)[171]	UK	'Elevated PSA'	Median (IQR) Naive: 6.2 (4.8–8.6) Repeat: 7.8 (4.8-8.6)	Suspicious DRE	20% BN 55% repeat 25% AS	Unclear PSA cut-off, but similar PSA of included patients. Greater proportion of patients with repeat biopsy, and number of naive patients is small.
Zhou (2018)[142]	China	> 4 ng/mL	Median (IQR) 9.5 (6.5–15.5)	Suspicious DRE	100% BN	Similar referral pathway: appropriate PSA cut-off and suspicious DRE. Concerns regarding high baseline PSA levels in the included patients. Differences in healthcare systems between UK and China.
Izadpanahi (2019)[82]	Iran	> 2–10 ng/dL	Mean (SD) 6.1 ng/dL (1.3)	Suspicious DRE	100% BN	Concerns regarding reporting of PSA-levels (report ng/dL). Limiting PSA levels to < 10 ng/dL was not deemed representative of UK practice. Differences in healthcare systems between UK and Iran.

AS, active surveillance; BN, biopsy naive; IQR, interquartile range.

The remaining four studies[88,96,169,173] were deemed to be most similar to NHS practice, based on population eligibility criteria. All studies applied focused on patients with an elevated PSA and included patients who were referred for suspicious DRE. We considered that only biopsy-naive patients should be included in the analysis, as the vast majority (~90%) of patients in NHS practice will be receiving a first biopsy. Therefore, in the studies where separable data were available, we only included the biopsy-naive patients, as the proportion of patients with repeat biopsy was often high.

Accuracy of cognitive fusion or software fusion biopsy

In order to determine the accuracy of CF or SF biopsy, studies which compared MRI-targeted biopsy (SF and/or CF) against template or saturation biopsy were identified. To determine true disease status as closely as possible, patients were reclassified according to a composite reference standard from both tests. Out of four studies,[141,142,170,171] two provided test accuracy data with the required granularity by ISUP grade.[141,142] The characteristics of these two studies are summarised in *Table 53*, *Appendix 8*. Zhou *et al.*[142] compared SF biopsies [including both SF biopsy (29% of patients) and CF biopsy (71% of patients)] with template-guided transperineal prostate saturation biopsy, although the study did not provide accuracy data for SF biopsy and CF biopsy separately. Mortezavi *et al.*[141] on the other hand, does provide data on accuracy specifically for SF biopsy compared to transperineal template saturation prostate biopsy. Mortezavi *et al.*[141] includes patients who are on active surveillance, who are likely to have a different GS distribution compared with biopsy-naive and prior negative-biopsy patients. However, as accuracy evidence is conditional on true disease status, any such differences in the patient population included are not likely to have a significant impact on conditional accuracy estimates.

Table 57, *Appendix 8*, provides the computed conditional (accuracy) probabilities of patients being identified at a particular grade with MRI-fusion given a particular true disease status given by the composite TMB and MRI fusion results.

The results show significant heterogeneity, with Zhou identifying a higher accuracy at ISUP grade 3 and above. To aid interpretation of these results, we next describe the two further studies which are UK-based and therefore have higher representativeness than both Zhou (2018) or Mortezavi (2018).

Two UK-based studies – Simmons *et al.*[170] and Hansen *et al.*[171] – did not report results with the necessary disaggregation of Gleason grade. Simmons *et al.*[170] reports a within-patient comparison (secondary analysis of PICTURE trial), of TMP biopsy and targeted biopsy (mixture of cognitive and software fusion) but only reported Gleason Grade 1, 2–3 and 4–5 (reported in *Table 58*, *Appendix 8*). The full accuracy matrix by ISUP grade could not be retrieved for Hansen *et al.*,[171] but sensitivity at ISUP grade thresholds of 1 or above, 2 or above and 3 or above could be calculated, against a composite reference standard. The table below compares these sensitivity values, with the results from the studies for which fuller reporting of the accuracy matrices was available (see *Table 59*, *Appendix 8*). As *Table 59* shows, there is also some variation in the sensitivity results between the UK-based studies. The results from Mortezavi (2018),[141] are more similar to Hansen *et al.*[171] at Gleason grade 3 or above, whereas the results of Zhou *et al.*[142] are more similar to Simmons (2018)[170] at the lower GGs. It is therefore unclear what are the relevant source(s) for the between-study heterogeneity observed between Zhou *et al.*[142] and Mortezavi *et al.*,[141] and the representativeness of both these studies to the UK context is uncertain.

TABLE 57 Accuracy probability for SF and/or CF against composite template mapping biopsy and MRI-fusion results

	Zhou (2018) [142] (Software and CF)					Mortezavi *et al.*[141]				
Composite reference standard	**NC**	**ISUP1**	**ISUP 2**	**ISUP 3**	**ISUP 4 or 5**	**NC**	**ISUP 1**	**ISUP 2**	**ISUP 3**	**ISUP 4 or 5**
NC	52/52 (1)	0	0	0	0	69/69 (1)	0	0	0	0
ISUP 1	11/25 (0.44)	14/25 (0.56)	0	0	0	24/35 (0.69)	11/35 (0.31)	0	0	0
ISUP 2	13/29 (0.45)	1/29 (0.03)	15/29 (0.52)	0	0	21/83 (0.25)	17/83 (0.20)	45/83 (0.54)	0	0
ISUP 3	1/20 (0.05)	1/20 (0.05)	2/20 (0.10)	16/20 (0.80)	0	10/45 (0.22)	2/45 (0.04)	9/45 (0.20)	24/45 (0.53)	0
ISUP 4 or 5	0/27 (0)	0/27 (0)	1/27 (0.04)	1/27 (0.04)	25/27 (0.93)	6/59 (0.1)	2/59 (0.03)	7/59 (0.12)	8/59 (0.14)	36/59 (0.61)

Results are presented as *N* (%).

TABLE 58 Accuracy probability for MRI fusion against composite template mapping biopsy and MRI-fusion results – Simmons *et al.*[170]

	MRI fusion biopsy (mix of software and cognitive)			
Composite reference standard	**NC**	**ISUP grade 1**	**ISUP grade 2 or 3**	**ISUP grade 4 or 5**
NC	15/15 (1)	0	0	0
ISUP grade 1	25/42 (0.60)	17/42 (0.40)	0	0
ISUP grade 2 or 3	15/135 (0.11)	21/135 (0.16)	99/135 (0.73)	0
ISUP grade 4 or 5	1/8 (0.13)	0/8 (0.00)	2/8 (0.25)	5/8 (0.63)

TABLE 59 Sensitivity of MRI-fusion biopsy against reference standard for UK studies, compared to studies with fuller reporting of accuracy matrices

	Sensitivity against composite reference standard			
	Hansen *et al.*[171]	**Simmons *et al.*[170]**	**Mortezavi *et al.*[141]**	**Zhou *et al.*[142]**
ISUP grade ≥ 1	0.670 (73/109)	0.778 (144/185)	0.725 (161/222)	0.752 (76/101)
ISUP grade ≥ 2	0.712 (52/73)	0.741 (106/143)	0.690 (129/187)	0.789 (60/76)
ISUP grade ≥ 3	0.529 (18/34)	NA	0.654 (68/104)	0.894 (42/47)

TABLE 60 Long-term outcome studies

Study	Design	Population	Treatment	Comparator	Outcome
Radical radiotherapy					
ACENDE-RT[103,174,175]	RCT *n* = 398	Intermediate–high risk. CPG 4–5	Low-dose-rate brachytherapy + esxternal beam radiotherapy	Dose-escalated external beam radiation therapy	Local recurrence, distant metastases, OS (KM). F-u up to 10years
HYPRO[104,176]	RCT, *n* = 820	Intermediate–high risk	Hypofractionated radiotherapy	Conventional radiotherapy	OS, 7-year relapse free survival, AE F-u up to 10years
PROFIT[105]	RCT, *n* = 1206	Intermediate	Hypofractionated radiotherapy	Conventional radiotherapy	OS, biochemical failure, AE, f-u up to 5years HRQOL-48 weeks
CCHiP[106,177]	RCT, *n* = 3216	Intermediate–high risk	Hypofractionated radiotherapy	Conventional radiotherapy	OS, relapse-free survival, AE F-u up to 8 years
HYPO-RT-PC[107,178]	RCT *n* = 1180	Intermediate–high risk	Ultra-hypofractionation	Conventional fractionated radiotherapy	Failure free survival and PCa-specific survival (5year) QoL (6years)
Marzi (2009)[108]	RCT, *n* = 162	Intermediate–high-risk Gleason 7–10	Hypofractionated radiotherapy	Conventional radiotherapy	OS. f-u 30 months

continued

TABLE 60 Long-term outcome studies (*continued*)

Study	Design	Population	Treatment	Comparator	Outcome
Radiotherapy + ADT vs. radiotherapy alone					
Kishan, (2022)[111]	IPD M-A	Intermediate–high risk	Radiotherapy + ADT (incl. as prolongation therapy)	Radiotherapy alone	Metastasis-free survival (KM) OS (KM). 11.4 years f-u. Biochemical recurrence, distant metastasis.
Prostatectomy vs. observation					
PIVOT[109,179]	RCT	Low, intermediate and high	Radical prostatectomy	Watchful waiting	OS, PCa death, distant metastases, AEs f-u 22.1years
SPCG4[110,180]	RCT	Localised, non-metastatic	Radical prostatectomy	Watchful waiting	Overall mortality, PCa death, distant metastases, AEs, QoL F-u: 29 years
Radical prostatectomy vs. radical radiotherapy vs. observation					
PROTecT[55,114]	RCT *n* = 1643	Localised, non-metastatic	Radical prostatectomy, radical radiotherapy	Active monitoring	PFS, patient-centred outcomes F-u: median 10years
DTX and hormone-sensitive therapy					
STAMPEDE[59,143]	RCT, *n* = 1776	High-risk PCa (Gleason 8–10) and metastatic	ADT plus DTX and estramustine	ADT alone	OS, PFS. F-u: 6.5years
GETUG 12[60,181]	RCT, *n* = 413	High-risk PCa (Gleason 8–10)	Addition of DTX, zoledronic acid/ estramustine, or both to first-line long-term hormone therapy	Long-term hormone therapy	OS, PFS F-u: 12 years
TAX-3501[61]	RCT *n* = 228	Metastatic, post-radical prostatectomy	DTX and leuprolide	Leuprolide alone	OS, PFS, AEs, f-u 3.4 years

TABLE 61 Summary of potentially eligible long-term evidence for PCa considered to parametrise the economic model

Study	Patient group, enrolment period	Location	Design, interventions if RCT	Mortality and disease progression-related outcomes, maximum FU	Conclusions
Bill-Axelson (2011) (SPCG4}[110]	Localised disease (1989–9)	Sweden, Finland, Iceland	RCT, watchful waiting vs. radical prostatectomy	Reported at 15 years: – all-cause mortality – PCa death – distant metastases – local progression	Radical prostatectomy was associated with a reduction in the rate of death from PCa.
Wilt (2012) (PIVOT) [109]	Localised disease (1994–2002)	USA	RCT, observation vs. radical prostatectomy	Reported at 10 years: – all-cause mortality – PCa death – bone metastases	Prostatectomy did not significantly reduce all-cause or PCa mortality.

TABLE 61 Summary of potentially eligible long-term evidence for PCa considered to parametrise the economic model (*continued*)

Study	Patient group, enrolment period	Location	Design, interventions if RCT	Mortality and disease progression-related outcomes, maximum FU	Conclusions
James (2015) (STAMPEDE)[113]	Metastatic disease (2005 and 2014)	UK and Switzerland	RCT, SOC arm (androgen deprivation therapy)	Reported at 5 years: – failure-free survival – all-cause mortality	Survival remains disappointing in men presenting with M1 disease who are started on only long-term androgen deprivation therapy.
James (2016) (STAMPEDE)[59]	High-risk and metastatic disease (2005 and 2013)	As above	RCT, SOC as above vs. SOC + zoledronic acid vs. SOC + DTX, vs. SOC + zoledronic acid and DTX	Reported at 7 years: – OS – failure-free survival	Zoledronic acid showed no evidence of survival improvement DTX showed evidence of improved survival accompanied by an increase in AEs.
Clarke (2019) (STAMPEDE)[143]	Metastatic disease (2005 and 2013)	As above	RCT, SOC arm (androgen deprivation therapy)	Reported at 6.5 years: – metastatic burden – OS – failure-free survival	The survival benefit for upfront DTX is maintained at longer follow-up. No evidence that the benefit differs by metastatic burden.
Hamdy (2016) (ProtecT) [55]	Localised disease (1999–2009)	UK	RCT, active monitoring vs. radical prostatectomy, vs. radiotherapy	Reported at 10 years: – adherence – PCa death – all-cause mortality – metastases – disease progression	No significant difference among – active monitoring; – radical prostatectomy; and – radiotherapy.
Bryant (2020) (ProtecT)[114]	As above	As above	As above	Reported at 10 years: – disease progression	There are differences in risk categorisation between men who progressed during PROTecT and those that did not. Different grade, low/intermediate/high risk.
Widmark (2019) (HYPO-RT-PC)[107]	Intermediate- to high-risk aPCa (2005–15)	Sweden and Denmark	–Ultra-hypofractionated vs. conventionally fractionated radiotherapy	Reported at 5 years: – failure-free survival – disease-free survival – PCa survival – OS	Ultra-hypofractionated radiotherapy is non-inferior to conventionally fractionated radiotherapy.
Gnanapragasam (2016)[112]	Localised or locally advanced disease (2000–10)	UK	Observational, exploring the prognostic ability of five levels of CPG scores	Reported at 13.7 years: – PCa death Reported at 9.6 years: – all-cause mortality	The five-stratum CPG system outperforms the standard three-stratum risk system in predicting the risk of PCa death.

Appendix 9 Review of cost-effectiveness evidence

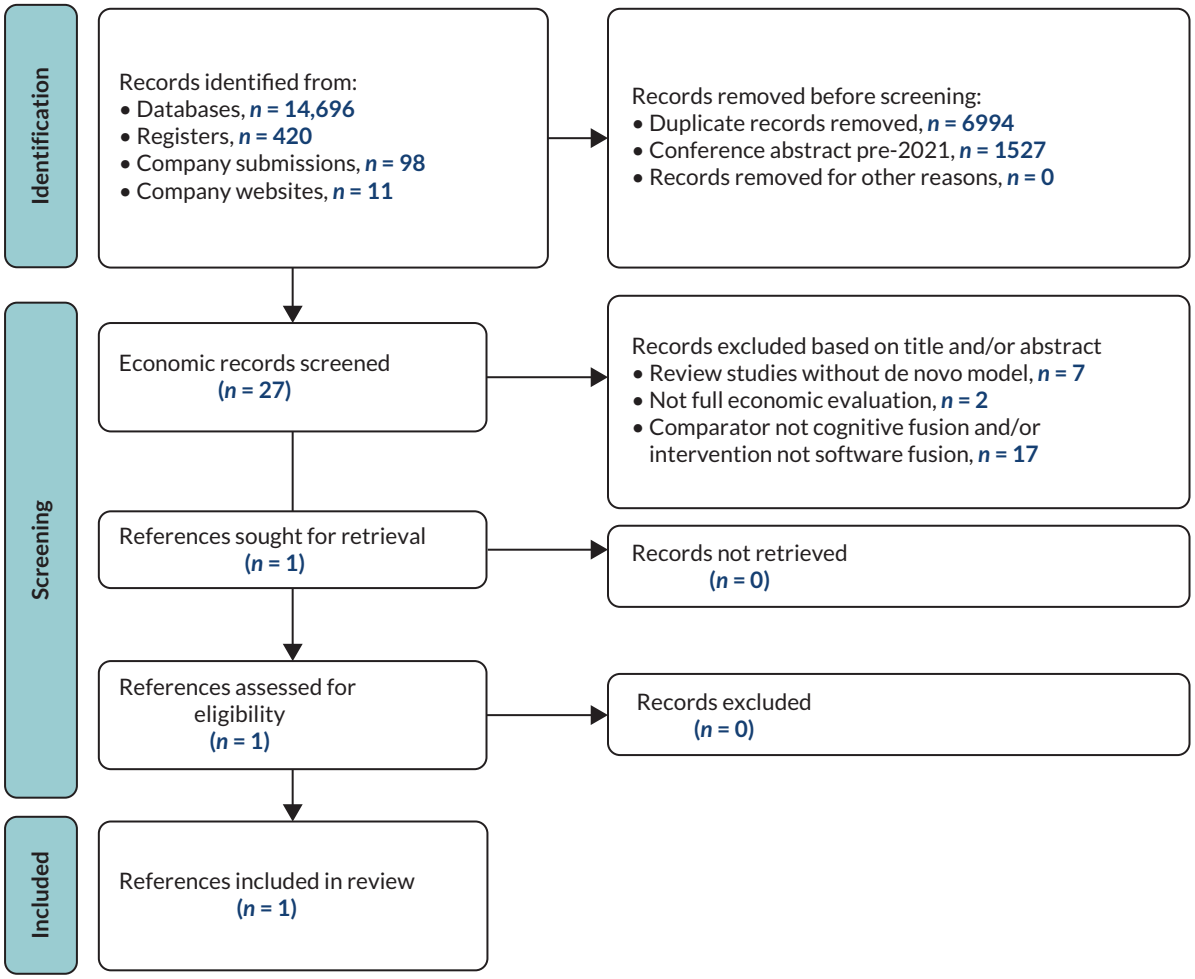


FIGURE 17 PRISMA flow diagram for cost-effectiveness of SF systems review.

Critical appraisal of cost-effectiveness studies of MRI Fusion systems Pahwa *et al.* (2017)

TABLE 62 Yang *et al.*[115] checklist for model-based economic evaluations of diagnostic tests: Pahwa *et al.*[117]

	Response (Y, N or NA)	Comments
1. Decision problem and scope specified		
Is there a clear statement of the decision problem?	Y	
Is the perspective of the model stated clearly?	N	
Has the target population been identified?	Y	

continued

TABLE 62 Yang (2019)[115] Checklist for model-based economic evaluations of diagnostic tests: Pahwa (2017)[117] (*continued*)

	Response (Y, N or NA)	Comments
Are the model inputs consistent with the stated perspective?	NA	Perspective not stated clearly.
Are the primary outcomes of the model consistent with the perspective, scope and overall objective of the model?	NA	Perspective not stated clearly.
2. Identification and description of the comparators		
Have all the feasible and practical options been identified?	Unclear	Authors do not state whether there are other feasible and relevant alternatives.
Have the comparators being evaluated been clearly described?	Y	
If comparators have been excluded from the evaluation, have these exclusions been justified?	NA	
3. Appropriate data identification		
Are the data identification methods transparent, systematic and appropriate given the objectives of the model?	N	The data identification methods are not described.
4. Sufficient detail for data incorporation		
Have all data incorporated into the model been described and referenced in sufficient detail?	Y	
Where choices have been made between data sources, are these justified appropriately?	N	
Are transition probabilities calculated appropriately?	NA	Not a state transition model.
Has discounting been conducted?	Y	
5. Quality and incorporation of test accuracy data		
Has the quality of the test accuracy data been assessed?	N	
Have diagnostic accuracy data been derived from high quality data sources (hierarchy of evidence)?	NA	Sources of data to inform data accuracy are not described in sufficient detail to establish quality of data.
Are tests in sequence treated dependently, where appropriate?	N	Dependencies between tests in a sequence not modelled (implicit assumption of independence between tests in each sequence).
6. Quality and incorporation of treatment data		
Has the quality of the treatment effect data been assessed?	N	Linkage to long-term outcomes is done via lifetime pay-offs applied to diagnostic decision tree – relative treatment effects are not applied in the model.
Have relative treatment effects been derived from high-quality data sources (hierarchy of evidence)?	NA	
7. Source and incorporation of cost data		
Has the source of cost data been presented clearly?	Y	
Have costs been inflated to a specific year, where appropriate?	Y	

TABLE 62 Yang (2019)[115] Checklist for model-based economic evaluations of diagnostic tests: Pahwa (2017)[117] (*continued*)

	Response (Y, N or NA)	Comments
8. Source and incorporation of utility data		
Is the source for the utility weights referenced and justified?	N	Assumption that 1 LY corresponds to 1 QALY in healthy individuals (no PCa) is not supported by empirical data.
Are the utilities incorporated into the model appropriately?	Unclear	Most QALYs are estimated directly from an external Markov model.
9. Model structure		
Have the reasons behind the type of decision-analytic model chosen been fully described and justified?	N	
Has a systematic review of existing economic evaluations been carried out?	N	
Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	NA	The structure of the model is not sufficiently described or depicted to assess whether it is consistent with the health condition.
Are the structural assumptions underpinning the model transparent and justified?	Partly	Not all assumptions are justified, and some assumptions are not explicit (e.g. independence between results of tests in a sequence).
Have the methods used to extrapolate short-term results to final outcomes been documented and justified?	NA	Linkage to long-term outcomes is done via lifetime pay offs applied to diagnostic decision tree.
Has the time horizon been stated and justified?	Y	
Has cycle length of Markov models been justified?	NA	Not a Markov model.
10. Uncertainty		
Has parameter uncertainty been addressed via sensitivity analysis?	Y	One-way sensitivity analysis.
Has probabilistic sensitivity analysis been carried out? If not, has this omission been justified?	Y	
If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Partly	The ranges used are not clearly justified for most parameters.
If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	N	Probability distributions for each parameter are not described.
Have structural uncertainties been addressed via sensitivity analysis?	N	
Have alternative assumptions related to final outcomes been explored through sensitivity analysis?	N	
Has value of information analysis been done?	N	
11. Validity		
Has the face validity been reviewed by someone external to the model developers?	N	Not described

continued

TABLE 62 Yang (2019)[115] Checklist for model-based economic evaluations of diagnostic tests: Pahwa (2017)[117] (*continued*)

	Response (Y, N or NA)	Comments
Has the mathematical logic of the model been assessed? (e.g. using null and extreme values)	N	Not described
Have the model and its results been compared to the findings of other models and studies, and any disagreements or inconsistencies been explained (cross-validity)?	Y	

LY, life-year; N, no; Y, yes.

Results of the additional targeted reviews to support model conceptualisation

The searches described in *Systematic review methods (study selection, data extraction, quality assessment)* identified 27 titles of which 16 did not meet the inclusion criteria based on title and/or abstract. Full-text publications were obtained for the remaining 10 records.[119,120,122,124–126,129–132] In addition, economic studies were identified from a systematic review in a previous DAR by the Southampton EAG.[116] We identified five additional publications from the previous DAR economic evidence review.[121,123,127,128,133]

In total, 16 titles comprising 15 cost-effectiveness models[116,119–133] were considered potentially relevant to inform the de novo model conceptualisation for inclusion. We note that the Wilson *et al.*[121] model is structurally similar (and shares many common evidence sources) to the cost-effectiveness model developed in the context of the PROMIS trial[125,126] (henceforth referred to as the PROMIS model), although it does not model the full range of strategies in PROMIS. Similarly, the Southampton DAR model[116] is an extension of the model developed in the context of the 2019 update of the NICE CG131[123] (henceforth referred to as the NICE CG131 model). These studies are summarised in *Table 63*.

The majority of identified studies aimed to evaluate the cost-effectiveness of strategies for initial PCa diagnosis involving biopsy approaches.[116,119,121,123,125,126,129–132] The study populations in some of these diagnostic studies included only biopsy-naive individuals[121,125,126,129–132] while others included biopsy-naive individuals and those with a previous negative biopsy.[116,123] The population in Mowatt *et al.*[133] included only individuals who had had a previous negative biopsy. Three studies evaluated alternative prostate diagnostic strategies in the context of PSA based screening.[120,122,124] One study examined alternative protocols of active surveillance for those diagnosed with low-risk PCa.[127] One study examined the use of mpMRI and MRI-influenced biopsy as an alternative in the evaluation of PCa biomarkers.[128]

In the majority of the identified studies a cohort simulation modelling approach using a combined decision tree and Markov model structure was applied.[116,119,121,123,125–130,132,133] In these models, the decision tree component modelled the diagnostic/screening pathway to classify individuals according to their true disease and diagnostic outcomes, while the Markov model component linked the diagnostic outcomes (and subsequent clinical management decisions) to the long-term effects on outcomes. Other cohort models relied solely on a decision tree structure[129] or a Markov model structure[131] to evaluate the cost-effectiveness of the alternative strategies. One cohort model was described as a partially observable Markov model,[124] and distinguishes between unobservable pretreatment [or preclinical (i.e. prior to the presentation of any disease signs or symptoms)] and observable (or clinical) states. Two studies used a continuous-time microsimulation (i.e. patient level) model calibrated to registry data. These models had two main model components to reflect 1) PCa natural history (from preclinical to clinical cancer) and 2) its diagnostic and treatment pathways.[120,122]

TABLE 63 Studies identified as potentially relevant to inform model conceptualisation

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Souto-Ribeiro (2022),[116] UK To assess the CE of LATP vs. LATRUS and GATP in men with suspected PCa for whom prostate biopsy is indicated	First biopsy (+): treated (–): % discharged/monitored and % Second biopsy; →second biopsy (–): discharged/monitored; second biopsy (+): treated Biopsy options: First biopsy – LATP (w/wo specific freehand devices)/GATP/LATRUS; second biopsy – LATRUS	Histopathological definition: GS ≥ 4 and/or a cancer core length ≥ 4 mm Clinical definition: - CNSPCa: GS ≤ 6, PSA ≤ 10 ng/ml and T1–T2a stage (=LR) - CSPCa: Gleason = 7, PSA 10–20 ng/ml and T2b stage (=IR); or GS ≥ 8, PSA > 20 ng/ml and ≥T2c stage (=HR)	Probabilities of TRUS detecting CNS and CSPCa (stratified by LR, IR, HR) RRs for PCa detection rates for LATP and GATP vs. LATRUS are applied to baseline probabilities (with LATRUS) Specificity of detecting PCa	Decision tree: classifies patients according to diagnostic accuracy, true disease status and underlying risk category. Tree also captures biopsy complications + Markov model capturing treatment allocation conditional on classification and longer-term outcomes Health states: No PCa; unDx LR; unDx IR; unDx HR; unDx metastatic; Dx LR; Dx IR; Dx HR; Dx metastatic; PCa death; other-cause death.	Via Markov model capturing sequential disease progression from lower to higher risk category (LR→IR→HR) of localised disease and from HR to metastatic disease. PCa mortality only applies to metastatic disease.
Wilson (2021),[121] UK To assess the CE of LATP vs. LATRUS for men at risk of PCa who are referred to secondary care investigations	mpMRI (No/CNSPCa): discharged/monitored; mpMRI (CSPCa); →first biopsy (CSPCa): treated; first biopsy (No/CNS PCa) →second biopsy (No/CNS PCa): discharged/monitored; second biopsy (CSPCa): treated Biopsy alternatives: LATP or LATRUS	Histopathological definition: NR Clinical definition: Text suggests LR is equivalent to CNS PCa, and IR/HR to CSPCa, but the risk categories are not defined.	Probabilities of detecting No PCa, LR, IR or HR conditional on true disease status and previous test results (mpMRI/biopsy) Specificity of detecting PCa	Decision tree: classifies patients according to diagnostic accuracy, true disease status and underlying risk category. Tree also captures biopsy complications and treatment allocation. + Markov model capturing longer-term outcomes Health states: no PCa (?); progression-free, metastatic disease, death	Via Markov model capturing disease progression from localised disease to metastatic disease. PCa mortality only applies to metastatic disease.

continued

TABLE 63 Studies identified as potentially relevant to inform model conceptualisation (*continued*)

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Cheng (2021),[119] Singapore To assess the CE of diagnostic strategies involving combined biopsy in sequences (with/wo SBx/ TPMB) for men with suspected PCa based on elevated PSA and/ or abnormal DRE	Test sequence in each strategy: 1. Combined biopsy 2. Combined biopsy→(−): SBx 3. Combined biopsy→(−): TPMB 4. Combined biopsy→(−): SBx→(−): TPMB 5. SBx→(−): Combined biopsy 6. SBx→(−): Combined biopsy→(−): TPMB Where combined biopsy means: mpMRI → PI-RADS 1,2: % no biopsy and % SBx; PI-RADS 3+: Combined biopsy; individuals with biopsy(+) receive treatment	Histopathological definition: NR; Clinical definition - CNSPCa: GS < 7, PSA < 10 ng/ml; and T1–T2a stage (=LR) - CSPCa: GS = 7, or PSA 10–20ng/ml; or T2b stage (=IR); or GS > 7, PSA > 20ng/ml; or ≥ T2c stage (=HR)	For SBx, TBx and combined biopsy: Probabilities of detecting LR, IR, HR conditional on true disease status and prior test results For TPMB: Specificity of detecting PCa, sensitivity to detect LR, IR, HR	Decision tree: classifies patients according to diagnostic accuracy, true disease status and underlying risk category + Markov model capturing treatment allocation conditional on classification and longer-term outcomes Health states: No PCa, unDx localised PCa, metastatic PCa, correctly Dx localised LR (3 separate treatment health states: WW, AS, RTx ± ADT) localised IR Dx LR (3 separate treatment health states: WW, AS, RTx ± ADT), correctly Dx localised LR (2 separate treatment health states: WW, RTx ± ADT), PCa death, all-cause death.	Via Markov model capturing: - Primary treatment allocation and subsequent treatment changes - disease progression from localised to metastatic disease PCa mortality only applies to metastatic disease.
Hao (2021), Sweden To assess the CE of diagnostic strategies involving TBx, SBx or combined biopsy for men undergoing (or eligible for) quadrennial PSA screening	1. No PSA screening (assumes average 2. SBx for symptomatic identification) Screening strategies If PSA ≥ 3 ng/mL: 2. SBx 3. mpMRI → PI-RADS < 3: rescreening; PI-RADS ≥ 3: TBx 4. mpMRI → PI-RADS < 3: rescreening; PI-RADS ≥ 3: Combined biopsy 5. mpMRI → PI-RADS < 3: SBx; PI-RADS ≥ 3: Combined biopsy Where individuals with biopsy (+) receive treatment, and those with biopsy (−) return to screening	NA	FN rates conditional on the true disease status (ISUP GG1 or GG ≥ 2) Specificity of detecting PCa	Continuous time microsimulation PCa natural history model Health states: – No PCa .Preclinical states: ISUP GG1, T1–T2; ISUP GG1, T3–T4; ISUP GG1 metastatic; ISUP GG2–3, T1–T2; ISUP GG2–3, T3–T4; ISUP GG2–3 metastatic; ISUP GG4–5,T1–T2; ISUP GG4–5, T3–T4; ISUP GG4–5, metastatic – Clinical states: ISUP GG1, ISUP GG1,T1–T2; ISUP GG1, T3–T4; ISUP GG1 metastatic; ISUP GG2–3,T1–T2; ISUP GG2–3, T3–T4; ISUP GG2–3 metastatic; ISUP GG4–5, T1–T2; ISUP GG4-5, T3–T4; ISUP GG4–5, metastatic. – Diagnosis and treatment submodel for clinical states: diagnosis; localised T1, T2, T3, T4, ISUP GG1 or GG2 + treatment (AS, RP and /or RT, post treatment follow-up), metastatic (treatment, palliative care, terminal illness) – other-cause death; PCa death	Via microsimulation model capturing – disease onset and progression from preclinical to clinical PCa. – preclinical states reflect disease onset by ISUP GG and progression by T stage to metastatic PCa (from T1–T2→T3–T4→metastatic PCa) – disease progression in clinical states seems to be from localised to metastatic – Primary treatment allocation and subsequent treatment changes PCa mortality only applies to metastatic disease in clinical states.

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Getaneh (2021),[122] The Netherlands To assess the CE of adding mpMRI as triage test between PSA and biopsy for population-based triennial screening	Screening strategies: 1. (not described) PSA screening protocol involving TRUS 2. PSA → PSA < 3 ng/mL: no further assessment; PSA ≥ 3 ng/mL: mpMRI → PI-RADS < 3: no biopsy; PI-RADS ≥ 3: TBx Individuals with biopsy (+) receive treatment, and those with biopsy (–) return to screening (not explicit)	NR	TBx: – Sensitivity to detect LG and HG[a] PCa – Misclassification rate (HG classified as LG) TRUS: – Biopsy sensitivity (not specified whether it applies to PCa or PCa significance) – Misclassification rate (HG classified as LG)	Microsimulation screening analysis; life history model w/wo screening Health states: – No PCa – Preclinical states: T1, GS < 7; T1, GS = 7; T1, GS > 7; T2, GS < 7; T2, GS = 7; T2, GS > 7; T3, GS < 7, T3, GS = 7; T3, GS > 7; each state can be local-regional or distant metastatic (18 health states in total) – Clinical states: T1, GS < 7; T1, GS = 7; T1, GS > 7; T2, GS < 7; T2, GS = 7; T2, GS > 7; T3, GS < 7, T3, GS = 7; T3, GS > 7; each state can be local-regional or distant metastatic; death (18 health states in total plus death)	Via microsimulation model capturing disease onset and progression from preclinical to clinical PCa by screening or clinical diagnosis preclinical states reflects disease onset at T1–GS < 7 or T1–GS > 7; then progression by T stage (T1→T2→T3→T4) and GS (GS < 7→GS = 7→GS > 7); any state can progress from local-regional state to distant state – Disease progression in clinical state is not modelled – Primary treatment allocation based on age, T stage, GS PCa mortality only applies at clinical states.
NICE (2019),[123] UK To assess the CE of follow-up protocols for people who have a raised PSA, MRI(–) and/or (–) biopsy	Alternative follow-up protocols, defined according to: - Type of screening test and the related threshold (e.g. PSA derivatives); - Frequency of the screening test; - Type of biopsy if the previous test positive (e.g. TRUS or TPMB); - Stopping rule – defines the duration of follow-up for each strategy.	Histopathological definition: GS ≥ 3 + 4 or cancer core length ≥ 4mm Clinical definition: - CNSPCa: Gleason scor < 7 or cancer core length < 4 mm or PSA ≤ 10 ng/mL (=LR) - CSPCa: GS = 7 or cancer core length ≥ 4 mm; PSA 10–20 ng/mL (=IR); or GS ≥ 8 or cancer core length ≥ 4 mm; PSA > 20 ng/mL (=HR)	Sensitivity to detect CNS and CSPCa for SBx, and: adjusted by relative sensitivity of TBx vs. SBx, if TBx) adjusted by relative sensitivity of first vs. subsequent biopsy if second biopsy	Decision tree: classifies patients according to diagnostic accuracy, true disease status and underlying risk category + Markov model capturing treatment allocation conditional on classification and longer-term outcomes Health states: No PCa; unDx LR; unDx IR; unDx HR; unDx metastatic; Dx LR; Dx IR; Dx HR; Dx metastatic; PCa death; other-cause death.	Via Markov model capturing disease onset and sequential disease progression from lower to higher risk category (LR→IR→HR) of localised disease and from HR to metastatic disease. PCa mortality only applies to metastatic disease.

continued

TABLE 63 Studies identified as potentially relevant to inform model conceptualisation (*continued*)

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Faria (2018)[125]/ Brown (2018),[126] UK To assess the CE of combinations of mpMRI, TRUS, TPMB for the diagnosis of PCa in men referred to secondary care investigations	383 strategies with alternative combinations of mpMRI, TRUS, and TPMB, which differ in terms of: - whether or not, and when (to guide TRUS or to inform repeat biopsy) to use mpMRI; - the type of biopsy (TRUS-guided or TPM); - whether repeat biopsy is allowed and who receives it conditional on previous test results; - definition of suspicious lesion on mpMRI (4 alternative cut-offs) - definitions of CSPCa (2 alternatives)	Histopathological definition: 1. dominant Gleason pattern ≥ 4 and/or any Gleason pattern 5 and/ or cancer core length ≥ 6mm; or 2. any Gleason pattern ≥ 4 and/ or cancer core length ≥ 4 mm Clinical definition: - CNS PCa: PSA ≥ 10 ng/ml and GS ≥ 6 (=LR) - CSPCa: PSA 10-15 ng/ml and GS (=IR); or GS ≥ 8 (=HR)	Probability of detecting PCa, CNS or CSPCa conditional on true risk category of LR, IR, HR Specificity of detecting PCa	Decision tree: classifies patients according to diagnostic accuracy, true disease status and underlying risk category + Markov model capturing treatment allocation and longer-term outcomes Health states: no PCa(?), localised PCa, metastatic disease, death	Via Markov model capturing disease progression from localised disease to metastatic disease. PCa mortality only applies to metastatic disease.
Barnett (2018),[124] US To assess the CE of diagnostic strategies involving MRI and TBx (alone or combined) for men undergoing biennial PSA screening	1. No PSA screening Screening strategies If PSA > 4 ng/mL: 2. SBx 3. MRI → PI-RADS < 3: SBx; PI-RADS 3+: TBx 4. MRI → PI-RADS < 3: no biopsy; PI-RADS 3+: TBx 5. mpMRI → PI-RADS < 3: SBx; PI-RADS 3+: Combined biopsy 6. mpMRI → PI-RADS < 3: no biopsy; PI-RADS 3+: Combined biopsy TBx performed with MRI fusion Individuals with biopsy (+) receive treatment, and those with biopsy (–) return to screening (not explicit)	Histopathological definition: - high-volume tumour and GS 3 + 4 or GS ≥ 4 + 3 (high grade disease) Clinical definition: any GS ≥ 7	SBx: – Sensitivity of detecting PCa – Probability of incorrect grading for (+) biopsy TBx and combined biopsy: – sensitivity and specificity for high-grade cancer	Partially observable Markov model capturing screening/diagnostic outcomes (via implicit decision tree[b] embedded in the model), treatment allocation and longer-term outcomes. Health states: – no PCa; other-cause death; – pretreatment PCa states (unobservable): organ confined GS < 7, organ confined GS = 7, organ confined GS > 7, EPLN – detected PCa: PCa treatment (AS or RP), no recurrence following treatment (NRFT), possible recurrence following treatment, metastatic PCa, PCa death.	Via partially observable Markov model capturing: – Onset of PCa – Primary treatment allocation – Disease progression from localised to metastatic disease PCa mortality only applies to metastatic disease in detected states.

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Patel (2018),[127] Netherlands To assess the CE of AS strategies for men with LR	1. 3-yearly SBx biopsy → biopsy (–): AS; biopsy (+): treated 2. 3-yearly mpMRI → mpMRI (–): AS; mpMRI (+): TBx → biopsy (–): AS; biopsy (+): treated 3. 3-yearly mpMRI → mpMRI (–): AS; mpMRI (+): treated mpMRI (+)/(–) defined in relation to presence of HR. All biopsies are performed via TRUS	Histopathological definition: GS ≥ 7 Clinical definition: NR, but text suggests that LR (PSA < 10 ng/ml, GS < 6, and stage T2a) is equivalent to CNS PCa and HR (GS ≥ 7) to CSPCa	Sensitivity and specificity of detecting HR	Markov model capturing diagnostic outcomes (via implicit decision tree embedded in the Markov model) and longer-term outcomes Health states: LR, HR, survival after treatment LR, survival after treatment HR, death (due to PCa or other causes)	Via Markov model capturing disease progression from LR to HR. PCa mortality only applies to individuals with HR.
Sathianathen (2018),[128] US To assess the CE of biomarkers in determining the need for biopsy in men with elevated PSA	1. SBx 2-5. biomarker → (< cut-off): followed-up (not explicit); (≥ cut-off): SBx 6. mpMRI → mpMRI(–): followed-up; mpMRI(+): TBx Biomarkers: phi, 4Kscore®, SelectMDx™ and the EPI [ExoDx™ Prostate (Intelli-Score)] Where individuals with biopsy (+) receive treatment, and those with biopsy (–) are followed up. SBx is performed via TRUS. mpMRI (+)/(–) is not defined	NR	Sensitivity of detecting LG and HG PCa	Decision tree: classifies patients according to diagnostic accuracy, true disease status + Markov model for Dx PCa (not described) + State transition model (not described) for unDx PCa capturing risk of clinical diagnoses due to symptoms and risk of metastasis by clinical diagnosis Health states: NR	NR
Pahwa *et al.*,[129] US To assess the CE of SBx and TBx (with alternative MRI-influence method (MRI fusion, CF or in-bore) for biopsy-naive men with elevated PSA and /or CS DRE	1. SBx 2–4. mpMRI→(no suspicious lesions): discharged; (suspicious lesions): TBx 5–7. mpMRI→(no suspicious lesions): SBx; (suspicious lesions): TBx Where individuals with biopsy (+) receive treatment, and those with biopsy (–) are discharged. All biopsies are performed via TRUS	Histopathological definition(?): CNS PCa: GS < 6 and tumour volume < 0.5 cm^3 Clinical definition: NR, but text suggests that CNS PCa is equivalent to LR and CSPCa to HR	Sensitivity for detecting PCa, CNS and CSPCa Specificity for PCa Probability of correctly classifying tumour aggressiveness	Decision tree classifies patients according to diagnostic accuracy, true disease status and allocates primary treatment	Via lifetime health and cost payoffs conditional on diagnostic status (diagnosed/missed), primary treatment, and age Pay-offs are informed by outcomes of an external Markov model (supplemented with assumptions for patient management options not examined in the external model)

continued

TABLE 63 Studies identified as potentially relevant to inform model conceptualisation (*continued*)

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Venderink (2017),[130] Netherlands To assess the CE of SBx and TBx (with alternative MRI-influence method used (MRI-fusion or in-bore) for biopsy-naive men with elevated PSA and /or abnormal DRE	1. SBx 2–3. mpMRI → (no suspicious lesions): discharged; (suspicious lesions): TBx (2. MRI fusion and 3. In-bore) Where individuals with biopsy (+) receive treatment, and those with biopsy (–) are discharged. All biopsies are performed via TRUS	Histopathological definition(?): GS ≥ 3 + 4 high-volume (IR/HR).	Sensitivity to detect CNS and CSPCa Specificity for PCa Probability of false CNS and CS	Decision tree: classifies patients according to diagnostic accuracy, true disease status (CS and CNS PCa) and treatment allocation + Markov model capturing longer-term outcomes Health states: No PCa, status after RP, status after RT, status after AS, death	Via Markov model capturing long-term outcomes
Cerantola (2016),[131] Canada To assess the CE of using MRI and TBx for biopsy-naive men with elevated PSA and abnormal DRE	1. SBx 2. mpMRI → (PI-RADS < 3): followed-up; (PI-RADS ≥ 3): TBx Where individuals with biopsy (+) receive treatment, and those with biopsy (–) are followed-up. SBx is performed via TRUS	NR CSPCa is not defined but manuscript suggests that it is equivalent to IR/HR	TBx: - Rate of biopsy (+) - Rate of CS among biopsy (+) SBx: - Rate of biopsy (+) - Rate of FN - Rate of CS among biopsy (+)	Markov model capturing diagnostic (via implicit decision tree embedded in the Markov model) and longer-term outcomes Health states: two set of health states 1. mpMRI, TBx, 2. SBx, SBx(+), (1) or (2) plus follow-up, LR PCa, IR/HR PCa, AS, curative treatment, biochemical recurrence, CRPC, PCa death, other-cause death	Via Markov model capturing: 1. biopsy alternatives: TBx or SB (+) 2. biopsy outcomes: No PCa (captured in follow-up), LR PCa, HR PCa; 3. Primary treatment allocation; 4. disease progression from localised disease (LR, IR/HR to relapse) to metastasis (CRPC) PCa mortality only applies to metastatic disease.
de Rooij (2014),[132] The Netherlands To assess the CE of using MRI and TBx for biopsy-naive men with elevated PSA	1. SBx 2. mpMRI → (no suspicious lesions): followed-up; (suspicious lesions): TBx re individuals with biopsy (+) receive treatment, and those with biopsy (–) are followed-up. SBx is performed via TRUS.	Histopathological definition: CNS PCa: GS ≥ 3 + 4 or large tumour with GS 3 + 3	Sensitivity and specificity for detecting PCa Probability of correctly classifying tumour aggressiveness	Decision tree: classifies patients according to diagnostic accuracy, true disease status (CS and CNS PCa) and treatment allocation + Markov model capturing longer-term outcomes Health state: alive, dead	Via Markov model capturing long-term outcomes

Study: First author (year), country Study aim	Diagnostic strategies	Definition of CSPCa	Biopsy diagnostic accuracy outcomes	Model structure and modelling approach	Evidence linkage to long-term outcomes
Mowatt (2013),[133] UK To assess the CE of using alternative MRS/MRI sequences to target TRUS biopsy, compared with SBx in individuals with suspected PCa and a previous (–) biopsy	1. SBx (extended (14–16) core TRUS) 2. MRI/MRS → MRI/MRS (–): followed-up; MRI/MRS (+): TBx 3. MRI/MRS → MRI/MRS (–): SBx; MRI/MRS (+): TBx Individuals with biopsy (+) receive treatment, and those with biopsy (–) follow-up (with a repeat saturation at 12 months if FN)	NA	Sensitivity and specificity of detecting PCa	Markov model capturing diagnostic (via implicit decision tree embedded in the Markov model) and longer-term outcomes Health states: No PCa or undetectable PCa, Dx localised T1–2 PCa (LR), Dx localised PCa (IR), Dx localised PCa (HR), Dx locally advanced T3 PCa (or extraprostatic cancer), unDx localised T1–2 PCa (LR), unDx localised PCa (IR), unDx localised PCa (HR), unDx locally advanced T3 PCa, Dx metastatic PCa, PCa death, other-cause death	Via Markov model capturing PCa onset, and disease progression from 1) localised to metastatic PCa, and 2) from locally advanced to metastatic PCa. PCa mortality only applies to individuals with metastatic cancer.

(+) positive result; (–) negative result; AS, active surveillance; CE, cost-effectiveness; CRPC, castration-resistant PCa; Dx, diagnosed; EBRT, external beam radiation therapy; FN, false negative; HG, high-grade prostate cancer); HR, high-risk prostate cancer; IR, intermediate-risk prostate cancer; LATRUS, local anaesthesia transrectal ultrasound; LG, low-grade prostate cancer; LR, low-risk prostate cancer; MRS, magnetic resonance spectroscopy; PCa3, prostate cancer antigen 3; phi, prostate health index; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; RTx, radical treatment; SBx, systematic biopsy; T, tumour stage; TBx, targeted biopsy; TPMB, template prostate mapping biopsy; w/wo, with or without; wo, without; WW, watchful waiting.
a Not explicit but there is some suggestion that low grade is referred to CNS and high grade to CS.
b decision rule in the original paper.

The biopsy diagnostic outcomes applied across studies allow classification of patients according to the presence of PCa alone (i.e. no PCa/PCa),[133] or based on disease presence and its clinical significance (i.e. clinically nonsignificant/significant PCa).[127,129,130] One study classified patients according to ISUP grades into three categories: no PCa (ISUP grade 0), PCa of ISUP grade 1, or 2 and higher.[120] It is worth noting, that biopsy results only provide histopathological information, usually expressed in terms GS and/or pattern (or as ISUP grade) and maximum core length. However, ascertaining the disease clinical significance for the purposes of guiding patient management requires knowledge of further prognostic information (e.g. T stage and PSA levels), as more radical treatment is only indicated for cancer with worse prognosis (i.e. those likely to progress at a quicker rate from localised to metastatic disease). The definition of clinical significance applied in the models to classify individuals according to biopsy results is based on the histopathological definition of clinical significance only. The full clinical definition of disease significance which is applied in the models to select patient management is conditional on biopsy results and other prognostic information. Establishing a link between histopathological and clinical definitions of disease significance (usually requiring judgements on how to map across definitions and/or risk stratification) is thus a feature of most models. However, not all studies make a clear distinction between the two types of definitions of clinical significance.[121,127,129,130,132] In some studies, the definition of clinical significance is not provided.[122,128,131]

Some studies[116,119,121,123,125,126] further classify PCa according to three-tier cancer risk classifications, which are generally similar (generally low-risk, intermediate-risk, high-risk PCa) despite some minor differences across classification in how each category is defined. While the exact definition of the risk categories varies across studies, individuals with PCa are in general assigned to a risk category on the basis of their PSA levels, histopathological presentation and disease (T) stage.

In the majority of identified studies, the link between diagnostic outcomes and subsequent treatment choice was established via a Markov or partially observable Markov model component.[116,119,121,123–133] The structure of most of these models allows capturing disease progression to metastatic disease[116,119,121,123–127,131] or high-risk disease.[127] The model by Barnett *et al.* (2018) allowed for progression in patients with undetected PCa (preclinical states) across health states defined by GS and whether disease localised, and from any of these states to metastatic disease. For patients with detected PCa who underwent radical prostatectomy the progression to metastatic disease was done via a cancer recurrence health state.[124] In all of these disease progression models, PCa mortality only applies to individuals with metastatic disease[116,119,121,123–127,131,133] or high-risk disease.[127] Two Markov models did not consider disease progression, with long-term outcomes directly conditioned on true disease status, diagnostic status (diagnosed or undiagnosed cancer) and primary treatment received.[130,132]

Hao *et al.*[120] and Getaneh *et al.*[122] modelled disease progression (and onset) within a calibrated microsimulation model. In Hao *et al.*[120] disease progression occurred sequentially from disease stage T1–T2 to T3–T4 and from T3 to T4 to metastatic disease in preclinical states and from localised to metastatic disease in clinical states. PCa mortality only applied to individuals with metastatic disease in clinical states. In Getaneh *et al.*[122] disease onset was assumed to imply a T1 tumour stage; disease progression would occur sequentially from the T1 stage to T2, and from this to T3. At each tumour stage, individuals also progressed across GSs (lower than 7 → equal to 7 → > 7). Individuals in each preclinical state could progress from local-regional to distant metastasis, but PCa mortality only applied to individuals in clinical states.

In one study, long-term outcomes were quantified by the decision tree alone, which assigned lifetime QALY and cost pay-offs to each terminal node, conditional on true disease status, diagnostic status (diagnosed or missed) and allocated treatment.[129]

Of the 16 studies identified at the first stage of the review, 9 were selected for a more in-depth review, as these were identified as the most appropriate to support the conceptualisation of the de novo model given the relevance of:

- the comparisons and position in the diagnostic pathway – studies which compared biopsies conducted with MRI-influence methods (i.e. targeted and/or combined biopsies) for PCa diagnosis[119,120,124,129,130]
- UK policy relevance.[116,121,123,125,126]

Although Mowatt *et al.*[133] were considered to have UK-policy relevance, it was not considered for the second stage of this review, given that diagnostic accuracy in this study only allowed classifying individuals according to PCa presence. Therefore, the evidence linkage in this study is unlikely to be suitable for the current decision problem, as the choice of PCa management needs to be linked as a minimum to some level of prognostic information (e.g. clinical significance of disease).

Studies included in the model conceptualisation review

Table 64 summarises the subset of identified studies included in the model conceptualisation review. A detailed description is provided next.

Population

The population in the majority of studies comprises individuals with suspected PCa who enter a secondary care diagnostic pathway,[116,119,121,123,125,126,129,130] while other studies consider patients being screened for PCa.[120,124]

Some of the studies on patients with suspected PCa consider a single homogeneous population in terms of disease (and CS disease) prevalence,[129,130] others model different baseline populations defined by their diagnostic story (MRI results, number of previous biopsies)[116,123] and underlying cancer risk category.[116,123,125,126] One study further considers subgroups defined by age brackets, with increased disease prevalence for older individuals (but the same CS prevalence for all subgroups).[129]

Hao *et al.*[120] considered a population eligible for PSA-based PCa screening. The manuscript mentions that individual heterogeneity is considered in the natural history model (informed by Swedish registry data) but does not clearly state which individual characteristics are modelled beyond PSA levels.

Biopsy approaches

A variety of biopsy approaches were compared in the studies; these differ by route of access (transrectal vs. transperineal), type of anaesthesia used (general vs. local anaesthesia), sample collection method (targeted vs. systematic vs. mapping or saturation biopsy) and MRI-influenced methods (SF, CF, and in-bore MRI).

In the studies, which compared alternative MRI-influenced methods with each other, one compared MRI followed by targeted biopsy approaches for those who tested positive on imaging with (1) all three[129] or (2) just two methods (in-bore and SF)[130] versus systematic biopsy (without prior MRI) for all patients. None of these studies specified the SF system modelled.

The study by Cheng *et al.*[119] evaluated sequences of prostate biopsies with alternative combinations of (1) systematic, (2) template mapping and (3) combined targeted and systematic biopsy. The MRI-influenced method used for the combined biopsies was not specified. Another study considered a wide number of diagnostic strategies for patients with suspected PCa, which included systematic, targeted and template mapping biopsies.[125,126] No MRI-influenced method was specified for the targeted biopsy approaches in either study.

Two other studies compared diagnostic strategies with a MRI-influenced component (targeted alone or combined with systematic biopsy) versus systematic biopsy, but in the context of PSA-based screening.[120,124] One study[120] did not specify whether MRI-influenced biopsies were performed with SF, CF or in-bore methods. In the other study[124] MRI-influenced biopsies were conducted with SF, but the technology used was not specified.

TABLE 64 Studies included in the model conceptualisation review

Study: First author (year), country Type of model	Population	Biopsy approaches modelled	Classification (via biopsy diagnostic accuracy)	Choice component	Evidence linkage to longer-term outcomes	
					PCa	No PCa
Souto-Ribeiro (2022),[116] UK Diagnostic	Main population: Biopsy-naive individuals with mpMRI Likert3 + for suspected localised PCa. Other populations: biopsy-naive mpMRI Likert 1,2; previous negative biopsy and mpMRI Likert 3+; previous negative biopsy and mpMRI Likert 1,2	LATP vs. LATRUS vs. GATP biopsy Repeat biopsy: with LATRUS for a proportion of those diagnosed as No PCa or CNS PCa (max: 1)	No PCa CNS PCa CSPCa	– No PCa: discharge if true negative (TN); PSA monitoring if FN – CNS PCa: either AS or radical treatment – CSPCa[a]: – intermediate risk: offered radical treatment, with option of AS; %WW (if no curative intent) – high risk: % Radical treatment; %WW (if no curative intent) – Metastatic PCa: ADT ± Chemo	Intermediate outcome: disease progression to metastatic disease – varies by underlying true risk category and being diagnosed as having CS or CNS PCa Survival: metastatic disease, diagnostic status of metastatic disease, age HRQoL: metastatic disease, age, AEs from treatment Costs: disease spread, age, diagnostic status, treatment received, EoL	Surv: Age HRQoL: NR Costs: Monitoring
Wilson (2021),[121] UK Diagnostic	Individuals with suspected PCa presenting for mpMRI	LATP vs. LATRUS biopsy Repeat biopsy: all diagnosed no PCa at previous biopsy (max: 1)	No PCa CNS PCa CSPCa	– No PCa: discharged back to primary care – CNS PCa: AS – CSPCa[a]: intermediate or high risk: AS or radical prostatectomy	Intermediate outcome: disease progression to metastatic disease – varies by underlying true risk category and treatment received Surv: metastatic disease, age HRQoL: metastatic disease, age Costs: treatment received	Surv: Age HRQoL: Age Costs: NR
Cheng (2021),[119] Singapore Diagnostic	Biopsy-naive individuals with elevated PSA level and/or abnormal DRE findings	Combined vs. systematic (12-core) vs. saturation (20-core) biopsy Repeat biopsy: all diagnosed no PCa at previous biopsy (# of repeat biopsies is strategy dependent, max: 2)	No PCa CNS PCa CSPCa	– No PCa: monitoring – CNS PCa: AS, WW or radical treatment – CSPCa[a]: intermediate or high risk: WW or radical treatment. WW only offered if no curative intent	Intermediate outcome: disease progression to metastatic disease – varies by underlying true risk category and diagnostic status Surv: metastatic disease, age HRQoL: metastatic disease, castration-resistant disease, age, treatment, underlying true risk category Costs: metastatic disease, castration-resistant disease; treatment received, EoL	Surv: Age HRQoL: Age Costs: Monitoring

Study: First author (year), country Type of model	Population	Biopsy approaches modelled	Classification (via biopsy diagnostic accuracy)	Choice component	Evidence linkage to longer-term outcomes	
					PCa	No PCa
Hao (2021),[120] Sweden Screening + diagnostic	Men eligible (55–69 years old) for quadrennial PSA screening of PCa	Targeted biopsy vs. systematic biopsy vs. combined biopsy Repeat biopsy: not modelled as part of the diagnostic component	ISUP GG0 ISUP GG1 ISUP GG ≥ 2	–ISUP GG0: return to screening –ISUP GG1 and GG2+: AS or radical prostatectomy and/or radiation therapy Metastatic PCa: metastatic drug treatment Treatment allocation also seems to consider disease stage at diagnosis (T1–T2, T3–T4).	Intermediate outcome: disease progression to metastatic disease – varies by underlying ISUP GG and T stage and diagnostic status Surv: Metastatic disease, other factors NR HRQoL: metastatic disease, age, treatment and time since treatment initiation received, being diagnosed, EoL Costs: treatment received, EoL	Surv: NR HRQoL: NR Costs: NR
NICE (2019),[123] UK Diagnostic	Individuals with raised PSA, negative MRI and/or a previous negative prostate biopsy	TPMB vs. TRUS Repeat biopsy: no consecutive biopsies allowed	No PCa CNS PCa CSPCa	– No PCa: monitoring (tests and testing schedule differ across strategies) – CNS or CSPCa[a]: mix of AS, brachytherapy, hormone therapy, radical prostatectomy, external radiotherapy with the distribution of treatments varying by underlying category of risk (low, intermediate or high risk). – Metastatic PCa: ADT ± Chemo	Intermediate outcome: disease progression to metastatic disease – varies by underlying true risk category and being diagnosed as having CS or CNS PCa Surv: Metastatic disease, diagnostic status of metastatic disease, age HRQoL: metastatic disease, age, AEs from treatment Costs: disease spread, age, diagnostic status, treatment received, EoL	Surv: Age HRQoL: Age Costs: NR
Faria (2018)[125] and Brown (2018),[126] UK Diagnostic	Biopsy-naive individuals with suspected localised PCa	TRUS vs. TPMB Repeat biopsy: who receives it (No PCa or CNS PCa) varied by strategy (max 1)	No PCa CNS PCa CSPCa	– No PCa: follow-up primary care – CNS PCa: AS – CSPCa: intermediate or high-risk radical prostatectomy	Intermediate outcome: disease progression to metastatic disease – varies by underlying true risk category and treatment received Surv: metastatic disease, age HRQoL: metastatic disease, age Costs: treatment received	Surv: Age HRQoL: Age Costs: NR

continued

TABLE 64 Studies included in the model conceptualisation review (*continued*)

Study: First author (year), country Type of model	Population	Biopsy approaches modelled	Classification (via biopsy diagnostic accuracy)	Choice component	Evidence linkage to longer-term outcomes	
					PCa	No PCa
Barnett (2018),[124] US Screening + diagnostic	Men eligible (55–69 years old) for annual PSA based screening of PCa	TRUS systematic vs. TRUS MRI fusion vs. TRUS combined biopsy Repeat biopsy: not modelled in the diagnostic component	No PCa CNS PCa CSPCa	– No PCa: routine screening – CNS PCa: if GS ≤ 6 – % AS, % radical prostatectomy; – CSPCa[a]: if GS ≥ 7 – radical prostatectomy; if PSA > 20 ng/mL or a Gleason score ≥ 8 – bone scan and a CT scan for staging – PCa (CNS and CS) and age > 80 years: WW	Intermediate outcome: disease progression to metastatic disease– varies by treatment received and indirectly by location of disease (organ confined vs. extraprostatic or with lymph node) Surv[b]: metastatic disease, age, HRQoL: metastatic disease; being diagnosed; treatment received and time since treatment initiation time post radical prostatectomy, EoL Costs: disease spread, treatment received, EoL by age	Surv: Age HRQoL: Age Costs: Monitoring
Pahwa *et al.*,[129] US Diagnostic	Biopsy-naive patients with elevated PSA level/abnormal DRE findings. Subgroups: 41–50, 51–60, 61–70 years old	Systematic TRUS, targeted CF, targeted MRI-fusion, targeted MRI in-bore. Repeat biopsy: not modelled	No PCa CNS PCa CSPCa	– No PCa: NR – CNS or CSPCa: mix of AS, WW, radiation therapy, brachytherapy, prostatectomy, ADT; treatment distribution varies by diagnosed clinical significance with a higher proportion of more aggressive treatment assumed for CSPCa	Surv: Diagnostic status, age, treatment type, underlying true disease status (including clinical significance) HRQoL: being diagnosed, age, treatment received and underlying true disease status (including clinical significance) Costs: diagnostic status, treatment received and underlying true disease status (including clinical significance)	Surv: Age HRQoL: NR Costs: NR
Venderink (2017),[130] The Netherlands Diagnostic	Biopsy-naive patients with elevated PSA level/abnormal DRE findings	Systematic TRUS, targeted TRUS MRI-fusion, targeted in-bore MRI biopsy Repeat biopsy: not modelled	No Pca CNS PCa CSPCa	– No PCa: NR – CNS or CSPCa: mix of AS, WW, radiation therapy, brachytherapy, prostatectomy, ADT; the distribution of treatments varies by diagnosed clinical significance with a higher proportion of more aggressive treatment assumed for CSPCa	Surv: diagnostic status, treatment received, and underlying true disease (including clinical significance) HRQoL: being diagnosed, treatment received and time since treatment initiation Costs: treatment received	Surv: Age HRQoL: NR Costs: NR

ADT, androgen depleting therapy; AS, active surveillance; Chemo, chemotherapy; EoL, end of life; FN, false negative; FP, false positive; LATRUS, local anaesthesia transrectal biopsy; Surv, survival; TP, true positive; TPMB, template prostate mapping biopsy; WW, watchful waiting.
a Classification for treatment allocation is not done via diagnostic accuracy alone.
b Not reported in full in the manuscript.

The type of anaesthesia under which biopsies are performed is only specified for the studies which focus their comparison on transperineal vs. transrectal biopsy approaches.[116,121] One assumes local anaesthesia for all biopsied patients regardless of biopsy route of access,[121] while the other considers local anaesthesia for those biopsied via the transrectal route and either general or local anaesthesia for TP.[116]

Souto-Ribeiro *et al.*[116] a previous DAR by the Southampton EAG, established two main comparisons between biopsy approaches: (1) LATP biopsy (with any type of biopsy device) versus local anaesthesia transrectal (LATRUS) biopsy and GATP biopsy and (2) LATP with specific freehand devices versus LATRUS and versus transperineal transrectal biopsy conducted with a grid and stepping device conducted under local or general anaesthetic.

The NICE CG131 model[123] evaluated alternative follow-up strategies of individuals with suspected PCa and placed little emphasis on alternative biopsy approaches. The main analysis presented results only for strategies which used transrectal biopsy, although strategies with transperineal mapping biopsy were considered in extended analyses only.

Another feature of the biopsy approaches modelled is whether repeat biopsies were allowed, the number of subsequent biopsies modelled and who would receive these. In the studies which considered the possibility of repeat biopsies, this has been modelled in the following ways:

- All patients with a no PCa diagnosis at previous biopsy were assumed to receive repeat biopsy with a maximum of one repeat biopsy allowed in the model (assumption not justified). It is not clear whether the repeat biopsy would follow the same biopsy approach as the index biopsy for all strategies, as only one strategy is fully illustrated.[121]
- All patients with a no PCa diagnosis at previous biopsy were assumed to receive a repeat biopsy, in the subset of strategies allowing repeat biopsy.[119] Strategies were defined in terms of the number of repeat biopsies allowed (up to a maximum of 2) and on the sample collection method (combined, systematic or saturation) conditional on the method of the previous biopsy in the testing sequence. Repeat biopsies were assumed to always follow a sample collection method different from the one in previous biopsies in the testing sequence.
- A proportion of patients with a no PCa or CNS PCa diagnosis receive one repeat biopsy with LATRUS (regardless of biopsy approach for the index biopsy).[116] The proportion of patients receiving a repeat biopsy was informed by the literature (single-centre observational study comparing TRUS, LATP and GATP biopsy) for the biopsy-naive populations, and by assumptions for those with previous biopsies (a lower proportion of repeat biopsy was assumed for the latter population). While the proportion of repeat biopsies was assumed to be the same across biopsy approaches in the base-case analysis for LATP, GATP, LATRUS, this assumption was relaxed in scenario analysis where LATRUS was assumed to result in more repeat biopsies than the TP approaches (LATP and GATP).
- Repeat biopsy was allowed across most strategies but depending on the strategy the biopsy would be performed in those diagnosed at index biopsy with (1) NC, (2) CNS cancer or both NC and CNS cancer. The type of biopsy approach (template mapping, systematic or targeted) would also vary across strategy, but no strategy allowed more than one repeat biopsy.[125,126]

Some studies did not model the possibility of repeat biopsy.[129,130] In other studies, the possibility of repeat biopsy was not modelled within the diagnostic component of the strategies, but repeat biopsies for individuals who returned to screening and were identified again for biopsy via screening.[120,124] The NICE CG131 model also did not consider consecutive biopsies in the diagnostic strategies.[123] All individuals with a 'no cancer' biopsy result returned to follow-up, but individuals could receive more than one biopsy if they tested positive again to the screening tests in their follow-up protocol.

Classification

In most studies, the diagnostic accuracy of the biopsy procedure classifies individuals as not having PCa or having non-CS or CSPCa.[116,119,121,123–126,129,130] The exception was the study by Hao *et al.* in which classification is done by ISUP grade.[120] Both types of classification are usually defined by histopathological features of the biopsied lesions (graded according to GSs).

The specificity of biopsy to detect PCa is assumed perfect across most models, so individuals without PCa cannot be misclassified as having the disease. However, studies differ in terms of other types of misclassification allowed for patients tested with biopsy procedures. Misclassification types allowed in the studies via both the structure and the parameterisation of the diagnostic accuracy for the biopsy approach include:

- individuals with PCa of any clinical significance diagnosed as not having the disease;[116,119,121,123–126,129,130]
- individuals with CSPCa misclassified as non-CS;[116,119,121,123–126,129,130]
- individuals with CNS PCa misclassified as CS.[124,129,130]

Choice of clinical management

Decisions on patient management at diagnosis could be determined by the biopsy diagnostic outcomes alone[125,126,129,130] or with other factors also influencing treatment allocation.[116,119–121,123,124]

In three models[125,126,129,130] patient management was attributed according to individuals' classification in terms of disease presence and clinical significance of disease. This classification was established based on the diagnostic accuracy of the biopsy approaches.

Some models tracked the individuals' underlying cancer prognostic risk and used this information jointly with the diagnostic outcomes to allocate treatment. For example, the Southampton DAR model[116] allocated treatments based on disease presence, clinical significance of disease and underlying cancer risk distribution. In order to classify patients according to these factors, the model stratified individuals with PCa into three cancer risk categories (low, intermediate, and high risk) according to the lesion's GS, disease stage and PSA levels in separate diagnostic sub-decision trees for individuals in each risk category (plus a sub-decision tree for individuals without PCa). Low-risk disease was assumed to correspond to CNS disease (as determined by the diagnostic accuracy – that is based on GS alone), and intermediate- and high-risk disease to CS disease.

Disease spread at diagnosis (localised vs. metastatic) was also considered a factor for treatment allocation in some studies,[116,120,123] which assumed that a proportion of individuals in the baseline population would have metastatic disease and, if disease was detected, received treatment with chemotherapy and/or androgen depleting therapy.

One study considered age and PSA levels alongside GS to determine PCa treatment allocation.[124] Patients older than 80 years old diagnosed with PCa of any clinical significance were treated with watchful waiting. Patients diagnosed with CS cancer and PSA levels higher than 20 ng/mL or GS >8 would undergo tests for staging purposes. It is not clear how treatment was then allocated conditional on the results of staging.

In the model by Cheng *et al.*[119] treatment allocation was determined by diagnosed disease clinical significance, age (with palliative care for those 75 years old or older) and cancer risk category. Although the text suggests that the distribution of treatments varies by diagnosed risk category, it is unclear how this is done since the biopsy only classifies patients according to clinical significance.

In summary, for patients diagnosed with PCa, the primary treatment allocation was conditional on:

1. diagnosed clinical significance of disease, true cancer risk category and disease spread;[116,123]
2. diagnosed disease clinical significance;[125,126,129,130]
3. GS, PSA level and age;[124]
4. type of biopsy (targeted or systematic), cancer risk category and age.[119]

In one study, the mechanism of treatment allocation for patients with diagnosed with cancer was not clear, but it may have been conditioned by ISUP grade (established by the biopsy diagnosis accuracy), disease T stage and spread. The manuscript suggests that the treatment pathways were informed by Swedish registry data, but does not describe how this was done.[120]

A range of evidence sources were used to inform the distribution of treatments for diagnosed PCa. Amongst these the following are relevant in the UK context:

- the Southampton DAR model[116] based treatment distribution by risk category on UK clinical guidance and observed treatment allocation from national audit data;[134]
- the NICE NG131 model[123] used observed primary treatment distributions by risk category from UK registry data;[112]
- the PROMIS trial[125,126] assumed that treatment choice was guided by diagnosed disease clinical significance alone.

Individuals diagnosed as not having PCa were discharged to follow-up,[121,123,125,126] or returned to the screening schedule.[120,124] One study,[116] conditioned the individuals' subsequent management after a no PCa diagnosis on whether they had been misclassified (TN results led to discharge and FN results [patients with PCa of any risk category] to routine PSA monitoring). This assumption was not justified and it is not clear how in clinical practice the two groups of individuals (TN and FN) would be distinguished so that distinct treatment decisions could be made for each group.

Outcomes

The evidence linkage approaches applied in the identified studies to connect patient classification and subsequent treatment choices with longer-term outcomes differed in whether PCa progression was explicitly modelled as an intermediate outcome or not.

Only two studies did not model disease progression.[129,130] Pahwa *et al.* [129] conditioned lifetime QALYs and cost pay-offs on diagnostic status (i.e. whether cancer had been diagnosed or remained undiagnosed), underlying true disease status (no PCa, CNS or CSPCa) and type of treatment received. The model applied a life-expectancy multiplier, to adjust payoffs according to alternative starting ages (scenario analysis). The lifetime pay-offs were mainly derived from an external Markov model[118] comparing alternative treatments for patients with low-risk localised PCa. The long-term Markov model in Venderink *et al.*[130] only allowed for transitions from alive to death states. Individuals with PCa health states were defined in terms of the primary treatment received (status after 1) active surveillance, (2) radical prostatectomy or (3) radiotherapy) or no treatment (for those who had been misclassified as not having cancer). In these patients, survival was conditional on type of treatment received and the underlying true disease clinical significance, with the diagnostic status (diagnosed vs. undiagnosed cancer) determining whether individuals received treatment.[130] In both these models, treatment had a direct impact on survival.[129,130]

All other models considered disease progression from localised to metastatic disease, although health states and possible state transitions varied across models.[116,119,121,123–126] Some studies modelled progression from localised to metastatic disease, and conditioned disease progression on underlying risk category and being correctly diagnosed/treatment received.[119,121,125,126] Other studies modelled sequential disease progression across disease risk categories (from low to intermediate-risk and from the latter to high-risk disease) for localised disease followed by progression from the high-risk localised

to metastatic disease. In these models, the probabilities of transitioning to later disease stages were conditioned on the underlying true disease status (including risk category) and being diagnosed as having CS or non-significant disease.[116,123] The screening studies modelled progression differently in the preclinical and clinical states.[120] In the microsimulation model,[120] individuals with PCa could transition between preclinical states defined in terms of ISUP grade, tumour stage and metastasis; within each ISUP grade individuals progressed sequentially from stage T1–T2 to T3–T4 and from T3 to T4 to metastatic disease. In the clinical states (for those whose PCa was detected) disease progression occurred from localised to metastatic disease. In the partially observed Markov model,[124] disease progression in the preclinical states could occur (1) sequentially between three localised disease health states defined according to GS (<7, =7, >7) (2) from any of the localised disease states to extra-prostatic or lymph node-positive cancer, or (3) from any of the preclinical states to observable (clinical) metastatic cancer. The rate of progression to metastatic cancer was the same for all pre-clinical states. In the clinical states, patients treated with radical prostatectomy could transition to one of the two post-treatment states: no recurrence following treatment (NRFT) or possible recurrence following treatment (PRFT) health states. Progression to metastatic cancer was only possible for individuals in the PRFT state, with those in the NRFT state assumed cured. The probability of transitioning from the PCa treatment health state to the post-treatment states was conditional on disease location (organ confined vs. extra prostatic or lymph node-positive cancer) and treatment received. Patients who were treated with active surveillance could progress to metastatic disease at the same rate as those who were untreated, unless they transitioned to surgical treatment. The model appears to track progression over time across GSs and disease location for those under active surveillance, in a manner similar to what happened in the pre-clinical states.

All the disease progression models shared the assumption that PCa mortality only applied to patients with metastatic disease. Treatment for patients identified as having cancer reduced disease progression to metastatic cancer compared to untreated patients, and thus reduced the probability of dying from PCa for these patients. The transition probabilities for treated and untreated patients in the Markov disease progression were estimated by calibration or partially observable Markov model decision processes (as progression is an unobservable process). The data sources and calibration methods used to estimate these transition probabilities differed across models, and are reviewed below.

The PROMIS model[125,126] calibrated the probability of progressing from localised to metastatic disease by risk category and treatment received, combining risk-stratified survival data and proportion of patients with metastases from the PCa Intervention versus Observation Trial (PIVOT),[109] with the mortality in the metastatic subgroup of the STAMPEDE trial.[113] The PIVOT observation arm was used to inform the transition probabilities for individuals with PCa who did not receive active treatment (due to correct classification on misclassification depending on the risk category). The PIVOT radical prostatectomy arm was used to inform the transition probabilities for those treated with active treatment (true positives with intermediate- and high-risk cancer). The 'treatment' effects of being diagnosed on disease progression were thus informed by randomised comparative efficacy evidence.

The models which disaggregated disease progression by cancer risk categories, also used calibration to estimate transition probabilities.[116,123] The calibration method estimated transition probabilities first for the transition from high-risk to metastatic disease, then from intermediate- to high-risk disease, and finally from low-risk to intermediate-risk disease can be derived. The calibration was done separately for the undetected and detected cancers using different data sources. Transition probabilities for the undetected cancers used cumulative metastases risk rates by cancer risk category from the watchful waiting arm in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG4) trial[135] jointly with and Swedish life-table data (from 1999 to reflect background mortality in the trial). For the diagnosed cancers, the data sources for calibration included: cancer-specific survival by risk category sourced from a UK registry study,[112] all-cause survival for people with metastatic PCa from the STAMPEDE trial,[59] and UK life-table (from 2010 to 2012 to reflect background trial mortality in STAMPEDE). Thus, this calibration approach relies on an indirect naive comparison to derive the 'treatment' effects of being diagnosed on disease progression, which may introduce bias on the probabilities of disease progression used in the model.

The screening model by Hao *et al.*[120] does not describe the calibration method used to parameterise disease progression transitions, mentioning only that the model is calibrated to UK registry data. The other screening model[124] also used calibration to estimate the transition probability from localised and extra-prostatic or lymph node-positive cancer (preclinical states). The authors varied the metastasis rate in 10-year periods and calibrated the values so that the resulting age-dependent risk of PCa-specific death under routine screening matched the values estimated from historical US cancer registry data. For the clinical states, the authors state that the probability of transitioning from recurrent to metastatic disease was informed by another US cancer registry data and using the methodology of an external partially observed Markov model. It is not clear how the methodology described for the external model was applied in the model developed by Barnett (2018). It is also not clear why the transition probabilities for the preclinical and clinical states were estimated by two different methods (i.e. calibration and partially observed Markov decision process).

One model[119] does not describe how transition probabilities were estimated and does not fully report the data sources used to inform these parameters.

In general disease progression models, survival outcomes for individuals with PCa were conditional on having metastatic disease and age. Two models[116,123] further conditioned mortality on whether metastatic disease was diagnosed (and therefore, received treatment for metastatic cancer) or not. Metastatic mortality data sources of relevance to the UK context include different publications of the STAMPEDE study, a UK-based trial which compared the survival outcomes of men with newly diagnosed metastatic, high-risk or node-positive cancer treated with alternative cancer treatments. The PROMIS and related models estimated the probability of metastatic death using early (median follow-up of 20 months) survival data of men with newly diagnosed metastatic PCa from the control arm (who received SOC consisting of androgen depleting therapy) of the STAMPEDE trial. The NICE NG131 and related models used a later survival data cut (median follow-up 43 months) from the DTX and control arms of the STAMPEDE trial that includes individuals with metastatic and non-metastatic disease.[59]

HRQoL outcomes of patients with PCa were conditional on:

- having metastatic disease[116,119–121,123–126] – negative impact on HRQoL
- having castration-resistant metastatic disease[119] – negative impact on HRQoL
- age[116,119–121,123–126] – decreasing utility with age
- being diagnosed with PCa[120,129,130] – negative impact on HRQoL
- receiving radical treatment[119] – positive impact on HRQoL
- underlying true disease status (including clinical significance)[129] – negative impact on HRQoL of having PCa, which is worsened by presence of CS disease
- AEs with radical treatment by true risk category[116,123] – negative impact on HRQoL
- treatment received and time since treatment initiation[120,124,130] – initial negative impact on HRQoL with improvement in post-treatment period
- end of life[120,124] – negative impact on HRQoL.

The UK-relevant utility sources for patients with PCa in the long-term outcome models include:

- Torvinen *et al.* (2013)[136] – for the disutility of metastatic disease
- Ara and Brazier *et al.* (2010)[137] – for the disutility of ageing
- Mowatt *et al.* (2013)[133] – for the disutility of treatment-related AEs [combined with rates of AEs from Donovan *et al.*(2016)].[138]

The long-term HRQoL outcomes of patients without PCa were dependent on age in most models,[119,121,123–126] with Ara and Brazier (2010)[137] the most frequently used source to inform age-adjusted utilities.

Most models considered the cost of treatment for patients with diagnosed localised or locally advanced PCa (radical treatment or active surveillance)[116,119–121,123–126,129,130] and management of treating AEs.[116,121,123,125,126] Patients with undiagnosed PCa would incur the costs of routine follow-up[116,119,121,123,125,126,129] or of delayed radical treatment.[129] The studies also considered the costs of metastatic disease treatment with or without staging and follow-up tests.[116,119,121,123–126] Two models assumed diagnosed metastatic disease would be treated differently if diagnosed (DTX would be added to androgen depleting therapy) compared to undiagnosed metastatic disease and that treatment with DTX would vary with age.[116,123] Some models included an end-of-life cost for patients who died from PCa,[116,119,120,123,124] with one study conditioning the end-of-life costs on age at death.[124]

The costs of individuals who did not have PCa were not clearly reported for most models, but, where reported, consisted of the costs of routine follow-up.[116,119,123,124]

In UK-relevant models, treatment and follow-up resource use was informed mainly by UK (clinical and TA) guidance, as well as other published data (e.g. a randomised control trial informed AE rates of treatment[138]) and supplemented with assumptions. End-of-life costs were uprated to the relevant price year based on Round *et al.*[139] Unit costs were sourced mainly from national published sources.

Value components

TABLE 65 Summary of biopsy value components identified in the studies

Value components requiring evidence linkage	Studies [first author (year)]	Mechanism
Improved outcomes due to increased/earlier detection of **cancer**, that is fewer PCa classified as no PCa	Souto-Ribeiro (2022);[116] Wilson (2021);[121] Cheng (2021);[119] Hao (2021);[120] NICE (2019);[123] Faria (2018)[125]/ Brown (2018);[126] Barnett (2018);[124] Pahwa *et al.*;[117] Venderink (2017)[130]	via diagnostic accuracy identifying true cancer status and treatment outcomes
Reduction of undertreatment: improved outcomes due to increased/earlier detection of CSPCa, that is fewer CSPCa treated as CNS PCa	Souto-Ribeiro (2022);[116] Wilson (2021);[121] Cheng (2021);[119] Hao (2021);[120] NICE (2019);[123] Faria (2018);[125] Brown (2018);[126] Barnett (2018);[124] Pahwa *et al.*;[117] Venderink (2017)[130]	via diagnostic accuracy and assumptions on treatment distribution and impact of treatment on outcomes, which is conditioned on true clinical significance of PCa, true cancer risk category or cancer grade
Reduction in overtreatment: improved outcomes due to improved detection of CNS PCa, that is fewer CNS PCa treated as CSPCa	Barnett (2018);[124] Pahwa *et al.*;[117] Venderink (2017)[130]	via diagnostic accuracy and assumptions on treatment distribution and impact of treatment on outcomes, which is conditioned on true clinical significance of PCa
Change the number of repeat biopsies with impacts on biopsy costs and AEs	Souto-Ribeiro (2022);[116] Wilson (2021);[121] Cheng (2021);[119] Faria (2018);[125] Brown (2018)[126]	via diagnostic accuracy and decision rule on which individuals are eligible for a repeat biopsy
Value components with direct impacts		
Biopsy procedure costs	Souto-Ribeiro (2022);[116] Wilson (2021);[121] Cheng (2021);[119] Hao (2021);[120] NICE (2019);[123] Faria (2018);[125] Brown (2018);[126] Barnett, (2018);[124] Pahwa *et al.*;[117] Venderink (2017)[130]	-
Harms and/or costs of biopsy AEs	Souto-Ribeiro (2022);[116] Wilson (2021);[121] Cheng (2021);[119] NICE (2019);[123] Faria (2018);[125] Brown (2018);[126] Barnett (2018);[124] Venderink (2017)[130]	-

Appendix 10 Extension of the evidence synthesis to determine diagnostic accuracy

Methods

Description of methods

Methods were developed to provide an internally consistent framework for evidence on the distribution of test results across a number of technologies (from the evidence synthesis), and data on the extent of misclassification of the technologies in relation to (true) disease status.

This framework relies on expressing the natural probability relationships between the different quantities of interest. The extent of misclassification is made explicit by the accuracy matrix. The accuracy matrix was expressed using conditional probabilities, with its elements being the probability of obtaining a particular test result with one method conditional on a particular level of (true) disease status, that is, the probability of a test (A) retrieving a particular result × in patients with a particular disease (D) level *y* – P[A = *x*|D = *y*] – or, using simplified notation, $p^{(A)}_{x|y}$. The set of conditional probabilities that fully define accuracy are shown in the matrix in *Table 66*. Together with prevalence estimates, P[D = *y*], or p_y in the simplified notation shown at the left side of *Table 66* this matrix determines the distribution of test results, P[A = *x*], shown at the top of *Table 66* using the simplified notation of $p^{(A)}_x$.

Note that, due to the nature of biopsy and histological examination of the biopsy specimen, it is reasonable to assume that false-positive results are not possible, that is, if cancer is histologically identified, then it is present. This implies that biopsy methods cannot identify a higher ISUP Grade than true disease status, and therefore zero probability is attributed to such cases in the above accuracy matrix.

Where two methods are of interest, the problem becomes more complex. *Table 66* formalises the problem by depicting the quantities of interest for two alternative biopsy methods, including the prevalence (i.e. the true distribution across ISUP grades), which is independent of test results,

TABLE 66 Relationship between distribution of test results, the prevalence and the accuracy matrix

Prevalence		Distribution of test results					Distribution of test results				
		$p^{(1)}_1$	$p^{(1)}_2$	$p^{(1)}_3$	$p^{(1)}_4$	$p^{(1)}_5$	$p^{(3)}_1$	$p^{(3)}_2$	$p^{(3)}_3$	$p^{(3)}_4$	$p^{(3)}_5$
		Cognitive fusion, (1)					Software fusion, (2)				
	D	1	2	3	4	5	1	2	3	4	5
p_1	1	$p^{(1)}_{1\|1}$	0	0	0	0	$p^{(3)}_{1\|1}$	0	0	0	0
p_2	2	$p^{(1)}_{1\|2}$	$p^{(1)}_{2\|2}$	0	0	0	$p^{(3)}_{1\|2}$	$p^{(3)}_{2\|2}$	0	0	0
p_3	3	$p^{(1)}_{1\|3}$	$p^{(1)}_{2\|3}$	$p^{(1)}_{3\|3}$	0	0	$p^{(3)}_{1\|3}$	$p^{(3)}_{2\|3}$	$p^{(3)}_{3\|3}$	0	0
p_4	4	$p^{(1)}_{1\|4}$	$p^{(1)}_{2\|4}$	$p^{(1)}_{3\|4}$	$p^{(1)}_{4\|4}$	0	$p^{(3)}_{1\|4}$	$p^{(3)}_{2\|4}$	$p^{(3)}_{3\|4}$	$p^{(3)}_{4\|4}$	0
p_5	5	$p^{(1)}_{1\|5}$	$p^{(1)}_{2\|5}$	$p^{(1)}_{3\|5}$	$p^{(1)}_{4\|5}$	$p^{(1)}_{5\|5}$	$p^{(3)}_{1\|5}$	$p^{(3)}_{2\|5}$	$p^{(3)}_{3\|5}$	$p^{(3)}_{4\|5}$	$p^{(3)}_{5\|5}$
		Accuracy matrix					Accuracy matrix				

the two conditional accuracy matrices, and the (marginal) distributions of test results, which are themselves a function of prevalence and accuracy. The key relationships that introduce complexity are:

- prevalence is independent of test results and therefore a common prevalence estimate needs to ground all distributions of test results, and be consistent with these
- explicit accounts of accuracy need to respect both the prevalence estimates and the marginal distribution estimates derived from the synthesis.

Where the distribution of test results has been related across tests without consideration for their accuracy against a reference standard, a structured approach is therefore required for characterising accuracy to ensure that probability relationships are maintained.

Note that such a model does not identify concordance between methods in biopsy test results. To consider concordance, the synthesis model would have had to be grounded on the underlying joint or conditional probabilities of classification across tests that, that is, the likelihood of identifying individuals in a particular category using one method and in another category using a different method (joint probabilities) or the likelihood of individuals identified in a particular category by one method being classified in another by a different method (conditional probabilities). Joint/conditional probabilities determine the potential concordance between tests, which cannot be ascertained by the marginal distributions alone, that is, the same marginal distributions can be retrieved under very different levels of concordance between tests.

The approach developed for the current assessment was designed to:

- be grounded on the results of the evidence synthesis model
- return a true distribution across ISUP grade categories (prevalence) that is internally valid, that is, that is not lower than the estimated ISUP grade detection rates of the different biopsy methods
- be grounded on available evidence on the likely accuracy of MRI fusion conditional on ISUP grade
- define accuracy matrices for the remaining biopsy methods of interest that are consistent with both prevalence and the distributions of biopsy results from the evidence synthesis.

To achieve this, an extension to the synthesis model was developed in WinBUGS,[140] drawing on the broader evidence in *Multinomial synthesis model*. To allow for an internally consistent approach, we grounded our methodology on evidence of the distribution of test results obtained with targeted-MRI methods, and of their accuracy. Given that disease prevalence is fully determined by these two results, the prevalence evidence identified in *Review of additional prevalence, test results and diagnostic accuracy evidence* and *Distribution of test results obtained with cognitive fusion or software fusion biopsy* will not be explicitly incorporated in our analyses but will instead be used qualitatively to put our results into context.

Describing distribution of test results

The distributions of test results across the disease categories for the relevant biopsy methods within each disconnected network of Model 1a were computed by applying network-specific baseline distributions to the results of the NMA. Building from the analyses in the evidence synthesis section, the baseline distributions were assumed uncertain by using a multinomial likelihood to describe the data from the empirical studies and an uninformative Dirichlet prior for its hyperparameters. The Dirichlet prior was implemented via a series of conditional beta distributions to facilitate the later use of constraints.

Note that the scope of this assessment is to compare targeted-biopsy methods; therefore, results on systematic biopsy, used in isolation, will not be shown here (by not including the broader literature on the accuracy of systematic biopsy, the results are also not relevant to support decision-making).

Describing the accuracy matrix for software fusion

Evidence on the accuracy of SF in identifying disease status according to the categories of interest was used to characterise this probabilistically in the model. A multinomial likelihood was used to describe the distribution of test results conditional on each particular level of true disease status (each line in the matrix in *Table 66*). The hyperparameters of the multinomial were attributed an uninformative Dirichlet distribution, implemented via a series of conditional beta distributions to facilitate the later use of constraints.

Deriving the prevalence distribution

The derivation of prevalence followed two steps.

Analytical derivation of prevalence from the marginal distribution and accuracy matrix for cognitive fusion

The prevalence and the accuracy matrix for a particular technology fully define the marginal distribution of test results for that technology. If represented in matrix form, the prevalence vector, **p**, multiplied by the accuracy matrix, **M**, retrieves the test result marginal distribution, **p(i)**, that is **p · M = p(i)**. We have used this relationship to derive the distribution of prevalence, that is **p = p(i)/M**. Because of the reverse calculation, a constraint was implemented to ensure prevalence results across categories would sum to 1.

Derivation and application of constraints for the prevalence distribution

Given the absence of false-positive results (i.e. that biopsy cannot retrieve results of ISUP grade higher than the true value), the true distribution of disease across ISUP grades is constrained by the marginal distributions of test results obtained across tests. This is because the prevalence of higher-grade tumours is expected to be at least equal to the maximum proportion in those groups identified across all tests. This means that:

- the true prevalence of ISUP grade 4 or 5 ($j = 5$) is equal or higher than the maximum proportion of ISUP grade 4 or 5 identified across all tests – $p_5 \geq \max_i(p^{(i)}_5)$
- the true prevalence of histology ISUP grade 3 and above ($j = 4$ or $j = 5$) is equal or higher than the maximum proportion of ISUP grade 3 and above identified across all tests – $p_5 + p_4 \geq \max_i(p^{(i)}_5 + p^{(i)}_4)$
- the true prevalence of histology ISUP grade 2 and above ($j = 3$, $j = 4$ or $j = 5$) is equal or higher than the maximum proportion of ISUP grade 2 and above identified across all tests – $p_5 + p_4 + p_3 \geq \max_i(p^{(i)}_5 + p^{(i)}_4 + p^{(i)}_3)$
- the true prevalence of histology ISUP grade 1 and above ($j = 2$, $j = 3$, $j = 4$ or $j = 5$) is equal or higher than the maximum proportion of ISUP grade 1 and above identified across all tests – $p_5 + p_4 + p_3 + p_2 \geq \max_i(p^{(i)}_5 + p^{(i)}_4 + p^{(i)}_3 + p^{(i)}_2)$.

The true prevalence distribution should meet these conditions. The boundaries for each of the inequalities defined (i.e. the values at equality) can be determined recursively (with calculations starting at the highest grade). These conditions were implemented in WinBUGS using inequality constrains (see code below).

Derivation of accuracy matrix for other technologies

The accuracy matrix for the remaining technologies is determined by the prevalence estimates and by their marginal distributions. The diagonal cells in each of the accuracy matrices were therefore defined as a function of prevalence, probability of test result and other relevant elements in the accuracy matrices, by using the structural relationships between these parameters. For example, for category 4, the diagonal of the accuracy matrix for biopsy method k was defined as:

$$p^{(k)}_{4|4} = (p^{(k)}_4 - p_5 \cdot p^{(k)}_{4|5})/p_4,$$

which subtracts those from category 5 that were incorrectly identified as 4's from the total with category 4 test results.

The remaining free elements of each line in the matrix were sampled from an uninformative Dirichlet distribution (defined as a set of conditional beta distributions). Given that the diagonal cells relating prevalence with distribution of test results used the non-diagonal elements of the matrix, information is already conveyed on these parameters, and therefore final inference on these will not be fully uninformative. All accuracy parameters were constrained to be between 0 and 1, as the inverse matrix calculation, on its own, does not ensure that.

Implementation

The extension to the evidence synthesis model was developed in WinBUGS and was appended to the synthesis model code to draw on the inferences from the synthesised log odds ratios. The constraints implemented within the code extension need the log odds ratios in the synthesis model to be influenced by these. This will ensure that the inferences on the log odds ratio from the extended model are plausible with the data incorporated (accuracy matrices and baseline distribution of test results) and with the structural relationships between the quantities of interest. To evaluate the influence over the unconstrained evidence synthesis inferences, we will compare the probabilities of test results derived from the synthesis model used in isolation [see *Model 1a: Multinomial synthesis model (base case)*] with those derived from the extended synthesis and accuracy model.

Additionally, non-diagonal elements of the accuracy matrices inferred by the model were simulated from a stochastic distribution, with information on them conveyed indirectly via the diagonal elements. For this reason, retrieving test results from inferences over the prevalence and accuracy matrix approximates, but does not equal, the distribution of test results retrieved by the synthesis model. Results were therefore also compared to determine the magnitude of differences.

WinBUGS code for extended synthesis model

Code

```
model{
for (i in 1:ns){ # studies reporting all categories 1,2,3,4,5
  for (k in 1:na[i]) {
    y[i,k,1:nc] ~ dmulti(q[i,k,1:nc], M[i,k])
    for (r in 1:nc) {
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
      # predicted number events
      yhat[i,k,r] <-  q[i,k,r] * M[i,k]
      # Deviance contribution
      dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
```

```
    dev[i,k] <- sum(dv[i,k,]) # deviance contribution of each arm
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:nc) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
   # summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
#relative effects of treatment 1 compared to itself are zero, for all categories
for (r in 2:nc) {d[1,r] <- 0}
for (k in 1:nt){
  # giving phi[i,k,1] = 1, logOR of  going from cat 1 to cat 1 for all treats
  d[k,1] <- 0
  for (r in 2:nc) {
    # vague priors for relative treatment effects: log-odds ratios
    d[k,r] ~ dnorm(0, 0.0001)
   }
 }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE A
for (i in (ns+1):(ns+nsA)){ # studies reporting categories 1,2-5
  for (k in 1:na[i]) {
    y[i,k,1] ~ dbin(q[i,k,1], M[i,k])
    # first category the same
    q[i,k,1] <- phi[i,k,1]/sum(phi[i,k,1:ncA])
    log(phi[i,k,1]) <- a[i,1] + d[t[i,k],1] - d[t[i,1],1]
     yhat[i,k,1] <-  q[i,k,1] * M[i,k]
     # Deviance contribution
     dev[i,k] <- 2 * (y[i,k,1] * (log(y[i,k,1])-log(yhat[i,k,1])) +  (M[i,k]-
y[i,k,1]) * (log(M[i,k]-y[i,k,1]) - log(M[i,k]-yhat[i,k,1])))
# last category is collapsed, type A
    q[i,k,2] <- 1- q[i,k,1]
    log(phi[i,k,2]) <- a[i,2] + dA[t[i,k],2] - dA[t[i,1],2]
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  a[i,2] ~ dnorm(0, 0.0001)
  a[i,1] <- 0
 # summed residual deviance contribution for this trial
 resdev[i] <- sum(dev[i,1:na[i]])
 }
dA[1,2] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dA[k,2] ~ dnorm(0, 0.0001)
   }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE B
for (i in (ns+nsA+1):(ns+nsA+nsB)){ # studies reporting categories 1,2,3-5
  for (k in 1:na[i]) {
    y[i,k,1:ncB] ~ dmulti(q[i,k,1:ncB], M[i,k])
    for (r in 1:(ncB-1)) {  # first 2 categories the same
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,1:ncB])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
     # predicted number events
     yhat[i,k,r] <-  q[i,k,r] * M[i,k]
     # Deviance contribution
     dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
# last category is collapsed, type B
    q[i,k,3] <- 1- sum(q[i,k,1:(ncB-1)])
    log(phi[i,k,3]) <- a[i,3] + dB[t[i,k],3] - dB[t[i,1],3]
   # predicted number events
   yhat[i,k,3] <-  q[i,k,3] * M[i,k]
   # Deviance contribution
    dv[i,k,3] <- 2*y[i,k,3]*(log(y[i,k,3]/yhat[i,k,3]))
     dev[i,k] <- sum(dv[i,k,1:ncB]) # deviance contribution of each arm
```

```
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:ncB) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
   # summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
dB[1,ncB] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dB[k,ncB] ~ dnorm(0, 0.0001)
   }
# STUDIES WITH COLLAPSED CATEGORIES: TYPE C
for (i in (ns+nsA+nsB+1):(ns+nsA+nsB+nsC)){ # studies reporting categories 1,2,3,4-
5
  for (k in 1:na[i]) {
    y[i,k,1:ncC] ~ dmulti(q[i,k,1:ncC], M[i,k])
    for (r in 1:(ncC-1)) {  # first 3 categories the same
      q[i,k,r] <- phi[i,k,r]/sum(phi[i,k,1:ncC])
      log(phi[i,k,r]) <- a[i,r] + d[t[i,k],r] - d[t[i,1],r]
      # predicted number events
      yhat[i,k,r] <-  q[i,k,r] * M[i,k]
      # Deviance contribution
      dv[i,k,r] <- 2*y[i,k,r]*(log(y[i,k,r]/yhat[i,k,r]))
     }
# last category is collapsed, type C
    q[i,k,4] <- 1- sum(q[i,k,1:(ncC-1)])
    log(phi[i,k,4]) <- a[i,4] + dC[t[i,k],4] - dC[t[i,1],4]
   # predicted number events
   yhat[i,k,4] <-  q[i,k,4] * M[i,k]
   # Deviance contribution
   dv[i,k,4] <- 2*y[i,k,4]*(log(y[i,k,4]/yhat[i,k,4]))
   dev[i,k] <- sum(dv[i,k,1:ncC]) # deviance contribution of each arm
   }
  # vague priors for BL log odds of transition from 1st category to cat r in study
i
  for (r in 2:ncC) {a[i,r] ~ dnorm(0, 0.0001)}
  a[i,1] <- 0
   # summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
 }
dC[1,ncC] <- 0
for (k in 1:nt){
  # vague priors for relative treatment effects: log-odds ratios
  dC[k,ncC] ~ dnorm(0, 0.0001)
   }
totresdev <- sum(resdev[])        # Total Residual Deviance
# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {
   for (k in (c+1):nt)  {
      for (r in 1:nc) {
        or[c,k,r] <- exp(d[k,r] - d[c,r])
        lor[c,k,r] <- (d[k,r]-d[c,r])
         }
     }
 }
# calculate absolute probabilities from relative effects (no uncertainty in
baseline)
# baseline intervention = 3 (software)
for (r in 1:nc){
  T[3,r] <- b1[r]  # baseline probabilities for software biopsy (from data)
  T[5,r] <- b2[r]  # baseline probabilities for software + SB (from data)
  # log-odds of being classified in category r using intervention 3=software
  A.T[r] <- log(T[3,r]/T[3,1])
  # log-odds of being classified in category r using intervention 5=software +SB
```

```
  B.T[r] <- log(T[5,r]/T[5,1])
 }
for (k in 1:2){                    # fully connected only T[2,] to T[3,]
  for (r in 1:nc){
    phi.T[k,r]  <- exp(A.T[r] - lor[k,3,r])
    T[k,r] <- phi.T[k,r]/(sum(phi.T[k,]))
   }
 }
for (r in 1:nc){
  phi.T[4,r]  <- exp(B.T[r] - lor[4,5,r])
  T[4,r] <- phi.T[4,r]/(sum(phi.T[4,]))
 }


# EXTENSION
####### calculation of probabilities  #######

##### baseline likelihood for ref biopsy method
## multinomial with Dirichlet vague prior implemented as conditional Betas (to
allow constraints ahead)

### baseline likelihood in 1st network, p[3,]
B.y[1:nc] ~ dmulti(p[3,1:nc], B.M)
for (i in 1:nc){ ax[i] <- 1 } # define parameters of Dirichlet distribution
p[3,1] ~ dbeta(ax[1], bx[1])
bx[1] <- nc-1
for (i in 2:(nc-1)) {
       aux[i] ~ dbeta(ax[i],bx[i])
       bx[i] <- sum(ax[(i+1):nc])
  p[3,i] <- (1 - sum(p[3,1:(i-1)])) * aux[i]
 }
p[3,nc] <- 1 - sum(p[3,1:(nc-1)])

### baseline likelihood in 2nd network, p[4,]
B.z[1:nc] ~ dmulti(p[5,1:nc], B.Mz)
for (i in 1:nc){ ax1[i] <- 1 }
p[5,1] ~ dbeta(ax1[1], bx1[1])
bx1[1] <- nc-1
for (i in 2:(nc-1)) {
       aux1[i] ~ dbeta(ax1[i],bx1[i])
       bx1[i] <- sum(ax1[(i+1):nc])
  p[5,i] <- (1 - sum(p[5,1:(i-1)])) * aux1[i]
 }
p[5,nc] <- 1 - sum(p[5,1:(nc-1)])


### calculation of probabilities for both networks from relative effects, lor
for (r in 1:nc) {
             A.1[r] <- log(p[3,r]/p[3,1])
             A.2[r] <- log(p[5,r]/p[5,1])
             }
for (k in 1:2){
 for (r in 1:nc){
             phi.B[k,r]  <- exp(A.1[r] - lor[k,3,r])
             p[k,r] <- phi.B[k,r]/(sum(phi.B[k,]))
   }
 }
for (r in 1:nc){
  phi.B[4,r]  <- exp(A.2[r] - lor[4,5,r])
  p[4,r] <- phi.B[4,r]/(sum(phi.B[4,]))
}


####### determining prevalence   #######
#-- likelihood of conditional accuracy matrix based on external evidence -- FUS
# pac[true disease status, test result]

##GG1
```

```
pac[3,1,1] <- 1

##GG2
y2.ac[1:2] ~ dmulti(pac[3,2,1:2], M.ac[1])
pac[3,2,1] ~ dbeta(p2.ac[1], p2.ac[2])       # non-inf beta prior for 1st
probability
for (k in 1:2) { p2.ac[k] <- 1}
pac[3,2,2] <- 1- pac[3,2,1]

##GG3
      y3.ac[1:3] ~ dmulti(pac[3,3,1:3], M.ac[2])   # true status GG2 (category 3)
# Dirichtlet prior implemented as conditional beta distributions
for (i in 1:3){ p3.ac1[i] <- 1 } # define parameters of Dirichlet distr for this
category
# conditioning start at 1
pac[3,3,1] ~ dbeta(p3.ac1[1], p3.ac2[1])
p3.ac2[1] <- sum(p3.ac1[2:3])
p3.ac2[2] <- p3.ac1[3]
p3.aux ~ dbeta(p3.ac1[2],p3.ac2[2])
pac[3,3,2] <- (1 - pac[3,3,1]) * p3.aux
pac[3,3,3] <- 1 - sum(pac[3,3,1:2])

##GG4
y4.ac[1:4] ~ dmulti(pac[3,4,1:4], M.ac[3])  # true status GG3 (category 4)
# Dirichtlet prior implemented as conditional beta distributions
for (i in 1:4){ p4.ac1[i] <- 1 } # define parameters of Dirichlet distr for this
category
# conditioning start at 1
pac[3,4,1] ~ dbeta(p4.ac1[1], p4.ac2[1])
for (i in 1:3){ p4.ac2[i] <- sum(p4.ac1[(i+1):4])  }
for (i in 2:3) {
  p4.aux[i] ~ dbeta(p4.ac1[i],p4.ac2[i])
  pac[3,4,i] <- (1 - sum(pac[3,4,1:(i-1)])) * p4.aux[i]
 }
pac[3,4,4] <- 1 - sum(pac[3,4,1:3])

##GG5
y5.ac[1:5] ~ dmulti(pac[3,5,1:5], M.ac[4])  # true status GG4 or GG5 (category 5)
# Dirichtlet prior implemented as conditional beta distributions
for (i in 1:5){ p5.ac1[i] <- 1 } # define parameters of Dirichlet distr for this
category
# conditioning start at 1
pac[3,5,1] ~ dbeta(p5.ac1[1], p5.ac2[1])
for (i in 1:4){ p5.ac2[i] <- sum(p5.ac1[(i+1):5])  }
for (i in 2:4) {
  p5.aux[i] ~ dbeta(p5.ac1[i],p5.ac2[i])
  pac[3,5,i] <- (1 - sum(pac[3,5,1:(i-1)])) * p5.aux[i]
 }
pac[3,5,5] <- 1 - sum(pac[3,5,1:4])

#-- define distribution for prevalence from accuracy matrix (assumed on reference
method)
prev[5] <- p[3,5]/pac[3,5,5]
prev[4] <- (p[3,4] - prev[5]*pac[3,5,4])/pac[3,4,4]
prev[3] <- (p[3,3] - prev[4]*pac[3,4,3]- prev[5]*pac[3,5,3])/pac[3,3,3]
prev[2] <- (p[3,2] - prev[3]*pac[3,3,2]- prev[4]*pac[3,4,2]-
prev[5]*pac[3,5,2])/pac[3,2,2]
prev[1] <- (p[3,1] - prev[2]*pac[3,2,1]- prev[3]*pac[3,3,1]- prev[4]*pac[3,4,1]-
prev[5]*pac[3,5,1])
      #check <- step(1-sum(prev[1:4]))

### constraint restricting prevalence to be internally consistent with
probabilities
# -- calculate bounds for prevalence (biopsy methods 1 to 3)
for (i in 1:5) { ind5[i] <- equals(rank(p[1:5,5], i),5)   }  # equals(rank(x, i),k)
#1 if ith element of x is kth, 0 otherwise
max.p[5] <- inprod2(ind5[],p[1:5,5])
```

```
for (i in 1:5) { aux4[i] <- sum(p[i,4:5]) }
for (i in 1:5) { ind4[i] <- equals(rank(aux4[1:5], i),5) }
max.p[4] <- inprod2(ind4[],aux4[]) - max.p[5]

for (i in 1:5) { aux3[i] <- sum(p[i,3:5])}
for (i in 1:5) { ind3[i] <- equals(rank(aux3[1:5], i),5) }
max.p[3] <- inprod2(ind3[],aux3[]) - sum(max.p[4:5])

for (i in 1:5) { aux2[i] <- sum(p[i,2:5])}
for (i in 1:5) { ind2[i] <- equals(rank(aux2[1:5], i),5)}
max.p[2] <- inprod2(ind2[],aux2[]) - sum(max.p[3:5])

max.p[1] <- 1- sum(max.p[2:5])

# -- apply constraint on prevalence distribution so that it is consistent with
marginals
for (i in 2:5) {
      z[i] <- 1
      z[i] ~ dbern(constraint[i])
      constraint[i] <- step(prev[i]-max.p[i])*step(1-prev[i])
      }

# -- apply constraint on prevalence distribution to select dist internally coherent
zz <- 1
zz ~ dbern(constraintz)
constraintz <- step(1-sum(prev[2:5]))

####### determining accuracy matrix for COG  #######

## GG2
      pac[1,2,2] <- (p[1,2]-prev[5]*pac[1,5,2]-prev[4]*pac[1,4,2]-
prev[3]*pac[1,3,2])/prev[2]
      pac[1,2,1] <- 1- pac[1,2,2]

## GG3
      pac[1,3,3] <- (p[1,3]-prev[5]*pac[1,5,3]-prev[4]*pac[1,5,4])/prev[3]
                        p31.ac2.aux[1] ~ dbeta(1, 2)
      pac[1,3,1] <- (1-pac[1,3,3])*p31.ac2.aux[1]
      pac[1,3,2] <- 1-pac[1,3,1]-pac[1,3,3]

## GG4
      pac[1,4,4] <- (p[1,4]-prev[5]*pac[1,5,4])/prev[4]
            p41.ac2.aux[1] ~ dbeta(1, 2)
      pac[1,4,1] <- (1-pac[1,4,4])*p41.ac2.aux[1]
            p34.ac2.aux[1] ~ dbeta(1, 1)
      pac[1,4,2] <- (1 - pac[1,4,1]-pac[1,4,4]) * p34.ac2.aux[1]
      pac[1,4,3] <- 1 - sum(pac[1,4,1:2]) - pac[1,4,4]

## GG5
      pac[1,5,5] <- p[1,5]/prev[5]
            p35.ac1.aux[1] ~ dbeta(1, 3)
      pac[1,5,1] <- (1-pac[1,5,5])*p35.ac1.aux[1]
            p35.ac2.aux[1] ~ dbeta(1, 2)
      pac[1,5,2] <- (1-pac[1,5,1]-pac[1,5,5])*p35.ac2.aux[1]
            p35.ac3.aux[1] ~ dbeta(1, 1)
      pac[1,5,3] <- (1-sum(pac[1,5,1:2])-pac[1,5,5])*p35.ac3.aux[1]
      pac[1,5,4] <- 1-sum(pac[1,5,1:3]) - pac[1,5,5]


####### determining accuracy matrix for COG + SB and SOFT +SB, k=4 and k=5 respec
#######
for (k in 4:5) {
## GG2
      pac[k,2,2] <- (p[k,2]-prev[5]*pac[k,5,2]-prev[4]*pac[k,4,2]-
prev[3]*pac[k,3,2])/prev[2]
      pac[k,2,1] <- 1- pac[k,2,2]
```

```
## GG3
       pac[k,3,3] <- (p[k,3]-prev[5]*pac[k,5,3]-prev[4]*pac[k,5,4])/prev[3]
                          p31.ac2.aux[k] ~ dbeta(1, 2)
       pac[k,3,1] <- (1-pac[k,3,3])*p31.ac2.aux[k]
       pac[k,3,2] <- 1-pac[k,3,1]-pac[k,3,3]

## GG4
       pac[k,4,4] <- (p[k,4]-prev[5]*pac[k,5,4])/prev[4]
              p41.ac2.aux[k] ~ dbeta(1, 2)
       pac[k,4,1] <- (1-pac[k,4,4])*p41.ac2.aux[k]
              p34.ac2.aux[k] ~ dbeta(1, 1)
       pac[k,4,2] <- (1 - pac[k,4,1]-pac[k,4,4]) * p34.ac2.aux[k]
       pac[k,4,3] <- 1 - sum(pac[k,4,1:2]) - pac[k,4,4]

## GG5
       pac[k,5,5] <- p[k,5]/prev[5]
              p35.ac1.aux[k] ~ dbeta(1, 3)
       pac[k,5,1] <- (1-pac[k,5,5])*p35.ac1.aux[k]
              p35.ac2.aux[k] ~ dbeta(1, 2)
       pac[k,5,2] <- (1-pac[k,5,1]-pac[k,5,5])*p35.ac2.aux[k]
              p35.ac3.aux[k] ~ dbeta(1, 1)
       pac[k,5,3] <- (1-sum(pac[k,5,1:2])-pac[k,5,5])*p35.ac3.aux[k]
       pac[k,5,4] <- 1-sum(pac[k,5,1:3]) - pac[k,5,5]
       }

## constraints  0<x<1
for ( i in 2:5) {
       for (j in 1:i) {
              z1[1, i,j] <- 1
              z1[1, i,j] ~ dbern(constraintt1[1, i,j])
       constraintt1[1,i,j] <- step(1-pac[1,i,j])*step(pac[1,i,j])
       }
}
for (k in 4:5) {
       for ( i in 2:5) {
              for (j in 1:i) {
                     z1[k, i,j] <- 1
                     z1[k, i,j] ~ dbern(constraintt1[k, i,j])
              constraintt1[k, i,j] <- step(1-pac[k,i,j])*step(pac[k,i,j])
                     }
              }
       }
}
```

Data

```
# ns = number of studies
# nt = number of treatments
# nc = number of categories
# nsX = number of studies of type X
# ncX = number of categories in studies type X

# T1=cog
# T2=SB
# T3=fus
# T4=cog+SB
# T5=fus+SB

list(ns=2, nt=5, nc=5, nsA=4, ncA=2, nsB=5, ncB=3, nsC=2, ncC=4,
#b1=c(0.379032,0.153226,0.209677,0.157258,0.100806),  # PAIREDCAP baseline probs - cognitive
#b1=c(0.286290,0.173387,0.282258,0.161290,0.096774),  # PAIREDCAP baseline probs - software (Artemis)
b1=c(0.468864,0.164835,0.197802,0.105311,0.063187),  # Filson (naive only) baseline probs - software (Artemis)
#b1=c(0.686792,0.086792,0.101887,0.077830,0.046698),  # Filson (prior neg) baseline probs - software (Artemis)
b2=c(0.355311,0.219780,0.223443,0.118321,0.083144)  # Filson (naive only) baseline probs - software + SB (Artemis) [split
by SB proportion in PAIREDCAP]
```

#b2=c(0.584906,0.150943,0.116981,0.086433,0.060737) # Filson (prior neg) baseline probs - software + SB (Artemis) [split by SB proportion in PAIREDCAP]
#b2=c(0.355311,0.219780,0.223443,0.125916,0.075549) # Filson (naive only) baseline probs - software + SB (Artemis) [split by Artemis proportion in PAIREDCAP]
)

na[]	t[,1]	t[,2]	t[,3]	M[,1]	M[,2]	M[,3]	y[,1,1]	y[,2,1]	y[,3,1]	y[,1,2]	y[,2,2]	
	y[,3,2]	y[,1,3]	y[,2,3]	y[,3,3]	y[,1,4]	y[,2,4]	y[,3,4]	y[,1,5]	y[,2,5]	y[,3,5]	#	study
ID	Study type											
3	1	2	3	248	248	248	94	52	71	38	46	43
	52	87	70	39	37	40	25	26	24	#	PAIREDCAP	
	all											
2	4	5	NA	100	99	NA	69	55	NA	19	25	NA
	6	13	NA	5	3	NA	1	3	NA	#	Izadpanahi	
	all											
3	2	3	5	169	169	169	53	49	36	116	120	133
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Wajswol 2020	
	A											
3	1	2	4	75	75	75	41	35	32	34	40	43
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Thangarasu	
2021	A											
3	1	2	4	63	63	63	30	33	25	33	30	38
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Kulis 2020	
	A											
2	1	3	NA	88	88	NA	57	48	NA	31	40	NA
	NA	NA	NA	NA	NA	NA	NA	NA	NA	#	Cornud	A
2	1	3	NA	78	79	NA	44	40	NA	8	12	NA
	26	27	NA	NA	NA	NA	NA	NA	NA	#	FUTURE	B
2	1	3	NA	125	125	NA	85	80	NA	16	16	NA
	24	29	NA	NA	NA	NA	NA	NA	NA	#	PROFUS	B
3	2	3	5	74	74	74	41	39	32	12	10	13
	21	25	29	NA	NA	NA	NA	NA	NA	#	Albisinni 2018	
	B											
3	2	3	5	191	191	191	103	106	85	36	25	34
	52	60	72	NA	NA	NA	NA	NA	NA	#	Fourcade 2018	
	B											
3	1	2	4	111	111	111	69	81	65	19	9	20
	23	21	26	NA	NA	NA	NA	NA	NA	#	Gomez-Ortiz	
2022	B											
3	2	3	5	48	48	48	23	20	16	11	11	13
	10	13	13	4	4	6	NA	NA	NA	#	Alberts 2018	
(all men)	C											
3	2	3	5	538	538	538	294	310	252	114	68	100
	74	81	92	56	79	94	NA	NA	NA	#	Filson 2016	
	C											
END												

#extension
list(
#B.y = c(94,38,52,39,25), B.M=248, #PAIREDCAP baseline cognitive
#B.y = c(71, 43, 70, 40, 24), B.M =248, #PAIREDCAP baseline fusion
B.y = c(128, 45, 54, 29, 17), B.M =273, ## FUS – filson naive
B.z = c(97, 60, 61, 32, 23), B.Mz=273, ## FUS+SB – filson naive
#B.y = c(182, 23, 27, 21, 12), B.M =265 ## FUS – filson prior negative
#B.z = c(155, 40, 31, 23, 16), B.Mz=265, ## FUS+SB – filson prior negative
# y2.ac = c(11,14) ,
# y3.ac = c(13,1,15),
# y4.ac= c(1,1,2,16),
# y5.ac= c(0,0,1,1,25),
# M.ac=c(25,29,20,27) # conditional accuracy matrix Zhou
y2.ac = c(24,11) ,
y3.ac = c(21,17,45),
y4.ac= c(10,2,9,24),
y5.ac= c(6,2,7,8,36),
M.ac=c(35,83,45,59) # conditional accuracy matrix Mortezavi
)

Initial values

```
#chain 1
list( a = structure(.Data = c(  NA,0,0,0,0,          NA,0,0,0,0,          NA,0,NA,NA,NA,          NA,0,NA,NA,NA,
NA,0,NA,NA,NA,          NA,0,NA,NA,NA,          NA,0,0,NA,NA,          NA,0,0,NA,NA,          NA,0,0,NA,NA,
NA,0,0,NA,NA,          NA,0,0,NA,NA,          NA,0,0,0,NA,          NA,0,0,0,NA),
.Dim = c(13,5)),
d = structure(.Data = c( NA,NA,NA,NA,NA,          NA,0,0,0,0,          NA,0,0,0,0,          NA,0,0,0,0,
NA,0,0,0,0),
.Dim = c(5,5)),
dA = structure(.Data = c(NA,NA,          NA,0,          NA,0,          NA,0,          NA,0),
.Dim = c(5,2)),
dB = structure(.Data = c(NA,NA,NA,          NA,NA,0,          NA,NA,0,          NA,NA,0,          NA,NA,0),
.Dim = c(5,3)),
dC = structure(.Data = c(NA,NA,NA,NA,          NA,NA,NA,0,          NA,NA,NA,0,          NA,NA,NA,0,
NA,NA,NA,0),
.Dim = c(5,4))
)

#chain 2
list( a = structure(.Data = c(  NA,2,-.5,1,-1,          NA,2,3,1,2,          NA,-2,NA,NA,NA,          NA,-2,NA,NA,NA,
NA,-2,NA,NA,NA,          NA,-2,NA,NA,NA,          NA,-2,1,NA,NA,          NA,1,-2,NA,NA,          NA,-2,1,NA,NA,
NA,-2,1,NA,NA,          NA,-2,1,NA,NA,          NA,.7,-2,-1,NA,          NA,1,-2,2,NA),
.Dim = c(13,5)),
d = structure(.Data = c( NA,NA,NA,NA,NA,          NA,-1,-2,1,2,          NA,.5,-2,-1,1,          NA,2,-2,.5,-2,
NA,1,2,1,-2),
.Dim = c(5,5)),
dA = structure(.Data = c(NA,NA,          NA,-2,          NA,2,          NA,1,          NA,2),
.Dim = c(5,2)),
dB = structure(.Data = c(NA,NA,NA,          NA,NA,1,          NA,NA,-1,          NA,NA,-2,          NA,NA,-1),
.Dim = c(5,3)),
dC = structure(.Data = c(NA,NA,NA,NA,          NA,NA,NA,2,          NA,NA,NA,.7,          NA,NA,NA,-.5,
NA,NA,NA,-2),
.Dim = c(5,4))
)
```

Additional results

TABLE 67 Distribution of test results, joint probabilities and prevalence probabilities (mean and 95% CrI) according to ISUP grade for biopsy-naive individuals

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.516 (0.416 to 0.615)	0.186 (0.131 to 0.249)	0.136 (0.068 to 0.211)	0.098 (0.052 to 0.157	0.064 (0.031 to 0.114)	0.457 (0.403 to 0.513)	0.173 (0.137 to 0.214)	0.196 (0.157 to 0.233)	0.108 (0.079 to 0.144)	0.066 [0.043 to 0.095]
		CF					SF				
		(Joint probability matrix)					(Joint probability matrix)				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.121 (0.007 to 0.238)	NC	0.121 (0.007 to 0.238)	0	0	0	0	0.121 (0.007 to 0.238)	0	0	0	0
0.318 (0.212 to 0.452)	1	0.265 (0.136 to 0.413)	0.053 (0.002 to 0.141)	0	0	0	0.215 (0.122 to 0.335)	0.103 (0.063 to 0.149)	0	0	0
0.262 (0.193 to 0.341)	2	0.08 (0.004 to 0.184)	0.094 (0.022 to 0.178)	0.088 (0.026 to 0.145)	0	0	0.066 (0.038 to 0.104)	0.054 (0.03 to 0.084)	0.142 (0.102 to 0.185)	0	0
0.183 (0.119 to 0.265)	3	0.035 (0.001 to 0.108)	0.026 (0.001 to 0.081)	0.035 (0.002 to 0.105)	0.086 (0.032 to 0.146)	0	0.042 (0.016 to 0.079)	0.011 (0.002 to 0.029)	0.038 (0.017 to 0.071)	0.092 (0.062 to 0.129)	0
0.116 (0.077 to 0.174)	4 or 5	0.015 (0.000 to 0.048)	0.013 (0.000 to 0.044)	0.013 (0.000 to 0.043)	0.012 (0.000 to 0.04)	0.064 (0.031 to 0.114)	0.013 (0.005 to 0.026)	0.006 (0.001 to 0.014)	0.015 (0.006 to 0.031)	0.016 (0.007 to 0.032)	0.066 (0.043 to 0.095)

continued

TABLE 67 Distribution of test results, joint probabilities and prevalence probabilities (mean and 95% CrI) according to ISUP grade for biopsy-naive individuals (*continued*)

Network 2		**(Distribution of test results)**					**(Distribution of test results)**				
		0.460 (0.335 to 0.583)	**0.250 (0.152 to 0.356)**	**0.127 (0.034 to 0.261)**	**0.131 (0.046 to 0.231)**	**0.033 (0.001 to 0.107)**	**0.348 (0.273 to 0.418)**	**0.223 (0.179 to 0.273)**	**0.232 (0.168 to 0.311)**	**0.115 (0.081 to 0.152)**	**0.082 (0.054 to 0.114)**
		Combined CF and systematic biopsy					**Combined SF and systematic biopsy**				
		(Joint probability matrix)					**(Joint probability matrix)**				
(Prevalence)	**ISUP**	**NC**	**1**	**2**	**3**	**4 or 5**	**NC**	**1**	**2**	**3**	**4 or 5**
0.121 (0.007 to 0.238)	NC	0.121 (0.007 to 0.238)	0	0	0	0	0.121 (0.007 to 0.238)	0	0	0	0
0.318 (0.212 to 0.452)	**1**	0.227 (0.08 to 0.382)	0.091 (0.004 to 0.212)	0	0	0	0.171 (0.051 to 0.306)	0.147 (0.054 to 0.219)	0	0	0
0.262 (0.193 to 0.341)	**2**	0.066 (0.002 to 0.185)	0.114 (0.017 to 0.229)	0.082 (0.007 to 0.208)	0	0	0.021 (0.000 to 0.080)	0.041 (0.003 to 0.122)	0.199 (0.141 to 0.251)	0	0
0.183 (0.119 to 0.265)	**3**	0.023 (0.000 to 0.093)	0.022 (0 to 0.09)	0.025 (0.000 to 0.097)	0.112 (0.023 to 0.212)	0	0.025 (0.001 to 0.098)	0.026 (0.001 to 0.092)	0.025 (0.001 to 0.089)	0.106 (0.063 to 0.146)	0
0.116 (0.077 to 0.174)	**4 or 5**	0.023 (0.000 to 0.078)	0.022 (0.001 to 0.078)	0.02 (0.000 to 0.069)	0.019 (0.000 to 0.067)	0.033 (0.001 to 0.107)	0.009 (0.000 to 0.042)	0.009 (0.000 to 0.037)	0.008 (0.000 to 0.037)	0.009 (0.000 to 0.038)	0.082 (0.054 to 0.114)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of main analysis.

Influence of the use of constraints on the network meta-analysis estimates

Comparison of inferences on distribution of test results with the synthesis code used in isolation and the synthesis code including the extension.

TABLE 68 Influence of the model extension on inferences over the probability of test results for biopsy naive. Main analysis

Model		Synthesis model	Extended synthesis and accuracy model		
Assumptions over baseline probability		Deterministic	Deterministic	Probabilistic	Probabilistic
Calculation of distribution of test results		Directly from synthesis	Directly from synthesis	Directly from synthesis	Back calculated from prevalence and accuracy matrix
Biopsy method	Category				
Network 1					
CF	NC	0.552 (0.475 to 0.624)	0.545 (0.477 to 0.612)	0.531 (0.446 to 0.616)	0.513 (0.414 to 0.610)
	1	0.174 (0.132 to 0.223)	0.177 (0.135 to 0.225)	0.185 (0.129 to 0.249)	0.185 (0.132 to 0.245)
	2	0.118 (0.081 to 0.164)	0.121 (0.085 to 0.165)	0.120 (0.078 to 0.173)	0.139 (0.070 to 0.217)
	3	0.094 (0.058 to 0.143)	0.095 (0.059 to 0.142)	0.098 (0.055 to 0.160)	0.097 (0.056 to 0.159)
	4 or 5	0.062 (0.034 to 0.104)	0.062 (0.035 to 0.099)	0.066 (0.032 to 0.117)	0.065 (0.032 to 0.115)
SF	NC	0.469	0.469	0.457 (0.403 to 0.509)	0.457 (0.403 to 0.513)
	1	0.165	0.165	0.172 (0.137 to 0.212)	0.173 (0.137 to 0.214)
	2	0.198	0.198	0.195 (0.159 to 0.236)	0.196 (0.157 to 0.233)
	3	0.105	0.105	0.109 (0.080 to 0.146)	0.108 (0.079 to 0.144)
	4 or 5	0.063	0.063	0.067 (0.045 to 0.095)	0.066 (0.043 to 0.095)
Network 2					
Combined CF **and systematic biopsy**	NC	0.402 (0.210 to 0.559)	0.451 (0.345 to 0.562)	0.455 (0.343 to 0.570)	0.460 (0.335 to 0.583)
	1	0.211 (0.102 to 0.326)	0.246 (0.16 to 0.349)	0.249 (0.156 to 0.362)	0.250 (0.152 to 0.356)
	2	0.109 (0.031 to 0.238)	0.136 (0.054 to 0.256)	0.134 (0.052 to 0.255)	0.127 (0.034 to 0.261)
	3	0.241 (0.058 to 0.586)	0.135 (0.048 to 0.245)	0.130 (0.045 to 0.230)	0.131 (0.046 to 0.231)
	4 or 5	0.037 (0.001 to 0.172)	0.033 (0.001 to 0.107)	0.032 (0.001 to 0.107)	0.033 (0.001 to 0.107)
Combined SF **and systematic biopsy**	NC	0.355	0.355	0.359 (0.305 to 0.413)	0.346 (0.274 to 0.408)
	1	0.220	0.220	0.223 (0.178 to 0.273)	0.222 (0.177 to 0.273)
	2	0.223	0.223	0.221 (0.177 to 0.270)	0.234 (0.170 to 0.313)
	3	0.118	0.118	0.115 (0.082 to 0.154)	0.116 (0.084 to 0.153)
	4 or 5	0.083	0.083	0.082 (0.055 to 0.114)	0.082 (0.054 to 0.114)

Results from this comparison show that for network 1 the structural extension model does not significantly influence synthesis estimates. For network 2, estimates of category 4 for the non-reference treatment (combined CF and systematic biopsy) are reduced in the extended model, which suggests a conflict between the structural extension (including data sources added) and the uncertainty derived from the multinomial log odds model implemented in the synthesis. For this category, there is only one study providing a direct comparison of combined software versus combined CF with very few patients classified in categories 4 or 5,[82] providing very sparse information. This study reports a proportion of 5% of test results in category 4 with combined cognitive, versus 3% in combined SF. Therefore, uncertainty is very wide for this category and the constrained model restricts the distribution of this category the most.

TABLE 69 Influence of the model extension on inferences over the probability of test results for previous negative biopsy. Subgroup analysis

Model		Synthesis model	Extended synthesis and accuracy model		
Assumptions over baseline probability		Deterministic	Deterministic	Probabilistic	Probabilistic
Calculation of distribution of test results		Directly from synthesis	Directly from synthesis	Directly from synthesis	Back calculated from prevalence and accuracy matrix
Biopsy method	ISUP grade				
Network 1					
CF	NC	0.750 (0.688 to 0.803)	0.744 (0.686 to 0.798)	0.719 (0.643 to 0.788)	0.703 (0.618 to 0.776)
	1	0.085 (0.062 to 0.114)	0.088 (0.065 to 0.12)	0.105 (0.069 to 0.153)	0.105 (0.071 to 0.155)
	2	0.057 (0.038 to 0.082)	0.058 (0.04 to 0.079)	0.061 (0.039 to 0.091)	0.077 (0.035 to 0.138)
	3	0.065 (0.039 to 0.101)	0.066 (0.038 to 0.101)	0.068 (0.036 to 0.116)	0.068 (0.033 to 0.120)
	4 or 5	0.043 (0.023 to 0.074)	0.044 (0.024 to 0.07)	0.047 (0.021 to 0.086)	0.046 (0.021 to 0.085)
SF	NC	0.687	0.687	0.661 (0.611 to 0.710)	0.661 (0.611 to 0.709)
	1	0.087	0.087	0.103 (0.075 to 0.137)	0.103 (0.076 to 0.135)
	2	0.102	0.102	0.107 (0.082 to 0.136)	0.107 (0.082 to 0.136)
	3	0.078	0.078	0.080 (0.055 to 0.110)	0.080 (0.055 to 0.111)
	4 or 5	0.047	0.047	0.049 (0.031 to 0.073)	0.049 (0.031 to 0.073)
Network 2					
Combined CF **and systematic biopsy**	NC	0.615 (0.382 to 0.76)	0.658 (0.557 to 0.75)	0.664 (0.56 to 0.761)	0.659 (0.561 to 0.752)
	1	0.135 (0.073 to 0.208)	0.152 (0.098 to 0.221)	0.155 (0.093 to 0.240)	0.157 (0.096 to 0.241)
	2	0.053 (0.015 to 0.120)	0.067 (0.025 to 0.135)	0.065 (0.023 to 0.136)	0.067 (0.015 to 0.152)
	3	0.171 (0.036 to 0.468)	0.095 (0.03 to 0.181)	0.090 (0.028 to 0.163)	0.091 (0.027 to 0.165)
	4 or 5	0.027 (0.000 to 0.125)	0.029 (0.001 to 0.099)	0.027 (0.001 to 0.087)	0.027 (0.001 to 0.081)
Combined SF **and systematic biopsy**	NC	0.585	0.585	0.591 (0.536 to 0.647)	0.583 (0.513 to 0.649)
	1	0.151	0.151	0.154 (0.114 to 0.201)	0.155 (0.114 to 0.198)
	2	0.117	0.117	0.113 (0.080 to 0.147)	0.120 (0.074 to 0.181)
	3	0.086	0.086	0.084 (0.056 to 0.118)	0.083 (0.057 to 0.117)
	4 or 5	0.061	0.061	0.058 (0.036 to 0.084)	0.058 (0.037 to 0.084)

Sensitivity analysis

TABLE 70 Influence of the model extension on inferences over the probability of test results for biopsy naive

Model		Synthesis model	Extended synthesis and accuracy model		
Assumptions over baseline probability		Deterministic	Deterministic	Probabilistic	Probabilistic
Calculation of distribution of test results		Directly from synthesis	Directly from synthesis	Directly from synthesis	Back calculated from prevalence and accuracy matrix
	ISUP				
Network 1					
CF	NC	0.363 (0.294 to 0.435)	0.364 (0.293 to 0.44)	0.392 (0.308 to 0.482)	0.368 (0.248 to 0.473)
	1	0.197 (0.148 to 0.255)	0.199 (0.152 to 0.253)	0.192 (0.133 to 0.263)	0.191 (0.140 to 0.256)
	2	0.182 (0.130 to 0.245)	0.184 (0.130 to 0.25)	0.169 (0.111 to 0.242)	0.196 (0.101 to 0.306)
	3	0.156 (0.100 to 0.226)	0.152 (0.095 to 0.219)	0.147 (0.084 to 0.232)	0.145 (0.079 to 0.228)
	4 or 5	0.102 (0.057 to 0.167)	0.102 (0.059 to 0.154)	0.100 (0.051 to 0.176)	0.101 (0.052 to 0.176)
SF	NC	0.286	0.286	0.313 (0.271 to 0.360)	0.314 (0.271 to 0.362)
	1	0.173	0.173	0.170 (0.135 to 0.209)	0.169 (0.137 to 0.207)
	2	0.282	0.282	0.262 (0.218 to 0.310)	0.263 (0.218 to 0.308)
	3	0.161	0.161	0.158 (0.117 to 0.203)	0.157 (0.117 to 0.204)
	4 or 5	0.097	0.097	0.097 (0.064 to 0.137)	0.098 (0.064 to 0.140)

Note
Sensitivity analysis to baseline distribution (PAIREDCAP's baseline, Mortezavi's accuracy).

TABLE 71 Influence of the model extension on inferences over the probability of test results for biopsy naive

Model		Synthesis model		Extended synthesis and accuracy model	
Assumptions over baseline probability		Deterministic	Deterministic	Probabilistic	Probabilistic
Calculation of distribution of test results		Directly from synthesis	Directly from synthesis	Directly from synthesis	Back calculated from prevalence and accuracy matrix
	ISUP				
Network 1					
CF	NC	0.552 (0.475 to 0.624)	0.555 (0.488 to 0.626)	0.531 (0.445 to 0.621)	0.525 (0.433 to 0.620)
	1	0.174 (0.132 to 0.223)	0.179 (0.132 to 0.232)	0.191 (0.132 to 0.264)	0.190 (0.131 to 0.256)
	2	0.118 (0.081 to 0.164)	0.117 (0.082 to 0.161)	0.112 (0.070 to 0.169)	0.122 (0.062 to 0.201)
	3	0.094 (0.058 to 0.143)	0.093 (0.059 to 0.137)	0.099 (0.055 to 0.160)	0.098 (0.053 to 0.158)
	4 or 5	0.062 (0.034 to 0.104)	0.056 (0.032 to 0.083)	0.066 (0.034 to 0.109)	0.065 (0.033 to 0.106)

continued

TABLE 71 Influence of the model extension on inferences over the probability of test results for biopsy naive (*continued*)

Model		Synthesis model		Extended synthesis and accuracy model	
Assumptions over baseline probability		Deterministic	Deterministic	Probabilistic	Probabilistic
Calculation of distribution of test results		Directly from synthesis	Directly from synthesis	Directly from synthesis	Back calculated from prevalence and accuracy matrix
	ISUP				
SF	NC	0.469	0.469	0.449 (0.396 to 0.503)	0.450 (0.400 to 0.509)
	1	0.165	0.165	0.176 (0.139 to 0.220)	0.175 (0.140 to 0.217)
	2	0.198	0.198	0.189 (0.149 to 0.234)	0.189 (0.147 to 0.236)
	3	0.105	0.105	0.112 (0.082 to 0.149)	0.112 (0.082 to 0.146)
	4 or 5	0.063	0.063	0.075 (0.053 to 0.105)	0.075 (0.053 to 0.103)

Note
Sensitivity analysis to accuracy matrix (Filson's baseline, Zhou's accuracy).

Detailed results for subgroup analysis on previous negative-biopsy individuals

In this analysis, the baseline distribution of test results for SF was sourced from Filson *et al.*,[96] but using the group of individuals recruited into this study that had previous negative-biopsy results. However, the diagnostic accuracy evidence synthesis and the accuracy matrix are still sourced as per the main analysis, grounded on evidence over biopsy-naive patients. *Table 72* presents summary results of distribution of test results and prevalence probabilities and results of the accuracy matrices are presented in *Appendix 10*.

The summary results in *Table 72* illustrate that, for individuals with a previous negative biopsy, a significantly increased proportion of 'no cancer' results are expected in relation to biopsy-naive individuals. This impacts the (implicit) prevalence estimates: for those with previous negative biopsy, the probability of NC is 43% (95% CrI 26% to 53%), while for biopsy naive it is 12% (95% CrI 0.7% to 24%). In comparing software with CF biopsy strategies, across both networks, we observe similar probabilities of ISUP grade 1, 3 and 4 or 5 results, and a slightly higher probability of ISUP grade 2 results for software strategies. This differs from the results of the synthesis model for ISUP grade 3 only, where the probability under combined CF was slightly higher than for combined fusion software (see *Table 4*). The accuracy matrix estimates (reported in *Appendix 10*) are similar to those estimated for biopsy-naive individuals (main analysis, *Table 9*).

TABLE 72 Distribution of test results and prevalence probabilities (mean and 95% CrI) according to ISUP Grade (D) for subgroup and sensitivity analysis

		Distribution of test results			
		Network 1		Network 2	
Prevalence	ISUP	CF	SF	Combined CF and systematic biopsy	Combined SF and systematic biopsy
Subgroup analysis (previous negative biopsy)					
0.428 (0.259 to 0.529)	NC	0.703 (0.618 to 0.776)	0.661 (0.611 to 0.709)	0.659 (0.561 to 0.752)	0.583 (0.513 to 0.649)
0.224 (0.138 to 0.39)	1	0.105 (0.071 to 0.155)	0.107 (0.082 to 0.136)	0.157 (0.096 to 0.241)	0.155 (0.114 to 0.198)

TABLE 72 Distribution of test results and prevalence probabilities (mean and 95% CrI) according to ISUP Grade (D) for subgroup and sensitivity analysis (*continued*)

		Distribution of test results			
		Network 1		Network 2	
Prevalence	ISUP	CF	SF	Combined CF and systematic biopsy	Combined SF and systematic biopsy
0.132 (0.091 to 0.188)	**2**	0.077 (0.035 to 0.138)	0.107 (0.082 to 0.136)	0.067 (0.015 to 0.152)	0.120 (0.074 to 0.181)
0.131 (0.079 to 0.199)	**3**	0.068 (0.033 to 0.120)	0.080 (0.055 to 0.111)	0.091 (0.027 to 0.165)	0.083 (0.057 to 0.117)
0.085 (0.053 to 0.127)	**4 or 5**	0.046 (0.021 to 0.085)	0.049 (0.031 to 0.073)	0.027 (0.001 to 0.081)	0.058 (0.037 to 0.084)
Sensitivity analysis to baseline distribution for biopsy naive (PAIREDCAP's baseline, Mortezavi's accuracy)					
0.031 (0.001 to 0.092)	NC	0.368 (0.248 to 0.473)	0.314 (0.271 to 0.362)	NA	NA
0.226 (0.163 to 0.319)	**1**	0.191 (0.140 to 0.256)	0.169 (0.137 to 0.207)	NA	NA
0.322 (0.222 to 0.42)	**2**	0.196 (0.101 to 0.306)	0.263 (0.218 to 0.308)	NA	NA
0.252 (0.154 to 0.37)	**3**	0.145 (0.079 to 0.228)	0.098 (0.064 to 0.140)	NA	NA
0.169 (0.104 to 0.254)	**4 or 5**	0.101 (0.052 to 0.176)	0.098 (0.064 to 0.140)	NA	NA
Sensitivity analysis to accuracy matrix for biopsy naive (Filson's baseline, Zhou's accuracy)					
0.170 (0.023 to 0.280)	NC	0.525 (0.433 to 0.620)	0.450 (0.400 to 0.509)	NA	NA
0.279 (0.196 to 0.400)	**1**	0.190 (0.131 to 0.256)	0.175 (0.140 to 0.217)	NA	NA
0.300 (0.211 to 0.436)	**2**	0.122 (0.062 to 0.201)	0.189 (0.147 to 0.236)	NA	NA
0.155 (0.109 to 0.223)	**3**	0.098 (0.053 to 0.158)	0.112 (0.082 to 0.146)	NA	NA
0.095 (0.067 to 0.136)	**4 or 5**	0.450 (0.400 to 0.509)	0.075 (0.053 to 0.103)	NA	NA

Note
Diagnostic accuracy extension to the evidence synthesis model.

TABLE 73 Distribution of test results, conditional accuracy and prevalence probabilities (mean and 95% CrI) according to ISUP Grade (D) for individuals with a previous negative biopsy

Network 1											
		0.703 (0.618 to 0.776)	**0.105 (0.071 to 0.155)**	**0.077 (0.035 to 0.138)**	**0.068 (0.033 to 0.12)**	**0.046 (0.021 to 0.085)**	**0.661 (0.611 to 0.709)**	**0.103 (0.076 to 0.135)**	**0.107 (0.082 to 0.136)**	**0.080 (0.055 to 0.111)**	**0.049 (0.031 to 0.073)**
		CF					**SF**				
	ISUP	**NC**	**1**	**2**	**3**	**4 or 5**	**NC**	**1**	**2**	**3**	**4 or 5**
0.428 (0.259 to 0.529)	NC	1	0	0	0	0	1	0	0	0	0
0.224 (0.138 to 0.39)	**1**	0.857 (0.575 to 0.995)	0.143 (0.005 to 0.425)	0	0	0	0.698 (0.557 to 0.826)	0.302 (0.174 to 0.443)	0	0	0
0.132 (0.091 to 0.188)	**2**	0.324 (0.026 to 0.722)	0.374 (0.066 to 0.718)	0.302 (0.049 to 0.557)	0	0	0.264 (0.183 to 0.35)	0.201 (0.13 to 0.288)	0.536 (0.436 to 0.626)	0	0
0.131 (0.079 to 0.199)	**3**	0.195 (0.005 to 0.571)	0.130 (0.003 to 0.428)	0.208 (0.007 to 0.579)	0.466 (0.181 to 0.793)	0	0.225 (0.129 to 0.344)	0.054 (0.011 to 0.125)	0.195 (0.103 to 0.301)	0.526 (0.404 to 0.648)	0
0.085 (0.053 to 0.127)	**4 or 5**	0.136 (0.002 to 0.439)	0.109 (0.002 to 0.324)	0.115 (0.003 to 0.363)	0.093 (0.004 to 0.315)	0.547 (0.283 to 0.902)	0.110 (0.044 to 0.193)	0.046 (0.01 to 0.114)	0.122 (0.055 to 0.216)	0.141 (0.071 to 0.226)	0.581 (0.462 to 0.694)
Network 2											
		0.659 (0.561 to 0.752)	**0.157 (0.096 to 0.241)**	**0.067 (0.015 to 0.152)**	**0.091 (0.027 to 0.165)**	**0.027 (0.001 to 0.081)**	**0.583 (0.513 to 0.649)**	**0.155 (0.114 to 0.198)**	**0.120 (0.074 to 0.181)**	**0.083 (0.057 to 0.117)**	**0.058 (0.037 to 0.084)**
		Combined CF and systematic biopsy					**Combined SF and systematic biopsy**				
	ISUP	**NC**	**1**	**2**	**3**	**4 or 5**	**1**	**2**	**3**	**4**	**5**
0.428 (0.259 to 0.529)	NC	1	0	0	0	0	1	0	0	0	0
0.224 (0.138 to 0.39)	**1**	0.693 (0.251 to 0.984)	0.307 (0.016 to 0.749)	0	0	0	0.497 (0.153 to 0.845)	0.503 (0.155 to 0.847)	0	0	0
0.132 (0.091 to 0.188)	**2**	0.272 (0.009 to 0.709)	0.448 (0.058 to 0.864)	0.281 (0.017 to 0.791)	0	0	0.087 (0.002 to 0.315)	0.176 (0.012 to 0.46)	0.736 (0.408 to 0.971)	0	0
0.131 (0.079 to 0.199)	**3**	0.136 (0.001 to 0.515)	0.121 (0.002 to 0.474)	0.140 (0.001 to 0.515)	0.603 (0.126 to 0.982)	0	0.138 (0.003 to 0.439)	0.132 (0.002 to 0.44)	0.131 (0.003 to 0.418)	0.600 (0.298 to 0.938)	0
0.085 (0.053 to 0.127)	**4 or 5**	0.207 (0.003 to 0.629)	0.196 (0.004 to 0.577)	0.147 (0.004 to 0.546)	0.135 (0.003 to 0.434)	0.315 (0.014 to 0.899)	0.071 (0.001 to 0.251)	0.074 (0.001 to 0.284)	0.073 (0.001 to 0.266)	0.083 (0.001 to 0.311)	0.699 (0.367 to 0.966)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of subgroup analysis.

TABLE 74 Distribution of test results, joint probability matrix and prevalence probabilities (mean and 95% CrI) according to ISUP Grade (D) for individuals with a previous negative biopsy

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.703 (0.618 to 0.776)	0.105 (0.071 to 0.155)	0.077 (0.035 to 0.138)	0.068 (0.033 to 0.12)	0.046 (0.021 to 0.085)	0.661 (0.611 to 0.709)	0.103 (0.076 to 0.135)	0.107 (0.082 to 0.136)	0.080 (0.055 to 0.111)	0.049 (0.031 to 0.073)
		CF					SF				
		(Joint probability matrix)					(Joint probability matrix)				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.428 (0.259 to 0.529)	NC	0.428 (0.259 to 0.529)	0	0	0	0	0.428 (0.259 to 0.529)	0	0	0	0
0.224 (0.138 to 0.39)	**1**	0.194 (0.092 to 0.363)	0.03 (0.001 to 0.085)	0	0	0	0.159 (0.082 to 0.313)	0.065 (0.037 to 0.098)	0	0	0
0.132 (0.091 to 0.188)	**2**	0.044 (0.003 to 0.103)	0.049 (0.009 to 0.095)	0.04 (0.006 to 0.076)	0	0	0.035 (0.02 to 0.057)	0.026 (0.014 to 0.043)	0.071 (0.047 to 0.104)	0	0
0.131 (0.079 to 0.199)	**3**	0.026 (0.001 to 0.087)	0.017 (0 to 0.056)	0.028 (0.001 to 0.085)	0.06 (0.02 to 0.113)	0	0.03 (0.013 to 0.061)	0.007 (0.001 to 0.019)	0.026 (0.011 to 0.047)	0.068 (0.041 to 0.101)	0
0.085 (0.053 to 0.127)	**4 or 5**	0.012 (0 to 0.041)	0.009 (0 to 0.029)	0.01 (0 to 0.031)	0.008 (0 to 0.03)	0.046 (0.021 to 0.085)	0.009 (0.003 to 0.018)	0.004 (0.001 to 0.011)	0.01 (0.004 to 0.021)	0.012 (0.005 to 0.023)	0.049 (0.031 to 0.073)

continued

TABLE 74 Distribution of test results, joint probability matrix and prevalence probabilities (mean and 95% CrI) according to ISUP Grade (D) for individuals with a previous negative biopsy (*continued*)

Network 2		(Distribution of test results)					(Distribution of test results)				
		0.659 (0.561 to 0.752)	0.157 (0.096 to 0.241)	0.067 (0.015 to 0.152)	0.091 (0.027 to 0.165)	0.027 (0.001 to 0.081)	0.583 (0.513 to 0.649)	0.155 (0.114 to 0.198)	0.120 (0.074 to 0.181)	0.083 (0.057 to 0.117)	0.058 (0.037 to 0.084)
		Combined CF and systematic biopsy					Combined SF and systematic biopsy				
		(Joint probability matrix)					(Joint probability matrix)				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.121 (0.007 to 0.238)	NC	0.428 (0.259 to 0.529)	0	0	0	0	0.428 (0.259 to 0.529)	0	0	0	0
0.318 (0.212 to 0.452)	1	0.159 (0.041 to 0.344)	0.065 (0.004 to 0.145)	0	0	0	0.118 (0.025 to 0.3)	0.106 (0.039 to 0.16)	0	0	0
0.262 (0.193 to 0.341)	2	0.037 (0.001 to 0.101)	0.059 (0.007 to 0.122)	0.036 (0.002 to 0.11)	0	0	0.012 (0 to 0.048)	0.024 (0.001 to 0.072)	0.096 (0.054 to 0.136)	0	0
0.183 (0.119 to 0.265)	3	0.018 (0 to 0.072)	0.016 (0 to 0.063)	0.018 (0 to 0.071)	0.079 (0.015 to 0.154)	0	0.019 (0 to 0.074)	0.018 (0 to 0.064)	0.018 (0 to 0.068)	0.075 (0.04 to 0.115)	0
0.116 (0.077 to 0.174)	4 or 5	0.018 (0 to 0.057)	0.017 (0 to 0.056)	0.012 (0 to 0.045)	0.012 (0 to 0.044)	0.027 (0.001 to 0.081)	0.007 (0 to 0.027)	0.007 (0 to 0.029)	0.007 (0 to 0.027)	0.008 (0 to 0.031)	0.058 (0.037 to 0.084)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of subgroup analysis.

Detailed results of sensitivity analyses

TABLE 75 Distribution of test results, conditional accuracy and prevalence probabilities (mean and 95% CrI) according to ISUP Grade for biopsy-naive individuals

Network 1											
		0.368 (0.248 to 0.473)	**0.191 (0.14 to 0.256)**	**0.196 (0.101 to 0.306)**	**0.145 (0.079 to 0.228)**	**0.101 (0.052 to 0.176)**	**0.314 (0.271 to 0.362)**	**0.169 (0.137 to 0.207)**	**0.263 (0.218 to 0.308)**	**0.157 (0.117 to 0.204)**	**0.098 (0.064 to 0.14)**
		CF					**SF**				
	ISUP	**NC**	**1**	**2**	**3**	**4 or 5**	**NC**	**1**	**2**	**3**	**4 or 5**
0.031 (0.001 to 0.092)	NC	1	0	0	0	0	1	0	0	0	0
0.226 (0.163 to 0.319)	**1**	0.754 (0.355 to 0.990)	0.246 (0.010 to 0.645)	0	0	0	0.634 (0.506 to 0.773)	0.366 (0.227 to 0.494)	0	0	0
0.322 (0.222 to 0.42)	**2**	0.300 (0.025 to 0.642)	0.288 (0.071 to 0.532)	0.412 (0.133 to 0.687)	0	0	0.229 (0.155 to 0.305)	0.197 (0.123 to 0.276)	0.575 (0.484 to 0.67)	0	0
0.252 (0.154 to 0.37)	**3**	0.175 (0.007 to 0.520)	0.121 (0.004 to 0.402)	0.183 (0.006 to 0.492)	0.521 (0.27 to 0.862)	0	0.191 (0.105 to 0.294)	0.058 (0.013 to 0.121)	0.222 (0.124 to 0.331)	0.530 (0.412 to 0.659)	0
0.169 (0.104 to 0.254)	**4 or 5**	0.121 (0.004 to 0.392)	0.086 (0.001 to 0.285)	0.105 (0.003 to 0.342)	0.088 (0.002 to 0.31)	0.599 (0.324 to 0.920)	0.102 (0.041 to 0.184)	0.044 (0.009 to 0.107)	0.127 (0.06 to 0.216)	0.144 (0.069 to 0.236)	0.583 (0.449 to 0.700)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of sensitivity analysis using PAIREDCAP baseline and Mortezavi accuracy.

TABLE 76 Distribution of test results, joint probability matrix and prevalence probabilities (mean and 95% CrI) according to ISUP grade for biopsy-naive individuals

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.368 (0.248 to 0.473)	0.191 (0.14 to 0.256)	0.196 (0.101 to 0.306)	0.145 (0.079 to 0.228)	0.101 (0.052 to 0.176)	0.314 (0.271 to 0.362)	0.169 (0.137 to 0.207)	0.263 (0.218 to 0.308)	0.157 (0.117 to 0.204)	0.098 (0.064 to 0.14)
		CF					SF				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.031 (0.001 to 0.092)	NC	0.031 (0.001 to 0.092)	0	0	0	0	0.031 (0.001 to 0.092)	0	0	0	0
0.226 (0.163 to 0.319)	1	0.171 (0.07 to 0.271)	0.055 (0.002 to 0.151)	0	0	0	0.143 (0.098 to 0.202)	0.083 (0.043 to 0.129)	0	0	0
0.322 (0.222 to 0.42)	2	0.099 (0.006 to 0.235)	0.092 (0.021 to 0.173)	0.131 (0.042 to 0.21)	0	0	0.074 (0.042 to 0.114)	0.063 (0.036 to 0.097)	0.185 (0.125 to 0.246)	0	0
0.252 (0.154 to 0.37)	3	0.045 (0.001 to 0.144)	0.03 (0.001 to 0.095)	0.047 (0.001 to 0.142)	0.13 (0.055 to 0.219)	0	0.048 (0.021 to 0.088)	0.015 (0.003 to 0.035)	0.057 (0.024 to 0.1)	0.132 (0.081 to 0.181)	0
0.169 (0.104 to 0.254)	4 or 5	0.021 (0.001 to 0.079)	0.015 (0 to 0.054)	0.018 (0 to 0.064)	0.015 (0 to 0.056)	0.101 (0.052 to 0.176)	0.018 (0.006 to 0.038)	0.008 (0.001 to 0.02)	0.022 (0.008 to 0.048)	0.025 (0.009 to 0.049)	0.098 (0.064 to 0.14)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of sensitivity analysis using PAIREDCAP baseline and Mortezavi accuracy.

TABLE 77 Distribution of test results, conditional accuracy and prevalence probabilities (mean and 95% CrI) according to ISUP Grade for biopsy-naive individuals

Network 1											
		0.525 (0.433 to 0.62)	0.190 (0.131 to 0.256)	0.122 (0.062 to 0.201)	0.098 (0.053 to 0.158)	0.065 (0.033 to 0.106)	0.450 (0.400 to 0.509)	0.175 (0.140 to 0.217)	0.189 (0.147 to 0.236)	0.112 (0.082 to 0.146)	0.075 (0.053 to 0.103)
		CF					SF				
	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.170 (0.023 to 0.280)	NC	1	0	0	0	0	1	0	0	0	0
0.279 (0.196 to 0.400)	1	0.787 (0.435 to 0.992)	0.213 (0.008 to 0.565)	0	0	0	0.472 (0.321 to 0.631)	0.528 (0.369 to 0.679)	0	0	0
0.300 (0.211 to 0.436)	2	0.327 (0.03 to 0.693)	0.362 (0.065 to 0.646)	0.312 (0.127 to 0.518)	0	0	0.415 (0.268 to 0.569)	0.048 (0.006 to 0.129)	0.537 (0.392 to 0.691)	0	0
0.155 (0.109 to 0.223)	3	0.152 (0.003 to 0.448)	0.113 (0.003 to 0.367)	0.147 (0.003 to 0.477)	0.588 (0.292 to 0.919)	0	0.094 (0.013 to 0.257)	0.077 (0.013 to 0.203)	0.144 (0.035 to 0.31)	0.685 (0.512 to 0.846)	0
0.095 (0.067 to 0.136)	4 or 5	0.083 (0.001 to 0.326)	0.074 (0.001 to 0.278)	0.080 (0.002 to 0.284)	0.080 (0.001 to 0.296)	0.683 (0.391 to 0.975)	0.037 (0.001 to 0.128)	0.034 (0.001 to 0.113)	0.075 (0.011 to 0.189)	0.068 (0.01 to 0.175)	0.787 (0.65 to 0.915)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of sensitivity analysis using using Filson's baseline and Zhou's accuracy.

TABLE 78 Distribution of test results, joint probability matrix and prevalence probabilities (mean and 95% CrI) according to ISUP Grade for biopsy-naive individuals

Network 1		(Distribution of test results)					(Distribution of test results)				
		0.525 (0.433 to 0.62)	0.190 (0.131 to 0.256)	0.122 (0.062 to 0.201)	0.098 (0.053 to 0.158)	0.065 (0.033 to 0.106)	0.450 (0.400 to 0.509)	0.175 (0.140 to 0.217)	0.189 (0.147 to 0.236)	0.112 (0.082 to 0.146)	0.075 (0.053 to 0.103)
		CF					SF				
(Prevalence)	ISUP	NC	1	2	3	4 or 5	NC	1	2	3	4 or 5
0.170 (0.023 to 0.280)	NC	0.170 (0.023 to 0.28)	0	0	0	0	0.170 (0.023 to 0.28)	0	0	0	0
0.279 (0.196 to 0.400)	1	0.221 (0.101 to 0.355)	0.059 (0.002 to 0.158)	0	0	0	0.134 (0.068 to 0.24)	0.145 (0.103 to 0.192)	0	0	0
0.300 (0.211 to 0.436)	2	0.102 (0.009 to 0.261)	0.106 (0.019 to 0.194)	0.092 (0.039 to 0.154)	0	0	0.127 (0.064 to 0.235)	0.015 (0.001 to 0.042)	0.158 (0.111 to 0.205)	0	0
0.155 (0.109 to 0.223)	3	0.024 (0 to 0.077)	0.018 (0 to 0.058)	0.023 (0 to 0.077)	0.09 (0.042 to 0.153)	0	0.015 (0.002 to 0.042)	0.012 (0.002 to 0.033)	0.023 (0.004 to 0.057)	0.105 (0.074 to 0.142)	0
0.095 (0.067 to 0.136)	4 or 5	0.008 (0 to 0.035)	0.007 (0 to 0.029)	0.008 (0 to 0.029)	0.008 (0 to 0.028)	0.065 (0.033 to 0.106)	0.004 (0 to 0.013)	0.003 (0 to 0.012)	0.007 (0.001 to 0.021)	0.007 (0.001 to 0.018)	0.075 (0.053 to 0.103)

Note
Diagnostic accuracy extension to the evidence synthesis model. Results of sensitivity analysis using using Filson's baseline and Zhou's accuracy.

Appendix 11 Model parameterisation

Classification in the diagnostic pathway

Table 79 illustrates the set of possible results (classification) of first, repeat biopsy (for the proportion of individuals who undergo a repeat biopsy), and final classification, according to the joint probabilities of being classified in ISUP grade *j* with test *k* conditional on being in true latent category *i*. The final classification is assumed to correspond to the highest result of the two biopsies, since we are assuming that misclassification at a higher category is not possible. Misclassification at the terminal nodes (final classification) of the model is highlighted in italics in *Table 79*.

TABLE 79 Test sequence and classification in the diagnostic pathway

True disease state	First biopsy classification	Repeat biopsy	Repeat biopsy classification	Final classification
No PCa	No PCa	95%[a] No	-	No PCa
		5%[a] Yes	No PCa	No PCa
	No PCa	95%[a] No	-	*No PCa*
ISUP grade 1		5%[a] Yes	No PCa	*No PCa*
(GS 3 + 3)	ISUP grade 1	85%[a] No	-	ISUP grade 1
		15%[a] Yes	No PCa	ISUP grade 1
			ISUP grade 1	ISUP grade 1
ISUP grade 2	No PCa	95%[a]No	-	*No PCa*
(GS 3 + 4)		5%[a] Yes	No PCa	*No PCa*
	ISUP grade 1	85%[a] No	-	*ISUP grade 1*
		15%[a] Yes	No PCa	*ISUP grade 1*
			ISUP grade 1	*ISUP grade 1*
			ISUP grade 2	ISUP grade 2
	ISUP grade 2	No	-	ISUP grade 2
ISUP grade 3				
(GS 4 + 3)	No PCa	95%[a]No	-	*No PCa*
		5%[a] Yes	No PCa	*No PCa*
	ISUP grade 1	85%[a] No	-	*ISUP grade1*
		15%[a] Yes	No PCa	*ISUP grade1*
			ISUP grade 1	*ISUP grade1*
			ISUP grade 2	*ISUP grade2*
			ISUP grade 3	ISUP grade 3
	ISUP grade 2	No	-	*ISUP grade 2*
	ISUP grade 3	No	-	ISUP grade 3
ISUP grade 4–5	No PCa	95%[a]No	-	*No PCa*
(GS ≥ 8)		5%[a] Yes	No PCa	*No PCa*

continued

TABLE 79 Test sequence and classification in the diagnostic pathway (*continued*)

True disease state	First biopsy classification	Repeat biopsy	Repeat biopsy classification	Final classification
	ISUP grade 1	85%[a] No	-	*ISUP grade 1*
		15%[a] Yes	No PCa	*ISUP grade 1*
			ISUP grade 1	*ISUP grade 1*
			ISUP grade 2	*ISUP grade 2*
			ISUP grade 3	*ISUP grade 3*
			ISUP grade 4–5	ISUP grade 4–5
	ISUP grade 2	No	-	*ISUP grade 2*
	ISUP grade 3	No	-	*ISUP grade 3*
	ISUP grade 4–5	No	-	ISUP grade 4–5

a Assumption.

Comparison of calibration parameter estimates with those from recent UK cost-effectiveness models

The review in *Results of the additional targeted reviews to support model conceptualisation* identified that cost-effectiveness models typically consider the increased, or earlier, identification of PCa cases to affect health outcomes by modifying the likelihood of progression to metastatic disease (via earlier, or more appropriate, cancer treatment). Two approaches are used in the long-term outcome component of these models. The first way is to condition speed of progression on true risk group at the time of (or close to) model start. Models that use this approach typically focus on the diagnostic pathway (leading on to treatment decisions). Implicitly, future changes in disease status or in further treatment are implicitly considered in the evidence informing the likelihood of progression over time. One such model is the PROMIS long-term model.[125,126]

The second approach implemented is to model explicitly progression across risk groups over time spent in model. Such explicit modelling of progression allows more granularity in the evaluation of monitoring, observation or watchful waiting type strategies, which in turn will determine future treatment decisions. Of the UK cost-effectiveness models, the long-term inference model developed to inform the NICE NG131 model[123] (also used in the Southampton DAR[116]) is of such a kind.

We compared predictions of PCa specific mortality at 2, 5 and 10 years by risk group and treatment from our inference model with those of other UK-relevant models: the NICE NG131 model[123] (used in the Southampton DAR[116]) and the PROMIS model.[125,126]

In summary, the outcomes component of the PROMIS model[125,126] calibrated the probability of progressing to metastatic disease by risk category and treatment received. Calibration targets were survival data and proportion of patients with metastases by treatment arm from PIVOT[109] (risk stratified) considering mortality in the metastatic subgroup from the STAMPEDE trial.[113]

The NICE NG131 model also used calibration to derive transitions between risk groups and to metastatic disease (over time), under the assumption that patients would have to be high risk before developing metastatic disease.[123] The calibration targets (risk stratified) were, for undiagnosed cancers, metastases risk from the watchful waiting arm in SPCG4[135] and, for diagnosed cancers, cancer-specific survival from Gnanapragasam *et al.*[112] For both groups, mortality in the metastatic subgroup from the STAMPEDE trial[59] was considered.

To compare the different models, results were conditioned on risk group and treatment. To condition on risk group, across all models, prevalence was set to 100% for each of the risk groups in turn. To condition on treatment, diagnostic accuracy was either set at 100% (to secure all patients are diagnosed and treated) or at 0% (to reflect the values if all patients are undiagnosed and untreated). Where relevant, diagnosis due to symptom presentation was not allowed. Where relevant, treatment allocation was set to 100% conservative management or, alternatively, to 100% radical treatment. To derive PCa specific mortality in the PROMIS model,[125,126] we only considered mortality in individuals with metastatic disease, and subtracted general mortality. The results of these analyses are presented in *Table 80*, *Appendix 11*.

TABLE 80 Comparison of 2-, 5- and 10-year PCa mortality predictions between alternative long-term outcome models

		PCa mortality at …		
True disease status	**Final classification/treatment**	**2 years (%)**	**5 years (%)**	**10 years (%)**
NICE NG131 model[123]				
LR	No PCa	< 0.1	0.7	7.1
	LR	< 0.1	0.1	1.6
IR	No PCa/LR	0.3	3.9	19.3
	IR	< 0.1	0.7	5.2
HR	No PCa/LR	1.6	9.5	28.9
	IR/HR	0.6	4.0	14.7
PROMIS[125,126]				
LR	WW	0.1	0.9	3.0
IR	WW	0.3	2.1	6.4
	RP	0.1	0.8	2.6
HR	WW	0.3	2.6	7.8
	RP	0.1	0.9	2.9
De novo inference model by treatment				
CPG1	Conservative	0.2	1.5	4.4
	Radical	0.1	0.6	2.0
CPG2	Conservative	0.5	3.5	9.8
	Radical	0.2	1.6	4.6
CPG3	Conservative	1.3	8.6	20.7
	Radical	0.6	4.1	10.8
CPG4 or 5	Conservative	3.5	18.9	36.2
	Radical	1.7	10.7	24.6
De novo inference model with weighted treatment estimates				
CPG1	Weighted	0.1	0.4	3.1
CPG2	Weighted	0.3	2.2	6.2
CPG3	Weighted	0.7	5.0	13.0
CPG4 or 5	Weighted	1.8	11.2	25.6

HR, high-risk; IR, intermediate-risk; LR, low-risk; RP, radical prostatectomy; WW, watchful waiting.

This table highlights that there are marked differences between the predictions, which are primarily due to the sources of long-term outcome evidence these inference models relied upon, which differed. *Table 81* depicts PCa mortality at 2, 5 and 10 years observed within the studies that served as calibration targets for the different models.

TABLE 81 Prostate cancer mortality at 2, 5 and 10 years observed within the studies that served as calibration targets for alternative long-term outcome models

			PCa mortality at …		
Study	**Population + treatment**		**2 years (%)**	**5 years (%)**	**10 years (%)**
PIVOT[109]	LR	Obs	< 0.1	1.8	2.2
		RP	< 0.1	1.0	1.5
	IR	Obs	< 0.1	1.7	8.3
		RP	1.2	2.4	5.3
	HR	Obs	0.5	3.1	17.2
		RP	2.6	5.1	5.1
SPCG4[135]	LR	WW	< 0.1	< 0.1	4.5
		RP	< 0.1	0.9	3.3
	IR	WW	< 0.1	3.8	17.8
		RP	< 0.1	1.9	7.8
	HR	WW	1.9	7.1	22.6
		RP	< 0.1	3.9	16.9
Gnanapragasam (2016),[112] 3-tier risk group[a]	LR	As per clinical practice	< 0.1	0.1	3.1
	IR		0.1	2.0	8.6
	HR		2.1	10.0	23.4
Gnanapragasam (2016),[112] 5-tier risk group[a]	CPG1	As per clinical practice	< 0.1	1.0	4.2
	CPG2		< 0.1	1.7	7.0
	CPG3		< 0.1	3.5	13.2
	CPG4		0.1	5.3	17.7
	CPG5		5.7	19.4	38.1
	CPG4 and 5[b]		2.1	10.2	24.8

HR, high-risk; IR, intermediate-risk; LR, low-risk; Obs, observation; RP, radical prostatectomy; WW, watchful waiting.
a Weighted average between training and testing data sets.
b Weighted average between CPG4 and CPG5.

Treatments distribution

TABLE 82 Metastatic disease treatment allocation by diagnosed category

Metastatic hormone-sensitive treatment	Southampton DAR (%)	Current DAR (%)
ADT alone	50	50
DTX + ADT	36	9
Enzalutamide + ADT	7	34
Apalutamide + ADT	7	7

TABLE 82 Metastatic disease treatment allocation by diagnosed category (*continued*)

Metastatic hormone-sensitive treatment	Southampton DAR (%)	Current DAR (%)
	Previously treated with	
Metastatic hormone-relapsed treatment	ADT alone (%)	Enzalutamide + ADT (%)
Abiraterone	35	0
DTX	10	60
Enzalutamide	35	0
BSC	20	40

BSC, best supportive treatment.

Adverse events

TABLE 83 Biopsy AE rates applied in the model

	AE rates			
AE	LATRUS (%)	Source	LATP (%)	Source
Mild AE	1.31	Rosario et al., 2012[182]	9.13	Pepe and Aragona et al., 2013[183] – emergency visits all patients
Non-elective admission[a]	3.74	Tamhankar et al., 2020	3.54	Tamhankar et al., 2020[184]
Death[a]	0.07		0.05	

LATRUS, local anaesthesia transrectal ultrasound.
a Within 28 days of biopsy.

Health-related quality of life

TABLE 84 Parameterisation of biopsy procedural disutility

AE	Disutility weight	Duration of AE (days)	QALY loss
Mild AE	0.29	3	0.002
Non-elective admission[a]	0.49	30	0.041
Death[a]	0.49	30	0.041

a Within 28 days of biopsy.

Resource use and costs

Biopsy procedure costs

This section details the costs associated with the biopsy procedure, which include the following components:

1. Cost of the SF system – costs of the fusion software and, in some cases, a workstation (or cart). This cost only applies to the diagnostic strategies which include a SF component.
2. Cost of the ultrasound – cost of the ultrasound probe/transducer, and any required software. This cost applies to diagnostic strategies with either software or cognitive function components, but some SF systems are not compatible with third-party ultrasounds.

3. Cost of SF system installation – cost of connecting the SF system to the NHS trust IT system. This cost only applies to the diagnostic strategies which include a SF component.
4. Cost of SF system maintenance – costs of service contracts to maintain the technology and keep software up to date. This cost only applies to the diagnostic strategies which include a SF component.
5. Costs of SF system training – staff time costs required to train NHS professionals to perform biopsies. The use of SF methods requires additional training compared to CF, but the cost of training also varies across biopsy approaches (by route of access).
6. Cost of staff time to perform the biopsy procedure – cost of urologists, nurses and anaesthetist (for procedures requiring general anaesthesia). This cost varies across biopsy approaches (by route of access and type of anaesthesia), but there is also a difference in procedural time between SF and CF.
7. Cost of the biopsy setting – costs of the setting in which the biopsy procedure takes place (outpatient room, theatre session); it varies by route of access, type of anaesthesia, and MRI-influenced method.
8. Costs of other biopsy devices and consumables – cost of (1) devices and equipment (e.g. freehand needle positioning devices, lithotomy beds and biopsy guns), and (2) needles and other materials requiring replacement (immediate or after a certain number of uses). These costs are often specific to the biopsy approach [transrectal or transperineal (stabilised, freehand or double freehand)], and may differ across MRI-influenced methods and across SF systems, due to compatibility issues.
9. Cost of histopathology analysis and report – costs of processing the biopsy sample and communicating the results to the patient in a consultation. This cost applies to all strategies but may differ for strategies using different sampling methods (combined vs. targeted-only biopsy), as these may result in different number of cores being sampled. These costs are reported in the *Appendix 11*, as they are not SF specific.

In the subsequent sections we start by discussing patient throughput and then provide more detail in each component of cost described above, with emphasis in those costs that vary by MRI-influenced method and/or across SF systems. Further information is provided in *Appendix 11*. All costs presented are exclusive of value-added tax, unless otherwise stated.

Patient throughput

The annual patient throughput represents the average annual number of targeted biopsies (alone or in combination with systematic biopsy) per NHS trust. The annual patient throughput is determinant to calculate the cost of biopsy. The EAG did not identify a source directly reporting this estimate. The evidence considered and the calculations used to inform our base case assumption of throughput are described below.

We considered the estimates of throughput applied in the Southampton DAR,[116] which assumed 18 weekly and 1000 annual biopsies (not distinguishing throughput between systematic and targeted biopsies). Clinical advisers to the EAG considered that the annual estimate is likely to overestimate the average total number of biopsies per NHS trust and may be more reflective of a very high throughput centre.

We also examined prostate biopsy activity numbers across all HRGs in the main schedule of NHS reference costs across three financial years (2018–9, 2019–20, 2020–1)[185–187] for the prostate biopsy currency codes across all HRG data [LB76Z (transrectal ultrasound guided biopsy of prostate) and LB77Z (transperineal template biopsy of prostate)] and contrasted these figures against those reported for the latest available NPCA annual report,[4] as illustrated in *Table 85*, *Appendix 11*. We did not consider earlier versions of the NPCA annual reports due to changes in the reporting style and high level of missing data, which hinder establishing meaningful comparisons across time. We note as a limitation of the NHS reference data that the TP currency code suggests these were transperineal template biopsies, so it is unclear how other types of transperineal biopsies were captured in the data set.

Although the NPCA reports data for both England and Wales, the total number of biopsies reported is lower than that reported for a similar period in the main schedule NHS reference costs; this is due to missing data issues. To estimate the average number of biopsies per NHS England trust and/or Welsh University Health board, we assumed the number of institutions from which the NCPA collected

TABLE 85 Evidence considered to estimate the patient throughput

	Data source					
	NHS reference costs; all HRG data			NPCA annual report[4]		
Data collection period	2018–9 financial year[184]	2019–20 financial year[185]	2020–1 financial year[186]	April 2019–March 2020		
Country	England			England	Wales	England and Wales
Biopsy route						
TP biopsy	39,211	30,451	11,492	20,623	969	21,592
TR biopsy	2,1424	21,674	22,332	13,756	300	13,756
Total biopsies per year	60,635	52,125	33,824	34,379	1269	35,348
Estimated annual number of biopsies preceded by a MRI/ NHS trust[a]	52,752	45,349	29,427	29,910	1104	30,753
Estimated annual number of biopsies/NHS trust[a]	415	357	232	236	221	235
Estimated annual number of targeted biopsies/NHS trust[a]	300	258	168	170	160	170

TP, transperineal; TRUS, transrectal.
a Or University Health Board if in Wales.

data in 2019–20 (127 NHS trusts and 5 University Health Boards).[188] Although clinical guidance has recommended performing a mpMRI before any biopsy is offered at least since 2019, NICE has identified data suggesting that in 2019[189] only 87% of biopsies were preceded by a mpMRI in England and Wales. Thus, we used the 87% estimate (varied in scenario analysis to 100%, *Multiparametric magnetic resonance imaging and compliance with National Institute for Health and Care Excellence guidance*, to explore the impact of complete compliance with clinical guidance) to adjust the average annual number of biopsies by NHS trust. Finally, we estimated the average annual number of targeted biopsies by assuming that 72.6% of biopsies preceded by a mpMRI had a Likert or PI-RADS score of at least 3, as this is the threshold at which targeted biopsy is recommended. The 72.6% was obtained by pooling the proportion of patients in two relevant RCTs [71.8% in PROMIS (UK) and 72.6% PRECISION (11 countries)][19,126] who had a mpMRI result of at least 3 (Likert or PI-RADS).

The evidence considered suggests the average annual number of targeted biopsies (alone or in combination with systematic biopsy) per NHS trust in England is in a range within 168 and 300. However, the two latest data cuts of NHS-reference costs[185–187] are likely to be affected to some extent the impact of COVID-related constraints on NHS service provision. Therefore, we consider that the expected patient throughput is likely to be closer to the upper bound of the estimated range and consider an annual throughput of 300 targeted biopsies in the base-case analysis.

Cost of the software fusion system and ultrasound components

The MRI-fusion systems under comparison differ in terms of their compatibility with third-party ultrasound devices (and are, therefore, sold without an ultrasound component), with the ultrasound component being an integral part of the SF system for some technologies (e.g. KOELIS Trinity). Therefore, the capital costs of the SF systems and ultrasound components are reported jointly in this section.

Only five companies provided information on the costs of the technologies under comparison; these were BK Medical UK Ltd (with MIM Software Inc. for bkFusion), Exact Imaging (for FusionVu), Focal Healthcare (for Fusion Bx 2.0), KOELIS (with Kebomed for KOELIS Trinity), and MedCom (BiopSee). No information was provided for the costs of ARTEMIS, iSR'obot Mona Lisa, and UroNav Fusion Biopsy

System. The capital costs of the SF systems and ultrasound components for bkFusion, FusionVu, Fusion Bx 2.0, KOELIS Trinity and BiopSee are summarised in *Table 86*, alongside the lifespan of the equipment.

For three SF systems (bkFusion, FusionVu, and KOELIS Trinity) the SF component is integral to the ultrasound component (or the micro-ultrasound component for FusionVu). In the other two systems (Fusion Bx 2.0 and BiopSee) the fusion software is installed on a standalone workstation (or cart), which is integral to the SF system, but does not comprise an ultrasound system. Fusion Bx 2.0 and BiopSee require third-party ultrasounds and transducers to perform prostate biopsies, for which the costs are NR in *Table 86* (as sold by third party). Both Fusion Bx 2.0 and BiopSee include a cart; the cart is an integral part of each technology.

For SF systems that are compatible with third-party ultrasounds (i.e. BiopSee and Fusion Bx 2.0), we assume the same cost for the ultrasound components as for CF. In the base-case, this cost was derived from the cost of the three standalone ultrasound machines in the Southampton DAR[116] (FUJIFILM transducer and Ultrasound System [inflated to 2020–21 price year according to the NHSCII;[154]BK ultrasound system and urology software with transducer; Trinity® 3D Prostate Suite plus KOELIS Sidefire Ultrasound probe). We averaged across the costs of these three technologies (with costs updated based on the information provided by bkMedical and KOELIS and Kebomed in the context of the current DAR for the BK ultrasound and Trinity ultrasound components) to estimate an average annual capital cost for ultrasound of £10,846 and £10,974 for transrectal and transperineal biopsies, respectively.

TABLE 86 Costs of SF systems and ultrasound components

Type of SF system	Technology	SF costs	Ultrasound costs	Lifespan (years)
Fully integrated system	bkFusion	Cart and software: 52,250[a]	bk3000 ultrasound: £37,500 Prostate procedural application: £1800 DICOM standard with encryption: £1700 Leakage test kit: £332 Transducer: £15,000 Sensor clamp for the transducer: £200	8 (4 for transducer and sensor clamp)
	FusionVu	£124,958[b]		5
	KOELIS Trinity	£23,620	Ultrasound: £45,000 Transrectal software: £39,948[c] Transperineal software: £41,754[c]	5
Compatible with third party= ultrasounds	BiopSee	Transrectal: - Software: £15,000 - Cart: £12,000 Transperineal: - Software: £20,000 - Cart for stabilised biopsy: £8000 - Cart for freehand biopsy: £20,000	NA	10
	Fusion Bx 2.0	Software: £24,244[d] Cart: £96,974[d]	NA	10

DICOM, Digital Imaging and Communications in Medicine.
a Cost provided for TP only.
b Costs originally included value accrued tax at 20.
c We note that the cost of the transrectal software was reported inconsistently in the company's response to the EAG's additional request for information (in table and response 7) as £39,431 and £39,948, and the cost of the transperineal software as £42,258 and £41,754.
d Costs originally expressed in US dollars and subsequently converted to Great British pounds at a rate of 0.80812 (represents the average exchange rate between 12 March 2022 and 6 September 2022).[190]

Note
The values used in the model were taken from *Table 1* of the company's response to the EAG's additional request for information.

For bkFusion, lifespan estimates provided by the company for the transducer (3–5 years) and leakage test kit (8 years) are said to be end-user dependent. We assumed that the transducer lifespan corresponded to the midpoint of the range provided by the company (i.e. 4 years). The lifespan of the sensor clamp for the transducer was not provided by the company despite the EAG request to provide this information for all components, so we assumed it was the same as for the transducer.

Commercial discounts may be available for bkFusion. The company stated that

> *We have a 5 years fixed service contract (excluding any civco and mim products) called Priority Care – at point of sale if the service contract is purchased we provide a 10% discount to the priority care quote. If priority care is not purchase within the systems first 2 years of life you can not access this contract again. Alternative contracts are available.*

However, the company did not detail what was included in the Priority Care quote and how much it costs. It is also not clear if the discount applies to maintenance or equipment costs, as we do not know what is covered by the Priority Care quote. Therefore, the information provided by the company is insufficient to implement the discount in the model, and this is not considered by the EAG.

FusionVu uses micro-ultrasound technology, and therefore, does not require ultrasound components. The cost presented for this technology in *Table 86* reflects the cost of all equipment and software components. We note that the company stated that they are willing to offer a discount to the UK NHS but that they could not finalise it within the timelines of this DAR.

KOELIS and Kebomed also stated that they can offer discount for multi-unit purchases of KOELIS Trinity, but these depend on the number of units purchased, method of purchase and specification of the units (response to EAG's RFI, question 11). The company did not provide further details on the discounts available, and therefore this is not modelled.

Commercial discounts may also be available for BiopSee according to MedCom, who states that these discounts are usually handled by distributors. As no further information on the applicability and size of the discounts was provided, we could not model discounted costs for BiopSee.

The costs of some SF systems and/or ultrasound components were specific to the biopsy approach in terms of route of access (transrectal or transperineal) and/or the fixation method [stabilised, (single) freehand and double-freehand], so for KOELIS Trinity and BiopSee costs will vary conditional on the diagnostic strategy they are being used in. The costs provided by the company for bkFusion were reported solely for a transperineal procedure, despite the EAG request to provide costs by biopsy approach. Therefore, it was assumed that the costs of bkFusion are the same across biopsy approaches.

The software costs assumed for Fusion Bx 2.0 (£24,244) assume the purchase of a perpetual licence. The company also provided the cost of an annual licence costing a third of the perpetual licence. Given the lifespan of Fusion Bx 2.0 exceeds 3 years (point beyond which the annual cost of a perpetual license becomes lower than the annual license), we did not consider annual licences as an option. The company stated that a discount on the software and hardware components of Fusion Bx 2.0 of up to 30% could be offered to the NHS, depending on the number of systems purchased. We did not implement this discount on our base-case analysis, as the company did not specify the level of discount applied conditional on number of units purchased.

Some SF systems had optional probe holders and software components, which were not considered in the costs of the ultrasound components, as these are not essential components of the technology. We note that the cost of Fusion Bx 2.0 includes one probe holder as an integral part of the system, and therefore, this cost was not excluded.

The costs of SF systems and ultrasound components were annuitised at a 3.5% discount. Annuitised costs and costs per biopsy are reported in *Table 87*.

Cost of installation of software fusion systems

One company (Medcom) reported the time required to install the software fusion technology to the NHS trust IT system as ranging between 30 and 60 minutes. We assumed that this results in a one-off staff time cost, which is applicable to all SF systems. The cost of installation was estimated assuming it would take 45 minutes (midpoint of the time range provided by Medcom) of an IT worker time [costed at £35.67 per hour (average working hour of band 4 hospital-based scientific and professional staff)[154]]. The cost was distributed over the annuitised (3.5% annual rate) average lifespan of the five SF systems for which the companies had submitted costing information. The resulting annual cost and cost per biopsy were estimated to be £3.97 and £0.01, respectively.

Cost of software fusion system maintenance

The costs of maintaining the SF systems mostly consist of the costs of service contracts. These contracts also include maintenance of the ultrasound components when the ultrasound components are integral to the SF system. The maintenance contracts are summarised in *Table 88* alongside the annual cost estimate applied in the model.

TABLE 87 Costs of SF and ultrasounds components applied in the mode

		Annuatized cost			Cost per biopsy		
	Biopsy approach	TR	TP stabilised	TP freehand	TR	TP stabilised	TP freehand
Technology	Type of system						
bkFusion	Fully integrated[a]	£17,152			£57.17		
FusionVu	Fully integrated[a]	£26,740			£89.13		
KOELIS Trinity	Fully integrated[a]	£23,233	£23,619	£23,619	£77.44	£78.73	£78.73
BiopSee	SF alone	£13,982	£14,227	£15,621	£46.61	£47.42	£52.07
Fusion Bx 2.0	SF alone	£24,928	£25,057		£83.09	£83.52	
bkFusion	CF	£10,846	£10,974		£36.15	£36.58	

TP, transperineal; TR, transrectal.
a Includes the cost of each technology own brand ultrasounds components.

TABLE 88 Software fusion maintenance contracts

		Costs of maintenance applied in the model	
Technology	Maintenance contract duration and cost	Annual cost	Cost per biopsy
bkFusion	5 years: £66,975.00	£13,395.00	£44.65
FusionVu	NR	£12,206.12	£37.20
KOELIS Trinity	Essential – 1 year: £5,500.00	£11,017.24	£29.76
	Comfort – 1 year: £7 465.52		
	Serenity – 1 year: £11,017.24		
BiopSee	NR	–	–
Fusion Bx 2.0	1 year: £9697.44[a]	£9697.44	£32.32

a Costs originally expressed in US dollars and subsequently converted to Great British pounds at a rate of 0.80812 (represents the average exchange rate between 12 March 2022 and 6 September 2022).[190]

Three companies provided information on the duration and cost of the maintenance contracts. Most contracts had an annual duration; only bkFusion had a 5-year maintenance contract. Given the lifespan of bkFusion is > 5 years, we distribute this cost equally over time and apply it as a cost of £13,395 per annum in the model. We note that there are discounts available for alternative maintenance contracts for bkFusion, which have been described above.

KOELIS Trinity has three levels of maintenance contract, which differ in terms of annual costs; the levels are: Essential, Comfort and Serenity. According to the company Serenity is the level most often purchased (50%) followed by Essential (34%), and Comfort (16%). In the model, we assume the annual cost of the contract to be a weighted average of the three contract levels by the corresponding 'market share', resulting in an annual cost and a cost per biopsy of £8926.90 and £29.76, respectively.

We note that the maintenance service contract cost for Fusion Bx 2.0 is an approximate estimate provided by the company, who stated that this would typically cost US $12,000 or less and that they plan to enlist a UK distributor to perform this service. Alternatively, the maintenance could be conducted by hospital staff who are responsible for performing preventative maintenance of other medical devices, and who would need to undergo annual on-site maintenance training (1–2 hours). The company also stated in the responses submitted to NICE that if the maintenance contract is longer than 1 year, the cost would be discounted accordingly. However, this does not provide information on the level of discount over time, so this potential discount cannot be implemented without more detail. In the model, we consider only the approximate cost of an annual maintenance service delivered by the company or their distributors.

No maintenance costs were provided for FusionVu and BiopSee. The company who commercialises FusionVu stated that their technology is serviced through a local distributor in the UK under annual or more contracts, but could not yet provide a cost estimate for the contract. Therefore, we have assumed that the FusionVu maintenance contract costs is an average of the two SF systems with fully integrated SF system and ultrasound components (bkFusion and KOELIS Trinity). Medcom stated that BiopSee does not require any maintenance, as damaged parts can be repaired on demand and reported cost range for repairing accessory equipment (e.g. £200–600 to replace a mouse or an accidentally damaged cable, and £100–3000 to replace a damaged stepper or stabiliser). However, it is unknown how often damage to different components is likely to occur, and so estimate a maintenance cost on a per damaged part basis. We could have assumed a maintenance cost similar to that of Fusion Bx 2.0 (the other SF system that does not have an integral ultrasound component); however, we note that the maintenance cost for Fusion Bx 2.0 is an approximate estimate provided by the company and assumes that there is a service contract (not available for BiopSee). In our base-case analysis, we assume that there is no cost attached to maintaining BiopSee.

The cost of software updates is included within the maintenance contract for most technologies. One of the exceptions is bkFusion, which only includes software malfunction fixes. No software update costs were provided for bkFusion, but we note that the lifespan of the hardware and software components for this technology are generally the same. The cost of software updates for BiopSee SF software is 50% of the software cost and new versions are usually released annually, according to the company. The company also stated they do not plan to withdraw the current version being used in the UK NHS. Therefore, we assume that no additional costs for software updates need to be considered for any of the technologies.

Cost of software fusion training

The technology specific cost of SF systems training consists of the cost of staff time to attend the training sessions, as companies do not charge for training provision. Each company provides a core training programme composed of different elements. The information provided by the companies on the NHS staff who should undergo core training and the time required per training component is summarised in *Table 89*.

TABLE 89 Essential training requirements – company information

Technology	NHS staff	Training components	Duration
bkFusion	Urologists, radiologists, radiation oncologists, sonographers and assisting staff	Not described	1 or 2 days
FusionVu	Urologists, radiologists, nurses and sonographers	eLearning	2 hours
		On-site training	1 hour
		Live expert support	10–15 cases
KOELIS Trinity	End user, consultant, radiologist, CNS	Pre-installation training	3 hours
	OPD staff, theatre staff, ODP	Installation training	1 hour
	End user, consultant, radiologist, CNS	Theatre List	4 or 5 cases
BiopSee	Urologists/radiologists	Not described	3 hours
	Nurses		1 hour
Fusion Bx 2.0	Urologists, nurses and/or sonographers	Video training	1 hour
		Hands-on training with phantom prostate	0.5–0.75 hour
		Support to clinical cases	10–20 casers over 2–3 days

CNS, clinical nurse specialist; IT, information technology; ODP, operating department practitioner; OPD, outpatient department.

To estimate an annual cost of training for the use of SF per trust for each technology, we assumed that core training would be delivered to two urologists, two nurses, one radiologist and one sonographer, and training would remain up to date for 5 years (the shorter lifespan across fusion software). We used the training duration provided by the companies to estimate staff time requirements, and assumed the same time for all categories of staff unless the company stated different times by category of staff. Where the companies provided training duration as a range we assumed the staff time requirement would correspond to the midpoint of that range. We did not include any staff time for theatre list or support to clinical cases, as we assumed that this would not result in additional time requirements in relation to the procedure time. The information used to estimate the costs of SF systems training is presented in *Table 90* alongside the annuitised annual cost (at 3.5% per annum) of training for each technology. Unit costs were sourced from the PSSRU (2021) unit costs report.[154]

We also considered the cost of training to perform biopsy procedures more generally; these were assumed to vary by biopsy access route (transperineal vs. transrectal) in line with the Southampton DAR. We assumed the same level resource use per biopsy approach as was assumed in the Southampton DAR and updated the unit costs to reflect our analysis price year.[154]

FusionVu has a free-of-charge optional training programme, the Mastery programme. The company did not provide clear information on the staff time requirements to undergo this optional training, or clarify to whom it would be delivered. The company stated that the effectiveness of the Mastery programme was studied in Cash *et al.* [158] but it was not possible to ascertain based on the information provided if the Mastery programme described by the company corresponded to the training programme assessed in this publication. Given this and the optional nature of this training component, we have not included this cost in our cost-effectiveness analysis.

TABLE 90 Software fusion training costs in the model

	NHS staff time				Annuitised annual cost	Cost per biopsy	Unit cost	
	Urologist	Nurse	Radiologist	Sonographer			Staff	Cost per working hour
Technology specific								
bkFusion	2 × 11.25 hours[a]	2 × 11.25 hours[a]	1 × 11.25 hours[a]	1 × 11.25 hours[a]	£1029.97	£3.43	Urologist and radiologist	£87.50, average of hospital-based registrar and medical consultant PSSRU (2021)[154]
FusionVu	2 × 3 hours	2 × 3 hours	1 × 3 hours	1 × 3 hours	£274.66	£0.92		
KOELIS Trinity	2 × 3 hours	2 × 3 hours	1 × 3 hours	1 × 4 hours[b]	£285.86	£0.95	Nurse	£46.00, average of hospital-based nurse specialist/ team leader (band 6) and nurse advanced/team manager (band 7) PSSRU (2021)[154]
BiopSee	2 × 3 hours	2 × 1 hour	1 × 3 hours	1 × 1 hour	£203.90	£0.68	Sonographer	£52.33, average hospital-based scientific and professional staff (band 6) PSSRU (2021)[154]
Fusion Bx 2.0	2 × 1.625 hours	2 × 1.625 hours	1 × 1 hour[c]	1 × 1.625 hours	£137.07	£0.46		
Biopsy approach specific								
Transrectal	5 × 1 hour	-	-	-	£437.50[d]	£1.46	Urologist	£123, medical consultant PSSRU (2021)[154]
Transperineal	5 × 8 hours	-	-	-	£3500.00[d]	£11.67		

a Assumes a working day corresponds to 7.5 hours.
b Assumes installation training is only undertaken by one sonographer.
c Assumes that phantom prostate biopsy training is not undertaken by the radiologist.
d Not annuitised as this was estimated as annual training requirement in the original source.

Cost of staff time to perform the biopsy procedure

The staff costs associated with the biopsy procedure are likely to vary depending on the biopsy route of access and the type of anaesthesia. We based our estimates of staff time requirements to conduct the biopsy on the Southampton DAR.[116]

In the Southampton DAR, each local anaesthesia biopsy was assumed to require one urologist and two nurses, with general anaesthesia biopsy further requiring one anaesthetist. The time required for LATP biopsy was sourced from the published literature for two devices (0.41 and 0.33 hour for CamPROBE and PrecisionPoint™, respectively), with an average of the two assumed for the devices for which there was no published evidence. For GATP biopsy, the procedure time was assumed to be 1 hour. To estimate the procedure time of local anaesthesia transrectal (LATRUS) biopsy, the EAG applied a ratio of procedure time between the transrectal and transperineal approach (0.84) derived from the literature to the time estimates by transperineal device.

In this study, we have assumed the procedure time of LATP conducted with PrecisionPoint, as the diagnostics consultation document (DCD) for the Southampton DAR[29] suggests that CamPROBE will not be recommended for use in the NHS UK. We applied the same LATRUS/LATP time ratio as in the Southampton DAR to the LATP time estimate to calculate the LATRUS procedure time and assumed GATP would take 1 hour. We also assumed that 50% of procedures would be undertaken by urologists and 50% by sonographers. The remaining staff requirements were assumed the same as in the Southampton DAR (i.e. two nurses plus one anaesthetist if GATP). We applied the same unit cost as those used to cost training costs (see *Table 90*) and assumed the same unit cost for anaesthetist time as for the urologist time. The procedure time costs by route of access and type of anaesthesia are summarised in *Table 91*.

Procedure time may further increase when this is performed with fusion software compared to CF. This additional time is due to the need (1) to contour the prostate in the MRI and ultrasound images, and (2) to connect the MRI-fusion system. The companies provided different estimates of how much time would be added to the biopsy procedure when using their technologies (see *Table 92*), but these were not supported by published evidence. As discussed in *Clinical effectiveness results*, the procedure

TABLE 91 Biopsy procedure staff time costs

Biopsy approach	Procedure time (hours)	NHS staff				Cost per biopsy (£)
		Urologist	Nurse	Sonographer	Anaesthetist	
LATP	0.33	0.5	2	0.5	-	60.36
GATP	1				1	270.42
LATRUS	0.28				-	50.70

LATRUS, local anaesthesia transrectal ultrasound.

TABLE 92 Additional time of SF vs. CF biopsy according to the companies

Fusion system	MRI contouring	Connect fusion system to ultrasound	Contouring ultrasound
bkFusion	3–5 minutes	NR	-[a]
FusionVu	1 minute	NR	10 seconds
KOELIS Trinity	5 minutes	NR	5 minutes
BiopSee	1–2 minutes	NR	< 1 minute
Fusion Bx 2.0	8–10 minutes	30 seconds	5–10 minutes

a Company states that bkFusion does not require ultrasound contouring.

time estimates in the diagnostic literature do not allow disentangling the additional procedure time due to software compared to CF from procedure time differences associated with the biopsy approaches. The clinical advisers to the EAG commented that the additional procedure time for SF (vs. CF) should be approximately 10 minutes in a high- throughput centre, 5 minutes of which would correspond to additional time to import and obtain the appropriate MRI sequences (radiologist time) and 5 minutes during the actual biopsy (urologist/sonographer and nurse time) to connect the SF systems and contouring the ultrasound. They also noted that these time estimates could be longer when the use of these interventions is first rolled out, due to lack of experience.

We calculated the additional staff time costs, required to conduct SF, based on the time estimates provided by the clinical advisers to the EAG. We assumed the same staff requirements per type of biopsy approach, as for the core biopsy procedure time, and further accounted for the additional time requirements for one radiologist. We applied the same unit cost as those used to cost training costs (see *Table 90*) and assumed the same unit cost for anaesthetist time as for the urologist time. The additional procedure staff time costs for SF compared to cognitive by route of access and type of anaesthesia are summarised in *Table 93*.

Cost of the biopsy setting

The Southampton DAR[116] examining the cost-effectiveness of LATP, GATP and LATRUS considered a cost for the setting on which the biopsy took place, with LATRUS and LATP being conducted in an outpatient room, and GATP in a theatre session. These costs were sourced from an unpublished study submitted by the sponsor of one of the technologies under assessment in the Southampton DAR[116] and suggested a unit cost of £43 and £129 per hour for the outpatient room and theatre session, respectively. These unit costs were inflated to 2020–1 price year using the NHSCII,[154] applied to the duration of the procedures for each biopsy approach, to estimate the cost of the setting.

The micro-costing study is not described in sufficient detail to understand what is included in the costs of biopsy setting. This DAR's EAG has decided to include the cost of setting for consistency with the Southampton DAR,[116] but notes the opacity of the cost estimates as a potential limitation.

The cost of biopsy setting, applied in the model for strategies using CF, was calculated by multiplying the time of the procedure by biopsy approach (see *Table 91*) by the unit costs by setting (inflated to 2020–1 price year)[154] in the Southampton DAR.[116] For strategies using SF, we assumed that the procedure would take 10 additional minutes (in line with the assumptions to estimate the additional staff time to conduct SF and assuming that the MRI is also done in an outpatient setting). Costs associated with biopsy setting by biopsy approach and MRI-influenced method, as well as the model inputs to estimate these, are summarised in *Table 94*.

Costs of other biopsy devices and consumables

The biopsy procedure requires other devices and consumables which may vary by biopsy approaches (GATP, LATP, LATRUS). While these devices and materials are not required to conduct biopsy

TABLE 93 Additional biopsy procedure staff time costs for SF

	NHS staff time (minutes)					
approach	Radiologist	Urologist	Nurse	Sonographer	Anaesthetist	Additional cost per SF biopsy
LATP	1 × 5	0.5 × 5	2 × 5	0.5 × 5	-	£22.53
GATP					5 × 1	£29.83
LATRUS					-	£22.53

LATRUS, local anaesthesia transrectal ultrasound.

TABLE 94 Costs of biopsy setting

Approach	Procedure time (hours)		Unit cost (per hour) (£)	Cost per biopsy	
	CF	SF		Cognitive fusion (£)	SF (£)
LATP	0.33	0.50	44.32	14.63	22.01
GATP	1.00	1.17	132.97	132.97	155.14
LATRUS	0.28	0.44	44.32	12.29	19.67

LATRUS, local anaesthesia transrectal ultrasound.

procedures with either software or CF, some technologies have compatibility issues which mean that costs of technology-specific materials may have to be considered where appropriate to fully account for differences in costs between the different SF systems. For example, FusionVu is only compatible with needle guides commercialised by Exact Imaging, meaning that in principle, you cannot use other needle guides that would be suitable for CF or other SF systems without compatibility issues. In our base-case analysis, we apply a simplifying assumption that the costs of the biopsy devices do not vary by MRI-influenced methods.

Transperineal biopsies can be conducted with a (1) grid and stepper unit; (2) freehand device (the Southampton DAR[116] assessed five of these devices) or (3) coaxial needle (one such device assessed in the Southampton DAR). Grid and stepper units are used for stabilised biopsies with the stepping unit usually fixed to a stabiliser (mounted onto a table or supported by a floor stand). The stepper is a reusable device used to hold the ultrasound probe, while a (single use or reusable) grid is used to guide the needle insertion. Grid and stepper units can be used to perform transperineal biopsies under or local general anaesthesia. Recent LATP techniques are performed using an access needle guide (or equivalent) to pierce the perineum and through which the biopsy needle passes to sample the prostate. These techniques can be performed using (1) freehand devices attached to the ultrasound probe or (2) a co-axial needle not attached to the probe (also known as double freehand technique).

We based the costs of a grid and stepper unit for stabilised GATP and LATP biopsy on the estimates used in the Southampton DAR for this cost element with adjustments to reflect our throughput estimates. We assumed a cost of reprocessing reusable materials of £5.15 (cost of cleaning and sterilising), sourced from the Southampton DAR and inflated to 2020–1 price year using the NHSCII.[154]

The information considered by the EAG for costing the freehand biopsy devices is summarised in *Table 95*.

For costing transperineal biopsies with (single) freehand techniques with CF, we have considered the costs of the five freehand devices evaluated in the Southampton DAR[116] [PrecisionPoint (BXTAccelyon), EZU-PA3U (Hitachi), UA1232 (BK Medical), Trinity® Perine (KOELIS and Kebomed), and SureFire (Delta Surgical); inflated to 2020–1 price year using the NHSCII].[154] We have updated the costs of Trinity Perine device based on the cost of the reusable Perine Grid 18G provided by KOELIS and Kebomed in the context of the current DAR (£779.31; 100 uses). We note that KOELIS and Kebomed also commercialise single use Trinity Perine grids (costed as £62.04 and £86.20 for a Mini grid and a Full grid, respectively – not modelled); this are not included in the model but would yield higher costs per biopsy than the single use devices. We included a £5.15 cost of reprocessing for the reusable devices [EZU-PA3U (Hitachi), UA1232 (BK Medical), Trinity® Perine (KOELIS and Kebomed)]. In the base case, the cost of freehand devices is an average of the costs for the five devices and applies equally to cognitive and SF.

TABLE 95 Summary of information on the costs of transperineal needle positioning freehand devices in a previous DAR and from the companies' responses to RFIs

Device	Manufacturer	Compatible with	Cost of device	Number of uses	Reprocessing	Co-axial needle	Source
PrecisionPoint	BXTAccelyon	KOELIS Trinity, BiopSee, Fusion Bx 2.0	£206.16	1	-	-	Southampton DAR;[116] Inflated to 2020–1 price year[154]
			£250.00	NR	NR	NR	KOELIS and Kebomed response to NICE and/or EAG RFI
			£350.00	NR	NR	NR	Focal Healthcare response to NICE and/or EAG RFI
			£150–250	NR	NR	NR	Medcom response to NICE and/or EAG RFI
FusionVu guide	Exact Imaging	FusionVu	£1333	24	-	-	Exact Imaging response to EAG RFI
EZU-PA3	Hitachi	?	£1971.66[a]	100[b]	£5.15	£22.06	Southampton DAR;[116] Inflated to 2020–1 price year[154]
UA1232	Bk Medical	bkFusion[c]	£1443.12	100[b]	£5.15	-	Southampton DAR;[116] Inflated to 2020–1 price year[154]
Trinity Perine	KOELIS and Kebomed	KOELIS Trinity	£777.64	100	£5.15	-	Southampton DAR;[116] Inflated to 2020–1 price year[154]
Perine Grid 18G			£779.31	100	NR	used with or without a guide needle	KOELIS and Kebomed response to NICE and/or EAG RFI
Full Grid 18G			£1303.44	100	NR		
Perine Mini Grid			£86.20	1			
Perine Full Grid			£62.04	1			
SureFire	Delta Surgical	Fusion Bx 2.0	£123.70	1		-	Southampton DAR;[116] Inflated to 2020/2021 price year[154]
			£125.00	NR	NR	NR	Focal Healthcare response to NICE and/or EAG RFI

continued

TABLE 95 Summary of information on the costs of transperineal needle positioning freehand devices in a previous DAR and from the companies' responses to RFIs (*continued*)

Device	Manufacturer	Compatible with	Cost of device	Number of uses	Reprocessing	Co-axial needle	Source
Unnamed reusable device	NR	BiopSee	£700.00	NR	NR	NR	Medcom response to NICE and/or EAG RFI

a Average unit cost for order of fewer than 5 units (£2000.00) and > 5 unit (£1825.50).
b Assumption in Southampton DAR.[116]
c No third-party freehand device validated.

The costs of transperineal devices applied in the model for the base-case analysis were, thus, £90.44 and £81.86 for stabilised and freehand biopsy, respectively.

We did not consider the costs of LATP with double-freehand technique, as the provisional DCD for the previous DAR does not recommend the use of double-freehand devices to conduct LATP. We also did not consider any device costs to conduct LATRUS in line with the Southampton DAR.[116]

We included the annuitised cost of a lithotomy bed (£10,308, 10-year lifespan) in the calculations of the cost per biopsy of TP; this cost was sourced from the Southampton DAR,[152] and inflated to 2020–1 price year using the NHSCII.[154]

The costs of general consumables by biopsy approach were also sourced from the previous DAR,[116,152] where they are detailed (see *Table 113* of the Southampton DAR). We applied a cost per biopsy of £80.7, £65.55, and £79.10 for LATP, GATP and LATRUS, respectively.

Cost of histopathology analysis and report

The Southampton DAR[152] assumed that the cost of histopathology analysis was dependent on the number of cores sampled and each biopsy involved sampling 12 cores.

There was limited comparative evidence to inform any differences in the number of cores sampled between cognitive and software fusion identified in the clinical review, as most diagnostic accuracy studies performed a fixed pre-specified number of cores per biopsy. One RCT[31] reported the median number of cores per subject undergoing a targeted biopsy; 4 [interquartile range (IQR): 3–5, *n* = 79] and 3 (IQR: 3–3; *n* = 78) for software and CF, respectively. This suggests that fewer cores than 12 would require analysis per targeted biopsy, and that differences between MRI-influenced methods are small. However, the study had a small sample size and this was not a primary outcome, so it is unlikely that the study was powered to identify any differences in this particular outcome between MRI-influenced methods.

The unit cost of histopathology analysis, of the cores sampled through biopsy, was sourced in the Southampton DAR[116,152] initially from a histopathology pricing document by the University of Surrey, and then corrected to a HRG cost (£36.58; currency code DAPS02: Directly Accessed Pathology Services – Histopathology and histology).[186] The resulting cost for the analysis of a 12-core biopsy was £438.96 in the Southampton revised base-case analysis, which assumed the unit costs applied to each core tested. This level of resource used applied is more in line with some systematic biopsies (see *Biopsy*).

In the York model, we assumed that the NHS reference cost applied in the Southampton model, also applied to a single targeted biopsy (with fewer than 12 cores sampled per biopsy). We sourced the same HRG currency cost (£16.29) from the latest version of the NHS reference costs[187] and applied it to each targeted biopsy. We also did not identify comparative evidence on the number of cores

sampled for targeted and combined biopsies, so no differences were assumed. We note that if we have underestimated the histopathology analysis cost of biopsy (targeted or combined) that this would only be likely to impact the cost-effectiveness estimates if there were considerable differences in the rates of subsequent biopsy between the intervention and comparator.

We also considered the cost of reporting to the patient the biopsy result. In line with the previous DAR,[152] this was assumed to require a 30-minute appointment with a urologist (medical consultant, £123 per hour),[154] resulting in a cost per biopsy of £61.50.

Costs per software and cognitive fusion biopsy

TABLE 96 Disaggregated biopsy costs with LATRUS

LATRUS	bkFusion (£)	FusionVu (£)	KOELIS Trinity (£)	BiopSee (£)	Fusion Bx 2.0 (£)	CF (£)
Technology specific						
MRI fusion and US	57.17	89.13	77.44	46.61	83.09	36.15
Installation	0.01	0.01	0.01	0.01	0.01	0.01
Maintenance	44.65	37.20	29.76		32.32	
Training	3.43	0.92	0.95	0.68	0.46	
Procedure time	22.53	22.53	22.53	22.53	22.53	
Biopsy setting	19.67	19.67	19.67	19.67	19.67	12.29
TP biopsy devices						
Total	147.48	169.47	150.37	89.51	158.10	48.44
Not technology specific						
Training	1.46					
Procedure time	50.70					
General consumables	79.10					
Lithomy bed						
Histology	77.79					
Total	209.05					
Total per biopsy	356.53	378.53	359.43	298.56	367.15	257.49

TABLE 97 Disaggregated biopsy costs with LATP

LATP	bkFusion (£)	FusionVu (£)	KOELIS Trinity (£)	BiopSee(£)	Fusion Bx 2.0 (£)	CF (£)
Technology specific						
MRI fusion and US	57.17	89.13	78.73	52.07	83.52	36.58
Installation	0.01	0.01	0.01	0.01	0.01	
Maintenance	44.65	37.20	29.76		32.32	
Training	3.43	0.92	0.95	0.68	0.46	
Procedure time	22.53	22.53	22.53	22.53	22.53	

continued

TABLE 97 Disaggregated biopsy costs with LATP (*continued*)

LATP	bkFusion (£)	FusionVu (£)	KOELIS Trinity (£)	BiopSee(£)	Fusion Bx 2.0 (£)	CF (£)
Biopsy setting	22.01	22.01	22.01	22.01	22.01	14.63
TP biopsy devices	81.86	81.86	81.86	81.86	81.86	81.86
Total	231.68	253.68	235.87	179.18	242.73	133.07
Not technology specific						
Training	11.67					
Procedure time	60.36					
General consumables	85.44					
Lithomy bed	3.99					
Histology	77.79					
Total	239.25					
Total per biopsy	470.93	492.93	475.12	418.43	481.98	372.32

TABLE 98 Disaggregated biopsy costs with GATP

GATP	bkFusion (£)	FusionVu (£)	KOELIS Trinity (£)	BiopSee (£)	Fusion Bx 2.0 (£)	CF (£)
Technology specific						
MRI fusion and US	57.17	89.13	78.73	47.42	83.52	36.58
Installation	0.01	0.01	0.01	0.01	0.01	0.01
Maintenance	44.65	37.20	29.76		32.32	
Training	3.43	0.92	0.95	0.68	0.46	
Procedure time	29.83	29.83	29.83	29.83	29.83	
Biopsy setting	155.14	155.14	155.14	155.14	155.14	132.97
TP biopsy devices	90.44	90.44	90.44	90.44	90.44	90.44
Total	380.67	402.67	384.86	323.52	391.72	260.00
Not technology specific						
Training	11.67					
Procedure time	270.42					
General consumables	170.29					
Lithomy bed	3.99					
Histology	77.79					
Total	534.15					
Total per biopsy	914.82	936.82	919.01	857.67	925.87	794.15

Biopsy adverse event costs

TABLE 99 Biopsy procedure AE costs

Biopsy AEs	Cost (£)	Resource use and unit costs
Mild AE	49.78	Resource use for outpatient urinary infection (Wilson, (2021),[121] including: • GP visit: £39.23 – PSSRU (2021)[154] GP – unit costs; per patient contact lasting 9.22 minutes • Urinalysis: £10.18 – NHS reference costs 2020–1[187] – Direct Access Pathology Services: currency code DAPS07, Microbiology • 7-day trimethoprim: £0.37 – eMIT (2021)[191] – trimethoprim 200 mg × 14 tablets
Non-elective admission[a]	Transrectal: 2580.24 Transperineal: 1952.98	Tamhankar (2020),[184] inflated to 2020–1 price year[154]
Death[a]	9560.56	NHS reference costs 2020–1[187] – Non-Elective: currency code WJ06A, Sepsis with multiple interventions, CC Score 9 + (weighted average of short stay and long stay patients)

eMIT, electronic market information tool.
a Within 28 days of the procedure.

Prostate cancer management costs

TABLE 100 Resource use and costs of monitoring for individuals diagnosed with localised PCa

Treatment assigned	Active surveillance				Radical treatment					Resource use and unit costs
Time	**First year**			**Subsequent years**	**First year**			**Second year**	**Subsequent years**	
Diagnosed CPG	CPG 1	CPG2–3	CPG4–5	CPG1–5	CPG 1	CPG2–3	CPG4–5	CPG1–5	CPG1–5	
Resource use										
PSA test	4			2	2			2	1	£1.85 – NHS reference costs 2020–21[187] – currency code DAPS04, Clinical Biochemistry, Direct Access Pathology Services
Nurse-led outpatient appointment	4			2	2			2	1	£11.00 – assumed as cost per 10 minutes, adjusted from cost per hour of band 7 community-based nurse – PSSRU (2021)[154]
DRE	1			1	0			0	0	£78.46 – assumed as cost per approximately 20 minutes of GP appointment – PSSRU (2021)[154] adjusted from GP – unit costs; per patient contact lasting 9.22 minutes
mpMRI	1			0	0			0	0	£294.70 – NHS reference costs 2020–1[187] – currency code RD03Z, Diagnostic Imaging, MRI Scan of One Area, with Pre- and Post-Contrast
CT scan	0	0.5	0.7	0	0	0.5	0.7	0	0	£150.62 – NHS reference costs 2020–1[187] – currency code RD21A, Diagnostic Imaging, Computerised Tomography Scan of One Area, with Post-Contrast Only, 19 years and over
Bone scan	0	0.5	0.7	0	0	0.5	0.7	0	0	£427.21 – NHS reference costs 2020–21[187] – currency code RN15A, Nuclear Medicine, Nuclear Bone Scan of Two or Three Phases, 19 years and over
Cost per year	£424.56	£713.48	£829.05	£104.16	£25.70	£314.62	£430.18	£25.70	£12.85	

CPG, Cambridge Diagnostic Group; CT, computerised tomography; mpMRI, multiparameter magnetic resonance image; PSA, prostate-specific antigen.

TABLE 101 Resource use and costs of radical treatment

Radical treatment	Cost of procedure and follow-up (£)	Resource use and unit costs
Radical prostatectomy	11,625.37	Robotic surgery: £11,245.08 – NHS reference costs 2020–1[187] – Elective inpatient, currency code LB69Z: Major Robotic, Prostate or Bladder Neck Procedures (Male) First surgery appointment: £87.14 – NHS reference costs 2020–1[187] – Outpatient procedure, currency code WF01B: Non-Admitted Face-to-Face Attendance, First (General surgery) Two follow-up appointments: 2 x £146.58 – NHS reference costs 2020–1[187] – Outpatient procedure, currency code WF01A: Non-Admitted Face-to-Face Attendance, Follow-up (General surgery)
External radiotherapy	5341.81	Preparation: £1721.79 – NHS reference costs 2020–1[187] Preparation of for Intensity Modulated Radiation Therapy, weighted average of currency codes DC40Z and DC41Z (Total HRGs) Fraction delivery – 20 x £181.00 – NHS reference costs 2020–1[187] – Deliver a Fraction of Treatment on a Superficial or Orthovoltage Machine, currency code SC12Z (Total HRGs)
Brachytherapy	9156.96	Preparation: £1550.22– NHS reference costs 2020–1[187] – Preparation for Interstitial Brachytherapy, weighted average of currency code SC55Z over day case, inpatient, outpatient and other setting Fraction delivery: £7606.74 – NHS reference costs 2020–1[187] – Deliver a Fraction of Intraluminal Brachytherapy, weighted average of currency code SC30Z over day case, inpatient outpatient, and other setting

TABLE 102 Metastatic treatment costs

Treatment	Cost (£)	Treatments included	Source of unit cost
Metastatic hormone sensitive – year 1 Metastatic hormone sensitive – year 2	15,603.87 15,602.88	- ADT: £973.76 for LHRH[a] (leuprorelin 11.25 mg, every 3 months; triptorelin 11.25 mg; or goserelin 3.6 mg, every 28 days) + £1.00 one-off bicalutamide 50 mg for 28 days (in year 1 only) .- ADT + DTX: £973.76 for LHRH[a] (as above) + £1404.00 (6 cycles of DTX[b] at a dose of 75 mg/m^2; a cycle every 3 weeks – divided equally over 2 years) + £1.00 one-off bicalutamide 50 mg for 28 days (in year 1 only) .- ADT + apalutamide: £973.76 for LHRH (as above) + £35,677.10 (apalutamide 240 mg daily) + £1.00 one-off bicalutamide 50 mg for 28 days (in year 1 only) - ADT + enzalutamide: £973.76 for LHRH[a] (as above) + £35,672.79 (enzalutamide 160 mg daily) + £1.00 one-off bicalutamide 50 mg for 28 days (in year 1 only)	BNF 2022,[192] eMIT 2022,[191] PSSRU 2021,[154] NHS reference costs 2020–1[187]
Metastatic hormone resistant – year 1	14,907.45	- Abiraterone: £23,784.73 (1000 mg daily, 8 months) - DTX[b]: £4509.64 (9.5 cycles of DTX at a dose of 75 mg/m^2; a cycle every 3 weeks) - Enzalutamide: £41,618.26 (160 mg daily, 14 months)	BNF 2022,[192] eMIT 2022,[191] PSSRU 2021,[154] NHS reference costs 2020–1[187]

BNF, British National Formulary; eMIT, electronic market information tool.
a Administered by a band 6 hospial-based nurse (15.5 minutes).
b Administered by perfusion [NHS reference costs currency codes for delivery of simple parental chemotherapy (SB12Z and SB15Z)].

Treatment adverse event costs

TABLE 103 Treatment AE unit costs

Treatment for	AE	Unit cost (£)	Source
Localised PCa	Erectile dysfunction	328.58	NHS reference costs 2020–1[187] – treatment of Erectile Dysfunction weighted average of the currency code LB43Z General Surgery, Genitourinary Medicine, Plastic Surgery, Urology
	Urinary incontinence	317.54	NICE NG131[123] – managed by containment pads. Inflated to 2020–1 price year[154]
	Bowel dysfunction	1941.19	NICE NG131[123] – mean weighted cost including costs associated with sigmoidoscopy, laser therapy, enemas and blood transfusion. Inflated to 2020–1 price year[154]
Hormone-sensitive metastatic PCa	Blood disorder	2428.70	NHS reference costs 2020–1[187] – weighted average of currency codes SA03G–SA03H, SA08G–SA08J, SA12G–SA12K non-elective long stay and non-elective short stay
	Cardiac disorder	2042.04	NHS reference costs 2020–1[187] – weighted average of currency codes EB10A–EB10E non-elective long stay and non-elective short stay
	Endocrine disorder	328.58	Assume the same as erectile dysfunction (as in Southampton DAR)[116]
	Gastrointestinal disorder	2019.47	NHS reference costs 2020–1[187] – weighted average of currency codes FD10A–FD10M non-elective long stay and non-elective short stay
	General disorder	39.90	- GP visit per patient contact lasting 9.22 minutes: £39.23 – GP – unit costs; PSSRU 2021[154] - 3-day Trimethoprim: £0.67 – eMIT 2021[191] – trimethoprim 200 mg × 6 tablets
	Musculoskeletal disorder	26.58	NHS reference costs 2020–1[187] – weighted average of currency codes HD26D–HD26G non-elective long stay and non-elective short stay
	Nervous system disorder	1933.29	NHS reference costs 2020–1[187] – weighted average of currency codes AA26C–AA26H non-elective long stay and non-elective short stay
	Neutropenia	9842.93	NHS reference costs 2020–1[187] – weighted average of currency codes PM45A–PM45D non-elective long stay and non-elective short stay
	Renal disorder	49.78	Assume the same as urinary infection (as in Southampton DAR)[116]
	Respiratory disorder	971.68	NHS reference costs 2020–1[187] – weighted average of currency codes DZ19H–DZ19N non-elective long stay and non-elective short stay
	Skin disorder	2191.91	NHS reference costs 2020–1[187] – weighted average of currency codes JD07A–JD07K non-elective long stay and non-elective short stay

DAR, Diagnostic Assessment Report; eMIT, electronic market information tool; NICE, National Institute of Health and Care Excellence.

Base-case parameterisation

TABLE 104 Model parameters – base-case analysis

Parameter	Value		Probabilistic setup	Source
Population characteristics				
Age	66 years		NA	Southampton DAR[116]
Prevalence and distribution across ISUP grade				
No PCa	0.12		Calculated from each 1000 iterations of network 1 and 2	See *Modelling of first biopsy results*
ISUP grade 1	0.32			
ISUP grade 2	0.26			
ISUP grade 3	0.18			
ISUP grade 4–5	0.12			
Diagnostic performance				
First biopsy and repeat biopsy with CF				
Probability of (diagnosis) | (true disease)	Targeted	Combined		
ISUP grade 4–5 | ISUP grade 4–5	0.552	0.573	Calculated from each 1000 iterations of network 1 for targeted and network 2 for combined	See *Modelling of first biopsy results*
ISUP grade 3 | ISUP grade 4–5	0.101	0.140		
ISUP grade 2 | ISUP grade 4–5	0.111	0.130		
ISUP grade 1 | ISUP grade 4–5	0.111	0.047		
No PCa | ISUP grade 4–5	0.125	0.111		
ISUP grade 3 | ISUP grade 3	0.479	0.510		
ISUP grade 2 | ISUP grade 3	0.192	0.207		
ISUP grade 1 | ISUP grade 3	0.140	0.059		
No PCa | ISUP grade 3	0.189	0.224		
ISUP grade 2 | ISUP grade 2	0.338	0.544		
ISUP grade 1 | ISUP grade 2	0.362	0.204		
No PCa | ISUP grade 2	0.300	0.251		
ISUP grade 1 | ISUP grade 1	0.171	0.329		
No PCa | ISUP grade 1	0.829	0.671		
No PCa | No PCa	1.000	1.000		
First biopsy and repeat biopsy with SF				
Probability of (diagnosis) | (true disease)	Targeted	Combined		
ISUP grade 4–5 | ISUP grade 4–5	0.281	0.724	Calculated from each 1000 iterations from network 1 for targeted and network 2 for combined	See *Modelling of first biopsy results*
ISUP grade 3 | ISUP grade 4–5	0.163	0.071		
ISUP grade 2 | ISUP grade 4–5	0.173	0.066		
ISUP grade 1 | ISUP grade 4–5	0.187	0.070		

continued

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value		Probabilistic setup	Source
No PCa | ISUP grade 4–5	0.195	0.069		
ISUP grade 3 | ISUP grade 3	0.616	0.603		
ISUP grade 2 | ISUP grade 3	0.134	0.130		
ISUP grade 1 | ISUP grade 3	0.124	0.135		
No PCa | ISUP grade 3	0.126	0.132		
ISUP grade 2 | ISUP grade 2	0.314	0.770		
ISUP grade 1 | ISUP grade 2	0.437	0.152		
No PCa | ISUP grade 2	0.249	0.078		
ISUP grade 1 | ISUP grade 1	0.291	0.472		
No PCa | ISUP grade 1	0.709	0.528		
No PCa | No PCa	1.000	1.000		
Probability of repeat biopsy				
if diagnosed as No PCa	5%		NA	Southampton DAR assumption[116]
if diagnosed as ISUP grade 1	15.45%		Beta distribution: α = 95; β = 520	Southampton DAR[116]
Biopsy AEs rates				
Mild AEs with TR biopsy	1.31%		Beta distribution: α = 15; β = 1132	Southampton DAR[116,152]
Mild AEs with TP biopsy	9.13%		Beta distribution: α = 274; β = 2726	
Leading to NEL with TR biopsy	3.74%		Beta distribution: α = 2845; β = 73,261	
Leading to NEL with TR biopsy	3.54%		Beta distribution: α = 1314; β = 35,763	
TR mortality	0.07%		Beta distribution: α = 53; β = 76,053	
TP mortality	0.05%		Beta distribution: α = 19; β = 37,058	
Distribution by biopsy approach at first biopsy				
LATRUS	35%		NA	Assumption informed by NHS reference data 2018–9[185]
LATP	65%		NA	
Distribution by biopsy approach at repeat biopsy				
LATRUS	30%		NA	Assumption informed by NHS reference data 2018–9[185] and clinical advice
LATP	60%		NA	
GATP	10%		NA	
Long-term model transitions				
Progression Localised/Locally advanced to Metastatic				
Lambda CPG 1 with observation	0.0143		Sampled from 1000 simulations of the calibration model joint output for the 4 CPG categories and treatment received	Calibrated (see *Modelling of long-term outcomes*)
Lambda CPG 2 with observation	0.0379			
Lambda CPG 3 with observation	0.1197			
Lambda CPG 4-5 with observation	0.3997			

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Lambda CPG 1 with radical treatment	0.0063		
Lambda CPG 2 with radical treatment	0.0164		
Lambda CPG 3 with radical treatment	0.0514		
Lambda CPG 4-5 with radical treatment	0.1683		
Metastatic to PCa death			
Weibull	$\gamma = 1.26$; $\lambda = 0.11$	Multivariate lognormal	The PCa death curve for the control arm in Clarke (2019)[143] was digitised by using WebPlotDigitizer;[145] a pseudo-IPD was reconstructed by using Guyot algorithm,[146] Weibull distribution was then fitted to the pseudo-IPD to obtain γ, λ and variance–covariance matrix using *flexsurv* package in R[147]
Mortality HR for DTX + ADT vs. ADT alone	0.78	Log-normal, 95% CI (0.66 to 0.93)	James (2016)[59]
Mortality HR for Enzalutamide + ADT vs. ADT alone	0.66	Log-normal, 95% CI (0.53 to 0.81)	ARCHES study[149]
Mortality HR for Apalutamide + ADT vs. ADT alone	0.65	Log-normal, 95% CI (0.53 to 0.79)	TITAN study[150]
Other-cause mortality	Age dependent	NA	ONS lifetables 2018–20[144]
Treatment distributions			
Localised disease disease			
Radical treatment and diagnosed (ISUP grade 4–5)	75.9%	Dirichlet distribution	Calculated as sum of proportions of radical prostatectomy and radiotherapy; Parry (2020)[151]
Radical treatment and diagnosed (ISUP grade 3)	66.3%		
Radical treatment and diagnosed (ISUP grade 2)	48.4%		
Radical treatment and diagnosed (ISUP grade 1)	11.3%		
Radical treatment and diagnosed (No PCa)	0%	NA	Assumption

continued

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Metastatic cancer			
ADT	50.0%	NA	Assumption informed by Southampton DAR[116] and NPCA report 2021[188]
ADT + DTX	9.4%	NA	
ADT + apalutamide	6.6%	NA	
ADT + enzalutamide	34.0%	NA	
Treatment AE rates			
Radical prostatectomy			
Sexual dysfunction	85.39%	Beta distribution: α = 304; β = 52	Southampton DAR[116]
Bowel dysfunction	2.47%	Beta distribution: α = 9; β = 355	
Urinary dysfunction	26.24%	Beta distribution: α = 95; β = 267	
Radiotherapy			
Sexual dysfunction	62.39%	Beta distribution: α = 219; β = 132	Southampton DAR[116]
Bowel dysfunction	5.85%	Beta distribution: α = 21; β = 338	
Urinary dysfunction	3.63%	Beta distribution: α = 21; β = 345	
Active surveillance			
Erectile dysfunction	50.88%	Beta distribution: α = 173; β = 167	Southampton DAR[116]
Bowel dysfunction	1.68%	Beta distribution: α = 6; β = 352	
Urinary incontinence	4.20%	Beta distribution: α = 15; β = 342	
Metastatic treatment			
ADT			
Blood disorder	0.00%		Southampton DAR[116]
Cardiac disorder	2.96%	Beta distribution: α = 35; β = 1149	
Endocrine disorder	12.25%	Beta distribution: α = 145; β = 1039	
Gastrointestinal disorder	3.04%	Beta distribution: α = 36; β = 1148	
General disorder	3.89%	Beta distribution: α = 46; β = 1138	
Musculoskeletal disorder	5.83%	Beta distribution: α = 69; β = 1115	
Nervous system disorder	1.69%	Beta distribution: α = 20; β = 1164	
Neutropenia	1.77%	Beta distribution: α = 21; β = 1163	
Renal disorder	6.00%	Beta distribution: α = 71; β = 1113	
Respiratory disorder	2.28%	Beta distribution: α = 27; β = 1157	
Skin disorder	0.00%		
ADT + DTX			
Blood disorder	0.00%		Southampton DAR[116]
Cardiac disorder	2.91%	Beta distribution: α = 16; β = 534	
Endocrine disorder	10.36%	Beta distribution: α = 57; β = 493	
Gastrointestinal disorder	8.18%	Beta distribution: α = 45; β = 505	
General disorder	6.18%	Beta distribution: α = 34; β = 516	
Musculoskeletal disorder	5.82%	Beta distribution: α = 32; β = 518	

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Nervous system disorder	3.45%	Beta distribution: α = 19; β = 531	Southampton DAR[116]
Neutropenia	27.27%	Beta distribution: α = 150; β = 400	
Renal disorder	4.18%	Beta distribution: α = 23; β = 527	
Respiratory disorder	5.27%	Beta distribution: α = 29; β = 521	
Skin disorder	0.00%		
ADT + apalutamide			
Blood disorder	2.10%	Beta distribution: α = 11; β = 513	Southampton DAR[116]
Cardiac disorder	8.40%	Beta distribution: α = 44; β = 480	
Endocrine disorder	0.00%		
Gastrointestinal disorder	1.15%	Beta distribution: α = 6; β = 518	
General disorder	3.44%	Beta distribution: α = 18; β = 506	
Musculoskeletal disorder	6.49%	Beta distribution: α = 34; β = 490	
Nervous system disorder	0.19%	Beta distribution: α = 1; β = 523	
Neutropenia	0.00%		
Renal disorder	0.76%	Beta distribution: α = 4; β = 520	
Respiratory disorder	0.00%		
Skin disorder	6.49%	Beta distribution: α = 34; β = 490	
ADT + enzalutamide			
Blood disorder	0.00%		Southampton DAR[116]
Cardiac disorder	4.90%	Beta distribution: α = 28; β = 544	
Endocrine disorder	0.35%	Beta distribution: α = 2; β = 570	
Gastrointestinal disorder	0.52%	Beta distribution: α = 3; β = 569	
General disorder	2.80%	Beta distribution: α = 16; β = 556	
Musculoskeletal disorder	4.37%	Beta distribution: α = 25; β = 547	
Nervous system disorder	2.10%	Beta distribution: α = 12; β = 560	
Neutropenia	0.35%	Beta distribution: α = 2; β = 570	
Renal disorder	0.00%		
Respiratory disorder	0.00%		
Skin disorder	0.35%	Beta distribution: α = 2; β = 570	
HRQoL			
Disutility of biopsy AEs			
Mild AEs	−0.289	NA	Southampton DAR;[116] assumed duration 3 days
Leading to NEL	−0.490	NA	Southampton DAR;[116] assumed duration 30 days

continued

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Death	−0.490	NA	Southampton DAR;[116] assumed duration 30 days
Baseline health state utility	Age and sex dependent	NA	Ara and Brazier (2010)[137]
Localised treatment disutility			
Sexual dysfunction	−0.0230	No-mild symptoms: Beta distribution: α = 578; β = 93 Moderate–severe symptoms: Beta distribution: α = 452; β = 87	Calculated as the difference between no-mild symptoms and moderate-severe symptoms (as per Southampton DAR)[116]
Urinary dysfunction	−0.0950	No-mild symptoms: Beta distribution: α = 1013; β = 154 Moderate–severe symptoms: Beta distribution: α = 131; β = 39	
Bowel dysfunction	−0.2090	No-mild symptoms: Beta distribution: α = 1097; β = 176 Moderate–severe symptoms: Beta distribution: α = 62; β = 33	
Metastatic disutility	−0.137	Localised 1: Beta distribution: α = 102; β = 11 Localised 2: Beta distribution: α = 404; β = 50 Localised 3: Beta distribution: α = 841; β = 126 Metastatic: Beta distribution: α = 165; β = 58	Calculated as the difference between metastatic and the average across localised 1, 2, 3 (as per Southampton DAR)[116]
Resource use and costs			
Annual patient throughput	300	NA	Assumed based on NHS reference costs 2018–9[185]
Cost per first CF biopsy (targeted or combined)	£332.13	NA	Calculated
Cost per first SF (targeted or combined)	£427.33	NA	Calculated
Cost per repeat CF biopsy (targeted or combined)	£380.05	NA	Calculated
Cost per repeat SF (targeted or combined)	£477.42	NA	Calculated
Cost of localised treatment			
Cost of radical prostatectomy	£11,625.37	NA	Calculated
Cost of radiotherapy for those who diagnosed as CPG1	£6283.42	NA	Calculated
Cost of radiotherapy for those who diagnosed as CPG2	£5754.11	NA	Calculated
Cost of radiotherapy for those who diagnosed as CPG3	£5510.29	NA	Calculated
Cost of radiotherapy for those who diagnosed as CPG4–5	£5402.04	NA	Calculated
Cost of ADT	£973.76	NA	Calculated (see *Table 102*)

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Cost of bicalutamide	£1.49	NA	21 days course of bicalutamide – BNF 2022[192] bicalutamide 50mg × 28 tablets
Cost of metastatic treatment			
Cost of first year hormone-sensitive treatment	£15,603.87	NA	Calculated (see *Table 102*)
Cost of second year hormone-sensitive treatment	£15,602.88	NA	
Cost of metastatic treatment in subsequent years (one-off)	£14,907.45	NA	
Cost of monitoring/active surveillance			
Cost of AS for those who diagnosed as CPG1 in first year	£424.56	NA	Calculated
Cost of AS for those who diagnosed as CPG2–3 in first year	£713.48	NA	Calculated
Cost of AS for those who diagnosed as CPG4–5 in first year	£829.05	NA	Calculated
Cost of AS for those who diagnosed as any CPG in subsequent years	£104.16	NA	Calculated
Cost of monitoring those who diagnosed as CPG1 receiving RT, in first year	£25.70	NA	Calculated
Cost of monitoring those who diagnosed as CPG2–3 receiving RT, in first year	£314.62	NA	Calculated
Cost of monitoring those who diagnosed as CPG4–5 receiving RT, in first year	£430.18	NA	Calculated
Cost of monitoring those who diagnosed as any CPG receiving RT, in second year	£ 25.70	NA	Calculated
Cost of monitoring those who diagnosed as any CPG receiving RT, in 2 + year	£12.85	NA	Calculated
Cost of monitoring those who have No PCa diagnosed as No PCa	£158.99	NA	Calculated
Cost of monitoring those who have No PCa diagnosed as ISUP grade 1	£242.02	NA	Calculated
Cost of monitoring metastatic patients (one off)	£577.83	NA	Calculated
Cost of managing AEs			

continued

TABLE 104 Model parameters – base-case analysis (*continued*)

Parameter	Value	Probabilistic setup	Source
Cost of managing AEs of biopsy procedure			
Cost per mild AE	£49.78	NA	Calculated
Cost per NEL event with LATRUS	£2580.24	NA	Calculated
Cost per NEL event with LATP/GATP	£1952.98	NA	Calculated
Cost per biopsy death	£9560.56	NA	Calculated
Cost of managing AEs of			
Active surveillance	£213.06	NA	Calculated
Radical prostatectomy	£411.91	NA	Calculated
Radiotherapy	£330.09	NA	Calculated
Metastatic treatment			
ADT	£397.49	See probabilistic setup for AE rates of ADT	Calculated
ADT + DTX	£3067.24	See probabilistic setup for AE rates of ADT + DTX	Calculated
ADT + enzalutamide	£196.62	See probabilistic setup for AE rates of ADT + enzalutamide	Calculated
ADT + apalutamide	£394.96	See probabilistic setup for AE rates of ADT + apalutamide	Calculated
End of life costs	£16,546.08	NA	Round (2015);[139] inflated to 2020–1 price year[154]

|, conditional on; AS, active surveillance; IPD, individual patient data; LATRUS, local anaesthesia transrectal ultrasound; NEL, non-elective admission; ONS, Office for National Statistics; RT, radical treatment; TP, transperineal; TR, transrectal.

Appendix 12 Additional cost-effectiveness results

Base-case analysis

TABLE 105 Probabilistic base-case cost-effectiveness results: (1) targeted and (2) combined biopsy

	Diagnostic model		Long-term model			Overall results							
Strategy	**QALY loss**	**Total costs (£)**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a] (£)**	**Total LYs[a]**	**Total QALYs[a]**	**Total costs[a] (£)**	**ICER[b] (£)**	**NHB at £20,000[b]**	**NHB at £30,000[b]**	**Probability CE at £20,000[b]**	**Probability CE at £30,000[b]**
Targeted CF	−0.00176	445	11.46	8.30	27,734	11.46	8.30	28,179		6.89	7.36	0.36	0.32
Targeted SF	−0.00175	543	11.48	8.31	27,702	11.48	8.31	28,245		6.90	7.37	0.64	0.68
Targeted	**Inc QALY loss**	**Inc costs**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**		
SF vs. CF	0.00001	98	0.02	0.01	−32	0.02	0.01	£65	6197	0.01	0.01		
Strategy	**QALY loss**	**Total costs**	**Total LYs[a]**	**Total QALYs[a]**	**Inc costs[a]**	**Inc LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**ICER[b]**	**NHB at £20,000[b]**	**NHB at £30,000[b]**	**Probability CE at £20,000[b]**	**Probability CE at £30,000[b]**
Combined CF	−0.00177	448	11.46	8.30	27,716	11.46	8.30	28,164		6.89	7.36	0.27	0.25
Combined SF	−0.00176	544	11.50	8.33	27,669	11.50	8.32	28,213		6.91	7.38	0.73	0.75
Combined	**Inc QALY loss**	**Inc costs**	**Inc LYs[a]**	**Total QALYs[a]**	**Total costs[a]**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a]**		**INHB at £20,000[b]**	**INHB at £30,000[b]**		
SF vs. CF	0.00002	96	0.04	0.02	−47	0.04	0.02	49	2199	0.02	0.02		

a Discounted at 3.5% per annum.
b Per additional QALY; CE, cost-effectiveness; Inc, incremental; INHB, incremental net health benefit; LYs, life years.

TABLE 106 Deterministic base-case prevalence, and final classification from the diagnostic pathway: targeted biopsy

	Prevalence					Proportion correctly classified[a]					
Strategy	**CPG 4-5**	**CPG G3**	**CPG 2**	**CPG 1**	**No PCa**	**CPG 4-5**	**CPG G3**	**CPG 2**	**CPG 1**	**No PCa**	**All categories**
CF	0.116	0.183	0.262	0.318	0.121	0.066	0.090	0.095	0.057	0.121	0.428
SF						0.067	0.095	0.149	0.108	0.121	0.540

a Final classification in the model.

TABLE 107 Deterministic base-case diagnostic pathway events, and disaggregated costs and QALY loss: targeted biopsy

	Proportion repeat biopsy		Proportion AEs			Cost			
Strategy	All	Unnecessary[a]	Death	Mild	Repeat biopsy	First biopsy (£)	Repeat biopsy (£)	AEs (£)	AEs QALY loss
CF	0.055	0.038	0.001	0.068	0.038	332	21	92	−0.00176
SF	0.050	0.035	0.001	0.067	0.038	427	24	92	−0.00175

a Unnecessary biopsy is defined as a second biopsy that did not raise the ISUP grade to at least 2.

TABLE 108 Deterministic base-case long-term undiscounted disaggregated costs: targeted biopsy

	Local disease – radical treatment					Local disease AEs								
	Immediate	Delayed				Immediate	Delayed				Metastatic disease			
Strategy	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	Treatment (£)	AEs (£)	Monitoring (£)	EoL (£)
CF	1844	103	280	568	252	688	12	84	276	146	17,241	456	948	16,510
SF	2158	76	260	395	202	850	10	78	192	117	17,008	449	1047	16,510

EoL, end of life.

TABLE 109 Deterministic base-case long-term undiscounted disaggregated health outcomes: targeted biopsy

			QALY loss		
Strategy	LYs	Baseline QALYs	Immediate radical treatment	Delayed radical treatment	Metastatic disease
CF	16.22	10.99	−0.09	−0.13	−0.52
SF	16.25	11.01	−0.13	−0.10	−0.51

LYs, life-years.

TABLE 110 Deterministic base-case prevalence, and final classification from the diagnostic pathway: combined biopsy

	Prevalence					Proportion correctly classified[a]					
Strategy	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	All categories
CF	0.116	0.183	0.262	0.318	0.121	0.034	0.115	0.089	0.096	0.121	0.455
SF						0.085	0.113	0.207	0.154	0.121	0.680

a Final classification in the model.

TABLE 111 Deterministic base-case diagnostic pathway events, and disaggregated costs and QALY loss: combined biopsy

	Proportion repeat biopsy		Proportion AEs			Cost			
Strategy	All	Unnecessary[a]	Death	Mild	Repeat biopsy	First biopsy (£)	Repeat biopsy (£)	AEs (£)	AEs QALY loss (£)
CF	0.062	0.043	0.001	0.068	0.038	332	23	93	−0.00177
SF	0.051	0.036	0.001	0.067	0.038	427	25	92	−0.00176

a Unnecessary biopsy is defined as a second biopsy that did not raise the ISUP grade to at least 2.

TABLE 112 Deterministic base-case long-term undiscounted disaggregated costs: combined biopsy

	Local disease – radical treatment					Local disease AEs								
	Immediate	Delayed				Immediate	Delayed				Metastatic disease			
Strategy	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	Treatment (£)	AEs (£)	Monitoring (£)	EoL (£)
CF	1835	169	205	574	214	723	20	62	280	124	17,172	454	1016	16,510
SF	2547	57	216	181	158	1048	7	65	88	92	16,705	441	1167	16,510

EoL, end of life.

TABLE 113 Deterministic base-case long-term undiscounted disaggregated health outcomes: combined biopsy

Strategy	LYs	Baseline QALYs	QALY loss		
			Immediate radical treatment	Delayed radical treatment	Metastatic disease
CF	16.21	10.98	−0.11	−0.12	−0.52
SF	16.29	11.03	−0.18	−0.07	−0.50

LYs, life-years.

Results of base-case by software fusion technology

In *Table 114*, *Appendix 12* we show the deterministic base-case analysis results of targeted SF by individual technology in pairwise comparison versus targeted cognitive. Corresponding results for the combined comparison are presented in *Appendix 12*.

TABLE 114 Deterministic cost-effectiveness results of the base-case analysis: targeted SF technologies pairwise comparisons with targeted CF

Strategy	Diagnostic model	Overall results					
	Inc costs (£)	Total LYs[a]	Total QALYs[a]	Total costs[a] (£)	ICER vs. CF[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
Targeted CF	-	11.45	8.29	28,364		6.87	7.34
Targeted software fusion	98	11.46	8.30	28,428	5623	6.88	7.35
Targeted bkFusion	101			28,431	5954	6.88	7.35
Targeted FusionVu	125			28,454	8001	6.88	7.35
Targeted KOELIS Trinity	105			28,435	6302	6.88	7.35
Targeted Fusion Bx 2.0	113			28,443	6968	6.88	7.35
Targeted BiopSee	44			28,374	890	6.88	7.35

CE, cost-effectiveness; Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 115 Deterministic cost-effectiveness results of the base case analysis: combined SF technologies pairwise comparisons with CF

Strategy	Diagnostic model	Overall results					
	Inc costs (£)	Total Lys[a]	Total QALYs[a] (£)	Total costs[a] (£)	ICER vs. CF[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
Targeted CF	-	11.75	8.68	22,457	-	7.56	7.93
Combined SF	99	11.76	8.69	22,536	9285	7.56	7.94
Combined bkFusion	103			22,540	9725	7.56	7.94
Combined FusionVu	126			22,563	12,443	7.56	7.94
Combined KOELIS Trinity	106			22,544	10,187	7.56	7.94

continued

TABLE 115 Deterministic cost-effectiveness results of the base case analysis: combined SF technologies pairwise comparisons wih CF (*continued*)

Strategy	Diagnostic model	Overall results					
	Inc costs (£)	Total Lys[a]	Total QALYs[a] (£)	Total costs[a] (£)	ICER vs. CF[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
Combined Fusion Bx 2.0	114			22,551	11,072	7.56	7.94
Combined BiopSee	45			22,483	2998	7.57	7.94

CE, cost-effectiveness; Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

The pairwise ICERs of the targeted SF strategies versus CF range between £28,374 and £28,454 per additional QALY for BiopSee and FusionVu, respectively. Results for the combined biopsy comparison show the same pattern. The only incremental difference between individual SF technologies strategies are the incremental costs in the diagnostic model.

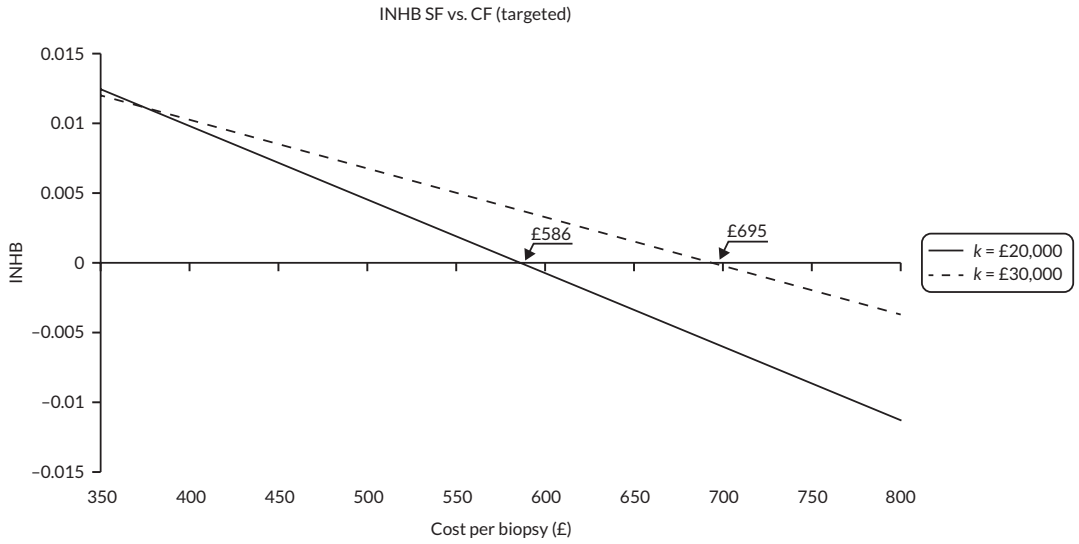


FIGURE 18 Targeted SF cost threshold analysis.

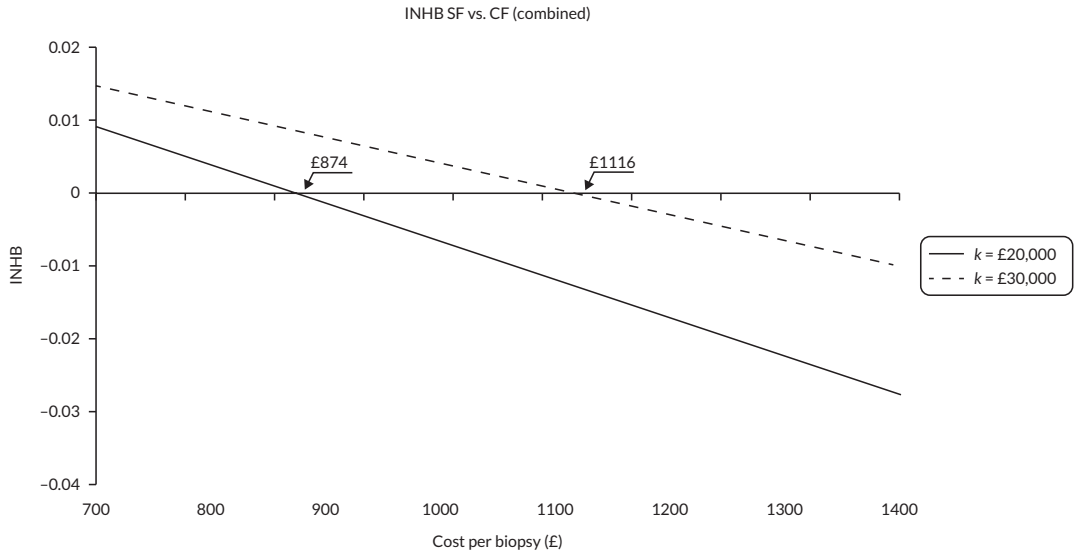


FIGURE 19 Combined SF cost threshold analysis.

Subgroup analyses

TABLE 116 Deterministic results for prior biopsy subgroup prevalence, and final classification from the diagnostic pathway: targeted biopsy

	Prevalence					Proportion correctly classified[a]					
Strategy	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	All categories
CF	0.085	0.131	0.132	0.224	0.428	0.048	0.063	0.043	0.033	0.428	0.614
SF						0.050	0.070	0.074	0.070	0.428	0.692

a Final classification in the model.

TABLE 117 Deterministic results for prior biopsy subgroup analysis diagnostic pathway events, and disaggregated costs and QALY loss: targeted biopsy

	Proportion repeat biopsy		Proportion AEs			Cost			
Strategy	All	Unnecessary[a]	Death	Mild	NEL	First biopsy (£)	Repeat biopsy (£)	AEs (£)	AEs QALY loss
CF	0.052	0.042	0.001	0.067	0.038	332	20	92	−0.00176
SF	0.049	0.040	0.001	0.067	0.038	427	23	92	−0.00175

NEL, leading to non-elective admissions.
a Unnecessary biopsy is defined as a second biopsy that did not raise the ISUP grade to at least 2.

TABLE 118 Deterministic results for prior biopsy subgroup long-term undiscounted disaggregated costs: targeted biopsy

	Local disease – radical treatment					Local disease AEs								
	Immediate	Delayed				Immediate	Delayed				Metastatic disease			
Strategy	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	Treatment (£)	AEs (£)	Monitoring (£)	EoL (£)
CF	1185	78	202	303	183	416	9	61	148	107	11,439	302	1109	16,509
SF	1394	55	183	204	148	522	7	55	99	86	11,287	298	1177	16,509

EoL, end of life.

TABLE 119 Deterministic results for prior biopsy subgroup long-term undiscounted disaggregated health outcomes: targeted biopsy

			QALY loss		
Strategy	LYs	Baseline QALYs	Immediate radical treatment	Delayed radical treatment	Metastatic disease
CF	16.72	11.27	−0.05	−0.09	−0.35
SF	16.74	11.28	−0.08	−0.06	−0.34

LYs, life-years.

TABLE 120 Deterministic results for prior biopsy subgroup prevalence, and final classification from the diagnostic pathway: combined biopsy

	Prevalence					Proportion correctly classified[a]					
Strategy	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	All categories
CF	0.085	0.131	0.132	0.224	0.428	0.028	0.081	0.040	0.071	0.428	0.648
SF						0.060	0.081	0.100	0.115	0.428	0.784

a Final classification in the model.

TABLE 121 Deterministic results for prior biopsy subgroup diagnostic pathway events, and disaggregated costs and QALY loss: combined biopsy

	Proportion repeat biopsy		Proportion AEs			Cost			
Strategy	All	Unnecessary[a]	Death	Mild	NEL	First biopsy (£)	Repeat biopsy (£)	AEs (£)	AEs QALY loss
CF	0.057	0.046	0.001	0.068	0.038	332	22	92	−0.00177
SF	0.053	0.043	0.001	0.068	0.038	427	25	92	−0.00176

NEL, leading to non-elective admissions.
a Unnecessary biopsy is defined as a second biopsy that did not raise the ISUP grade to at least 2.

TABLE 122 Deterministic results for prior biopsy subgroup long-term undiscounted disaggregated costs: combined biopsy

	Local disease – radical treatment					Local disease AEs								
	Immediate	Delayed				Immediate	Delayed				Metastatic disease			
Strategy	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	Treatment (£)	AEs (£)	Monitoring (£)	EoL (£)
CF	1187	124	152	306	147	448	14	46	149	85	11,385	301	1172	16,508
SF	1612	45	157	105	104	633	6	47	51	61	11,127	294	1272	16,508

EoL, end of life.

TABLE 123 Deterministic results for prior biopsy subgroup long-term undiscounted disaggregated health outcomes: combined biopsy

			QALY loss		
Strategy	Life years (LYs)	Baseline QALYs	Immediate radical treatment	Delayed radical treatment	Metastatic disease
CF	16.71	11.27	−0.07	−0.08	−0.34
SF	16.76	11.29	−0.11	−0.05	−0.34

Scenario analyses

TABLE 124 Deterministic results for scenario 1 – PAIREDCAP (2019) baseline – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00175	442	11.17	7.99	32,490	11.17	7.99	32,932		6.34	6.89
SF	−0.00174	538	11.19	8.00	32,432	11.19	7.99	32,970		6.35	6.90
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00001	96	0.02	0.01	−58	0.02	0.01	39	4428	0.01	0.01

Inc, incremental; LYs, life years; NHB, incremental net health benefit.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 125 Deterministic results for scenario – PAIREDCAP (2019) baseline – prevalence, and final classification from the diagnostic pathway: targeted biopsy

	Prevalence					Proportion correctly classified[a]					
Strategy	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	CPG 4–5	CPG G3	CPG 2	CPG 1	No PCa	All categories
CF	0.169	0.252	0.322	0.226	0.031	0.103	0.135	0.140	0.058	0.031	0.467
SF						0.100	0.136	0.193	0.086	0.031	0.544

a Final classification in the model.

TABLE 126 Deterministic results for scenario 1 – PAIREDCAP (2019) baseline – diagnostic pathway events, and disaggregated costs and QALY loss: targeted biopsy

	Proportion repeat biopsy		Proportion AEs			Cost			
Strategy	All	Unnecessary[a]	Death	Mild	NEL	First biopsy (£)	Repeat biopsy (£)	AEs (£)	AEs QALY loss
CF	0.048	0.028	0.001	0.067	0.038	332	18	92	−0.00175
SF	0.042	0.025	0.001	0.067	0.038	427	20	91	−0.00174

NEL, leading to non-elective admissions.
a Unnecessary biopsy is defined as a second biopsy that did not raise the ISUP grade to at least 2.

TABLE 127 Deterministic results for scenario 1 – PAIREDCAP (2019) baseline – long-term undiscounted disaggregated costs: targeted biopsy

	Local disease – radical treatment					Local disease AEs								
	Immediate	Delayed				Immediate	Delayed				Metastatic disease			
Strategy	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	All CPG (£)	CPG 4–5 (£)	CPG 3 (£)	CPG 2 (£)	CPG 1 (£)	Treatment (£)	AEs (£)	Monitoring (£)	EoL (£)
CF	2638	134	350	626	162	970	16	105	304	94	21,381	565	934	16,512
SF	2937	107	325	449	136	1120	14	98	218	79	21,154	559	998	16,512

EoL, end of life.

TABLE 128 Deterministic results for scenario 1 – PAIREDCAP (2019) baseline – long-term undiscounted disaggregated health outcomes: targeted biopsy

			QALY loss		
Strategy	Life years (LYs)	Baseline QALYs	Immediate radical treatment	Delayed radical treatment	Metastatic disease
CF	15.78	10.73	−0.13	−0.10	−0.65
SF	15.80	10.75	−0.16	−0.09	−0.64

TABLE 129 Deterministic results for scenario 2 – Zhou *et al.*[142] diagnostic – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00176	446	11.55	8.41	26,652	11.55	8.40	27,098		7.05	7.50
SF	−0.00175	543	11.58	8.43	26,638	11.58	8.43	27,180		7.07	7.52
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00001	97	0.03	0.03	−14	0.03	0.03	83	3105	0.02	0.02

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 130 Deterministic results for scenario 3 – degradation of repeat biopsy accuracy – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00176	445	11.44	8.29	27,922	11.44	8.29	28,367		6.87	7.34
SF	−0.00175	543	11.46	8.30	27,887	11.46	8.30	28,429		6.88	7.35
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00001	98	0.02	0.01	−35	0.02	0.01	63	5477	0.01	0.01

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 131 Deterministic results for scenario 3 – degradation of repeat biopsy accuracy – cost-effectiveness results: combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00177	448	11.44	8.28	27,892	11.44	8.28	28,340		6.86	7.33
SF	−0.00176	544	11.49	8.31	27,843	11.49	8.30	28,386		6.88	7.36
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00002	95	0.05	0.03	−49	0.05	0.03	46	1801	0.02	0.02

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 132 Deterministic results for scenario 4 – SF as quality assurance – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**ICER[b] (£)**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
CF	−0.00176	445	11.45	8.29	27,864	11.45	8.29	28,310		6.87	7.34
SF	−0.00174	537	11.45	8.29	27,859	11.45	8.29	28,396		6.87	7.34
	Inc QALY loss	**Inc costs (£)**	**Inc LYs[a] (£)**	**Inc QALYs[a]**	**Inc costs[a] (£)**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a] (£)**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00002	92	0.00	0.00	−6	0.00	0.00	87	874,744	0.00	0.00

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 133 Deterministic results for scenario 4 – SF as quality assurance – cost-effectiveness results: combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**ICER[b] (£)**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
CF	-0.00177	448	11.44	8.28	27,833	11.44	8.28	28,282		6.86	7.34
SF	-0.00174	538	11.44	8.28	27,824	11.44	8.28	28,363		6.86	7.33
	Inc QALY loss	**Inc costs (£)**	**Inc LYs[a] (£)**	**Inc QALYs[a]**	**Inc costs[a] (£)**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a] (£)**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00003	90	0.00	0.00	−9	0.00	0.00	81	581,847	0.00	0.00

a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 134 Deterministic results for scenario 5 – radical treatment for all identified CPG ≥ 2 and conservative treatment for CPG1 – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00176	445	11.55	8.37	28,816	11.55	8.37	29,261		6.90	7.39
SF	−0.00175	543	11.59	8.40	28,601	11.59	8.40	29,144		6.94	7.43
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00001	98	0.04	0.03	−215	0.04	0.03	−117	Dominates	0.04	0.03

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 135 Deterministic results for scenario 5 – radical treatment for all identified CPG ≥ 2 and conservative treatment for CPG1 – cost-effectiveness results: combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00177	448	11.55	8.36	28,786	11.55	8.35	29,234		6.89	7.38
SF	−0.00176	544	11.63	8.41	28,390	11.63	8.41	28,934		6.96	7.44
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00002	95	0.08	0.05	−396	0.08	0.05	−300	Dominates	0.07	0.06

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 136 Deterministic results for scenario 6.1 – throughput (150/year) – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**ICER[b] (£)**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
CF	−0.00176	495	11.45	8.29	27,956	11.45	8.29	28,451		6.87	7.34
SF	−0.00175	661	11.46	8.30	27,919	11.46	8.30	28,580		6.87	7.35
	Inc QALY loss	**Inc costs (£)**	**Inc LYs[a] (£)**	**Inc QALYs[a]**	**Inc costs[a] (£)**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a] (£)**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00001	166	0.02	0.01	−37	0.02	0.01	129	11,425	0.00	0.01

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 137 Deterministic results for scenario 6.1 – throughput (150/year) – cost-effectiveness results: combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	**QALY loss**	**Total costs (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**Total LYs[a] (£)**	**Total QALYs[a] (£)**	**Total costs[a] (£)**	**ICER[b] (£)**	**NHB at £20,000[b]**	**NHB at £30,000[b]**
CF	−0.00177	498	11.44	8.28	27,924	11.44	8.28	28,422		6.86	7.33
SF	−0.00176	662	11.49	8.31	27,870	11.49	8.30	28,532		6.88	7.35
	Inc QALY loss	**Inc costs (£)**	**Inc LYs[a] (£)**	**Inc QALYs[a]**	**Inc costs[a] (£)**	**Inc LYs[a]**	**Inc QALYs[a]**	**Inc costs[a] (£)**		**INHB at £20,000[b]**	**INHB at £30,000[b]**
SF vs. CF	0.00002	164	0.05	0.03	−54	0.05	0.03	110	4,275	0.02	0.02

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 138 Deterministic results for scenario 6.2 – throughput (450/year) – cost-effectiveness results: combined biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00177	432	11.44	8.28	27,878	11.44	8.28	28,309		6.86	7.34
SF	−0.00176	504	11.49	8.31	27,831	11.49	8.30	28,335		6.89	7.36
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00002	73	0.05	0.03	−47	0.05	0.03	26	1009	0.02	0.02

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

TABLE 139 Deterministic results for scenario 6.2 – throughput (450/year) – cost-effectiveness results: targeted biopsy

	Diagnostic model		Long-term model			Overall results					
Strategy	QALY loss	Total costs (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	Total LYs[a] (£)	Total QALYs[a] (£)	Total costs[a] (£)	ICER[b] (£)	NHB at £20,000[b]	NHB at £30,000[b]
CF	−0.00176	428	11.45	8.29	27,907	11.45	8.29	28,335		6.87	7.34
SF	−0.00175	503	11.46	8.30	27,873	11.46	8.30	28,377		6.88	7.35
	Inc QALY loss	Inc costs (£)	Inc LYs[a] (£)	Inc QALYs[a]	Inc costs[a] (£)	Inc LYs[a]	Inc QALYs[a]	Inc costs[a] (£)		INHB at £20,000[b]	INHB at £30,000[b]
SF vs. CF	0.00001	75	0.02	0.01	−33	0.02	0.01	42	3689	0.01	0.01

Inc, incremental; INHB, incremental net health benefit; LYs, life years.
a Discounted at 3.5% per annum.
b Per additional QALY.

EME
HSDR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library