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The Prostate Cancer Diagnostic Pathway: Reporting a Pilot of a One-Stop Cognitive Magnetic Resonance Imaging Targeted Service

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Abstract

Objectives

To evaluate the suitability and feasibility of a novel multiparametric magnetic resonance imaging (mpMRI) and cognitive fusion transperineal targeted biopsy led prostate cancer (PCa) diagnostic service with regard to cancer detection and reducing time to diagnosis and treatment.

Patients & Methods

Men referred with a raised prostate specific antigen (PSA) or abnormal digital rectal examination (DRE) between 02/2015 and 03/2016 were investigated for PCa. An mpMRI was performed prior to patients attending clinic, on the same day. If required, MRTB was offered. Results were available within 48 hours and discussed at a specialist multidisciplinary team (MDT) meeting. Patients returned for counselling within 7 days.

Results

112 men were referred to the service. 111 (99.1%) underwent mpMRI. Median PSA was 9.4ng/mL [IQR 5.6-21.0]. 87 patients had a target on mpMRI with 25 scoring Likert 3/5 for likelihood of disease, 26 4/5 and 36 5/5.

57 (51%) patients received a local anaesthetic, MRTB. Cancer was detected in 45 (79%). 43 (96%) had University College London (UCL) definition 2 disease or greater. The times to diagnosis and treatment were a median of 8 and 20 days respectively.

Conclusion

This approach greatly reduces the time to diagnosis and treatment. Detection rates of significant cancer are high. Similar services may be valuable to patients with a potential diagnosis of PCa.

Strengths and limitations of this study

- First prospective study demonstrating the clinical feasibility of a 'one stop', rapid diagnostic prostate cancer pathway, using both multiparametric magnetic resonance imaging and transperineal targeted biopsy.
- Inclusion criteria reflecting 'real world' practice in the United Kingdom.
- This study incorporates a standardised multiparametric MRI acquisition and a validated system for defining clinically significant prostate cancer.
- Cognitive targeted biopsy performed only, rather than mpMRI / ultrasound fusion.
- Transperineal, rather than transrectal approach offers minimal septic complications post biopsy.

Introduction

Accurate risk stratification for men presenting with localised prostate cancer is vitally important. In its absence, patient centred management cannot be offered. Men with low-risk disease can be safely managed with active surveillance, whereas men with a good life expectancy and intermediate to high-risk disease are likely to benefit from interventional treatment[1-2]. Currently, standard practice uses prostate-specific antigen (PSA) value, digital rectal examination (DRE) and transrectal ultrasound guided biopsy (TRUSGB). However, TRUSGB is inherently random. The tumour cannot be visualised with certainty, and thus leads to overdiagnosis of insignificant disease in up to 50% of men[3], and missing significant disease in 18% of men, especially if cancer is located in anterior or apical regions of the prostate[4]. This creates difficulty for urologists and adds anxiety to patients[5] who have to undergo a repetitive cascade of diagnostic tests, which inevitably has cost implications for healthcare providers.

Transperineal mapping or zonal biopsies (TPM) of the prostate offer a diagnostic alternative to TRUS biopsy with demonstrable diagnostic success. However, the burden on patients is high. Firstly, the extensive biopsies demand general anaesthesia. Secondly, the rates of urinary retention following the procedure are

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3 high, making postoperative catheterization commonplace. Thirdly, the large number
4 of cores taken requires many hours of labour to assess. Thus, a patient may have to
5 wait significantly longer for a result, adding to their anxiety. This may also delay
6 necessary treatment. Whether this results in adverse outcomes is not known.
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8 However, all of these established difficulties do confer added costs. Indeed, if every
9 patient undergoing TRUSGB instead underwent a TPM, the cost of such a move
10 would likely be exceedingly high. Therefore, the challenge presents itself as biopsy
11 offering superior clinically significant detection rates to the existing standard, whilst
12 not conferring an added cost.
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19 Multiparametric magnetic resonance imaging (mpMRI) of the prostate has proved a
20 useful tool in the diagnosis and risk stratification of prostate cancer. MpMRI has
21 demonstrated its ability to detect significant cancers, whilst not detecting those
22 which are insignificant[4]. Suspicious areas on mpMRI can be targeted with
23 subsequent transperineal biopsy (MRTB). MRTB has demonstrated greater sampling
24 efficiency and accuracy when compared with standard TRUS-guided protocols[6-8],
25 and has demonstrated accuracy when compared to the reference standard of radical
26 prostatectomy (RP)[9]. This allows for a more accurate assessment of Gleason
27 grade, and therefore an improved risk stratification and treatment plan at
28 diagnosis[10]. Furthermore, the efficiency advantage, i.e. taking fewer cores at
29 biopsy, confers significant benefits in cost, patient tolerability and post biopsy sepsis
30 rates.
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40 Three methods of transperineal MRTB currently exist. First and most common is
41 'cognitive targeting'. This approach requires the urologist to review the mpMRI
42 images and aim the needle toward the corresponding area on ultrasound (US)
43 imaging[11]. Alternatively, the reporting urologist draws a diagrammatic
44 representation of the gland and any suspicious area contained within, which guides
45 the urologist to potential cancer. Second, 'in-bore MRTB' is performed whilst the
46 patient is in the MRI scanner, allowing for real time targeting of suspicious areas
47 with MRI compatible biopsy equipment. Third, 'fusion targeting' uses specifically
48 designed software to allow combination of the mpMRI images with real time US
49 imaging[4]. The latter two methods have implications in terms of equipment
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3 availability and cost, and as of yet the question of superiority of any one over
4 another remains elusive[4].
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7 Currently, prostate cancer diagnostic pathways remain built around TRUSGB.
8 MpMRI is more commonly being used prior to TRUSGB. However, the use of an
9 mpMRI and MRTB pathway remains a rarity despite the potential advantages of such
10 an approach. The reasons for this are multiple and commonly relate to the
11 techniques being in their relative infancy. The lack of standardised mpMRI
12 reporting[12], a learning curve for operators[13], mpMRI availability and cost[14]
13 and concern regarding missed diagnosis from not sampling the whole gland have all
14 been cited as reasons not to accept widespread adoption. Despite this, MRI-guided
15 targeted biopsy pathways have been utilised before, albeit via the transrectal rather
16 than the transperineal route[15-17]. The recent findings of the PRECISION [18] trial
17 has clearly addressed concerns in regard to superiority of an MRI-targeted biopsy
18 approach over systematic TRUS biopsy, demonstrating superiority in clinically
19 significant cancer detection rate and a reduction in the detection of insignificant
20 disease.
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23 Thus, the objective of this study was primarily to determine the suitability and
24 feasibility of a transperineal MRI-targeted biopsy pathway for prostate cancer in
25 'real-world' clinical practice. Outcome measures in this regard included the time to
26 diagnosis and treatment of patients referred with a suspicion of prostate cancer.
27 Quality control outcome measures included clinically significant and total cancer
28 detection rates.
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32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 **Patients and Methods**

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48 This prospective study analyses the clinical and service outcomes of an mpMRI and
49 MRTB led prostate cancer diagnostic pathway (*figure 1*) from 02/2015 to 03/2016.
50 Inclusion criteria were men presenting with a biochemical or clinical suspicion of
51 prostate cancer under the United Kingdom two week wait program and undergoing
52 mpMRI and if necessary subsequent cognitive targeted prostate biopsy. Patients
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3 without negative urine cultures or with estimated glomerular filtration rates of <30
4 micromol/L were excluded. The patient was contacted on referral and an mpMRI
5 was arranged. This was reported before the patient attended clinic in the early
6 afternoon of the same day. If a targetable lesion was identified (Likert ≥ 3), a
7 transperineal-targeted biopsy was offered. Results were available within 48 hours
8 and were discussed at a specialist MDT. Patients returned for counselling within
9 seven days.

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16 MpMRI acquisition was performed according to the European guidelines of Uro-
17 radiology previously described by the University College London (UCL)
18 group[12,19,20]. In summary this includes the use of a 1.5 or 3.0 Tesla MRI scanner
19 acquiring T2-weighted axial and coronal, axial diffusion weighted coefficient and
20 high *b*-value as well as T1 weighted dynamic contrast enhancement (intravenous
21 Gadolinium) images. Each scan was reported by an experienced uro-radiologist as
22 previously described [21,22] and a pictorial diagrammatic map drawn (*figure 2*).
23 Regions of interest (ROIs) were scored using a Likert-like scale of 1-5[22] using the
24 overall impression of the radiologist to characterise the level of suspicion for
25 prostate cancer. ROIs scoring 4 or 5 were thought 'likely' or 'highly likely' to contain
26 a malignant lesion, which was either ≥ 0.2 mL in volume and/or had high-grade
27 components within (Gleason $\geq 3+4$)[23]. ROIs 3 were rated as indeterminate for such
28 disease and this score of 3, or higher, was chosen as the threshold for a positive
29 mpMRI. Our choice of scoring system was based on the outcomes of the 2011
30 European Consensus Meeting[12] which met prior to the Prostate Imaging and Data
31 Reporting System (PIRADS) MP-MRI reporting consensus meeting[19] and has
32 demonstrated equivalency with the PIRADS system[24].

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46 The procedure was performed as a day case under local anaesthesia and
47 antimicrobial prophylaxis in the lithotomy position, by either a consultant urologist
48 or urology clinical fellow as previously described[25]. This biopsy technique has
49 demonstrated a median procedure length of 30 minutes and good patient toleration,
50 with median visual analogue pain scores of 1.0[26].

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55 Data was collected on a case report form compliant with the Standards of Reporting

for MRI-targeted Biopsy Studies (START) of the prostate[11]. Included data were patients demographics, indications for biopsy, PSA value, prostate volume, number of targets per patient, and Likert score per target[11]. Additionally, for each biopsy collected the total number of cores taken, biopsy density, number of positive cores, maximum and overall Gleason scores and the maximum cancer core length (MCCL). Biopsy efficiency was calculated by the number of cores demonstrating clinically significant disease divided by the number of cores taken. For the purpose of this study, clinically significant disease was defined using the University College London (UCL) classification for interpreting transperineal biopsy findings, which sets the significance threshold at Gleason score \geq to 3 + 4 and/or MCCL \geq 4 mm for definition 2 and \geq to 4 + 3 and/or MCCL \geq 6 mm for definition 1[26] (*figure 3*).

Finally, to assess the time to diagnosis and treatment as well as the treatments elected by men were determined by examination of the hospital trust's electronic data system.

Patient and Public Involvement

This study received approval from the local audit committee. An informative consent process was performed for each patient prior to biopsy.

Results

Table 1

| A. Patient Demographics | | |
|--------------------------------|-----|----------------------|
| Men included | | 112 |
| Median Age (years) | | 68 [IQR 62-78] |
| Median PSA (ng/mL) | | 9.4 (IQR 5.6 - 21.0) |
| B. MpMRI Outcomes | | |
| | n | % |
| Men undertaking mpMRI | 111 | 99% |
| Median Prostate Volume (mL) | | 50 (IQR 35 - 78) |
| Positive mpMRI (Men) | 87 | 78% |
| Negative mpMRI (Men) | 24 | 22% |
| Total ROIs | | 162 |

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| 1 ROIs / man | | 39 | 35% | | |
| 2 ROIs / man | | 25 | 23% | | |
| 3 ROIs / man | | 22 | 20% | | |
| 4 ROIs / man | | 1 | 1% | | |
| <i>Likert score per man</i> | | | | | |
| Likert 3 | | 25 | 23% | | |
| Likert 4 | | 26 | 23% | | |
| Likert 5 | | 36 | 32% | | |
| Total ROIs | | 162 | | | |
| Median ROI volume (mL) | | 0.5 (IQR 0.2 - 1.0) | | | |
| <i>Likert score per lesion</i> | | | | | |
| Likert 3 | | 71 | 44% | | |
| Likert 4 | | 49 | 30% | | |
| Likert 5 | | 42 | 26% | | |
| C. Biopsy Outcomes | | | | | |
| | n | | % | | |
| Men undertaking biopsy | | 57 | 51% | | |
| Median cores per patient | | 9 (IQR 5 - 12) | | | |
| Total cores | | 514 | | | |
| Cores positive (UCL 2) | | 241 | 47% | | |
| Biopsy efficiency | | 47% | | | |
| Median cores per lesion | | 4 (IQR 4 - 5) | | | |
| Median biopsy density (cores / ROI mL) | | 10 (IQR 3.5 - 20) | | | |
| Cancer detection by man | | | | | |
| Any Cancer | | 45 | 79% | | |
| UCL 2 | | 43 | 75% | | |
| UCL 1 | | 34 | 60% | | |
| Gleason $\geq 3+4$ | | 43 | 75% | | |
| Gleason $\geq 4+3$ | | 23 | 40% | | |
| Median MCCL (mm) | | 7 (IQR 3 - 10) | | | |
| Cancer detection by lesion | | | | | |
| Likert 3 (lesions biopsied) | | 40 | 13 | 10 | 4 |
| Likert 4 (lesions biopsied) | | 38 | 24 | 19 | 15 |
| Likert 5 (lesions biopsied) | | 35 | 35 | 35 | 28 |
| D. Diagnosis and Treatment Outcomes | | | | | |
| Median time to diagnosis (days) | | 8 (IQR 5 - 12) | | | |
| Median time to treatment (days) | | 20 (IQR 8 - 40) | | | |

| <i>Treatment type (Post Biopsy)</i> | n | % |
|-------------------------------------|----|-----|
| Discharged | 4 | 7% |
| PSA Surveillance | 6 | 11% |
| Active Surveillance | 5 | 9% |
| Focal therapy | 6 | 11% |
| Robotic Prostatectomy | 9 | 16% |
| External Beam Radiotherapy | 10 | 18% |
| Brachytherapy | 2 | 4% |
| Androgen Deprivation Therapy | 9 | 16% |
| Chemotherapy | 4 | 7% |
| Antibiotics | 1 | 2% |
| Repeat biopsy | 1 | 2% |

Patient demographics

In total, 112 consecutive biopsy naive men with a median age of 68 attended the prostate cancer one stop clinic between 02/2015 and 03/2016 (*Table 1A*). All but one man (99%) received an mpMRI scan prior to clinic. The patient in question had an MRI incompatible cardiac pacemaker.

MpMRI Outcomes

The median prostate volume was 50mL. Eighty-seven men (78%) had a positive mpMRI (Likert score ≥ 3) and 24 (22%) had a negative scan (Likert score ≤ 2) and did not go on to biopsy. Twenty-five men (29%) had an mpMRI scan with an overall Likert score of 3, 26 (30%) an overall score of 4 and 36 (41%) an overall Likert score of 5. There were 162 ROIs identified on mpMRI with a median volume of 0.5mL when measured on T2 MRI sequencing. Thirty-nine men (45%) had a single ROI on mpMRI, 25 men (29%) had two, 22 men (25%) had three and a single man (1%) had four. Seventy-one lesions (30%) were Likert 3, 49 (30%) at Likert 4 and 42 (26%) and Likert 5. After mpMRI, nine with negative mpMRIs (38%) were discharged for PSA surveillance in the community, 10 (42%) remained on PSA surveillance in secondary care, four (17%) underwent investigations for lower urinary tract symptoms and one (4%) underwent a full template biopsy under general anaesthetic (*Table 1B*).

Biopsy Outcomes

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3 Fifty-seven men (51%) underwent a local anaesthetic MRTB as described following
4 mpMRI (*Table 1C*). Fifteen (17%) men chose not to undergo biopsy under local
5 anaesthetic and were listed for a biopsy under sedation. Thirteen men (15%) did not
6 have a biopsy due to clinical reasons. Any cancer was detected in 45 (79%) of men.
7
8 Of these, 43 (96%) satisfied the UCL 2 criteria for clinical significance and 34 (76%)
9 satisfying the UCL 1 criteria. The median MCCL of positive biopsies was 7mm. The
10 calculated biopsy efficiency for UCL 2 disease was 47%. The median number of cores
11 taken per ROI was 4, with a median calculated biopsy density of 10 cores/mL of ROI.
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13 Of the 20 men who had more than one lesion on mpMRI and underwent biopsy, two
14 had a secondary lesion, which harboured either higher grade or volume disease. In
15 only one of these men was the secondary lesion a lower Likert score. Both such men
16 went on to radical prostatectomy.
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27 ***Diagnosis and Treatment Outcomes***

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29 The median time to a man being told his diagnosis was eight days, and the median
30 time by which treatment had been started was 20 days, although in five cases this
31 time period was not clear (*Table 1D*). The treatment outcomes are shown in table
32 1D. Of note, 20 (18%) men were discharged after biopsy with 19 (17%) men starting
33 PSA surveillance. Forty-four (40%) went on to undergo treatment and nine (8%) men
34 underwent a further biopsy either due a perceived false negative or diffuse disease
35 requiring a biopsy under sedation or general anaesthetic. Eleven (10%) patients
36 underwent further assessment or treatment for benign disease.
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44 **Discussion**

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46 An optimal PCa diagnostic strategy should encapsulate maximal significant cancer
47 detection whilst avoiding insignificant disease or repeat biopsy. Furthermore, it
48 should convey enough information for urologists and patients to accurately devise a
49 treatment plan according to the risk of progression. However, as things stand, the
50 diagnostic pathway is still commonly led by TRUSGB, despite its accepted inaccuracy,
51 especially for disease located in the anterior or apical regions of the prostate[27]. In
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3 particular the negative predictive value (NPV) of the originally described six core
4 TRUSGB is poor, with false negative rates of around 35%[28,29]. This inherent
5 disadvantage is somewhat mitigated by extending the biopsy to a 12 or even 24 core
6 technique, however increasing the number of cores past 12 leads to increased
7 numbers of insignificant cancers being detected[30,31] which is present in 40% of
8 men over the age of 50[32]. These cancers are rarely affect life expectancy or its
9 quality in any meaningful way and revealing them simply adds unnecessary burdens
10 to patients. Furthermore, increasing the number of cores may increase incidence of
11 post TRUSGB sepsis[33] and with the incidence already on the rise alongside
12 increasing prevalence of colonisation with resistant organisms such strategies pose
13 an increasing potential for harm[34] for which our clinical options are worryingly
14 limited. As a result, transperineal zonal or mapping biopsies (TPM) have become
15 more popular. In particular, one recent series reported a 0% readmission rate for
16 infective complications after targeted transperineal biopsy[35], in comparison to
17 rates of sepsis of up to 6.3% after TRUSGB[36]. However, there are significant
18 concerns regarding its cost, need for general anaesthetic, increased complications
19 and patient burden. Such concerns have justly prevented its wider use and certainly
20 a TPM led diagnostic pathway has not been seriously suggested.
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35 However, the development and refinement of mpMRI demands that its use in
36 leading an approach to diagnosis must be contemplated. MpMRI has demonstrated
37 high levels of accuracy for the detection of clinically significant cancer when
38 compared to both TPM[37] and whole-mount prostatectomy specimens[9]. Indeed,
39 a systematic review by Fütterer et al found that mpMRI detected clinically significant
40 disease in up to 84% of men with a NPV of up to 98% where either TPM or
41 prostatectomy was used as the reference standard[20]. More recently the results of
42 the PROMIS trial demonstrate the sensitivity and negative predictive value of mpMRI
43 in detecting clinically significant disease as 93% and 89% respectively[38].
44 Furthermore, the PROMIS trial demonstrated that 27% of men could avoid a
45 biopsy[38]. Despite these findings, both the European Association of Urology
46 (EAU)[39] and National Institute of Clinical Excellence (NICE)[40] still do not
47 recommend mpMRI prior to an initial set of biopsies. In this study, leading with
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3 mpMRI allowed 24 (21.6%) men to avoid a biopsy entirely. However, the majority
4 would remain on PSA surveillance due to the small – but understood - risk of a false
5 negative mpMRI. There is perhaps a concern that in less experienced centres
6 overcall images as PIRADS 3 is an issue that will expose men to unnecessary biopsies
7 and thus reducing the benefit of an image-guided pathway. However, as the PIRADS
8 v2[41] scoring system is increasingly adopted, with its ability to define a PIRADS 4
9 lesion over a 3 by utilisation of the second parameter (DCE and DWI for peripheral
10 zone and transition zone lesions respectively), alongside its more easily understood
11 and applicable design, should reduce such an effect going forward.
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19 Clearly, there is enough evidence now to introduce an image-guided biopsy to the
20 PCa diagnostic pathway, bringing it in line with the current practice in other solid
21 organ malignancies. However, currently there is concern that targeted biopsies
22 alone risk missing areas of significant disease that appear normal on mpMRI. This
23 may be viewed as a limitation. However, our current approach to this cohort of men
24 was introduced after our paired analyses of mpMRI versus template biopsies
25 demonstrated that mpMRI cognitive biopsies had equivalent detection rates to zonal
26 mapping biopsies[37]. Furthermore, numerous centres have now reported
27 improved cancer detection rates of MRTB strategies when compared to systematic
28 approaches [42,43], as well as improved biopsy efficiency and reduced false negative
29 rates for significant cancer[8]. To underline this, another series of men who
30 underwent both fusion MRTB and systematic TPM showed a difference of clinically
31 significant cancer detection rates of 4% (28% for MRTB and 24% for systematic
32 biopsy), although combined biopsies outperformed each approach in isolation[44].
33 Naturally, such results have been reported by specialist centres and as such, concern
34 remains in regard to the level of operator dependency with targeted biopsy
35 techniques. However, authors have found no difference between cancer detection
36 rates with targeted techniques regardless of the experience of the operator, albeit
37 with TRUSGB[45].
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52 As with mpMRI, MRTB is not a perfect test, both can miss significant disease.
53 However, this is an improvement on our current standard diagnostic test which is
54 demonstrably poor[27-30]. As recent studies have shown, in comparison to TRUSGB,
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3 MRTB is more likely to detect disease once a suspicious area has been
4 identified[6,17]. Furthermore, the recently published PRECISION randomised
5 controlled trial clearly demonstrated the superior clinically significant cancer
6 detection rate of MRTB and a reduced insignificant cancer detection rate when
7 compared to systematic TRUS biopsy[18].
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12 A potential limitation of the MRTB technique in this study is the use of ‘cognitive
13 fusion’ rather than US/mpMRI fusion or ‘in-bore’ targeting. However, no superiority
14 of one technique over another has been clearly demonstrated, whilst ‘cognitive
15 fusion’ is clearly a less costly option[46]. Another potential limitation of the targeted
16 biopsy strategy is the ‘satisfaction of search’ bias. Essentially, this means that after
17 the primary lesion is scored, less attention to detail is given to subsequent lesions,
18 which may therefore be undercalled or undersampled. However, in this series this
19 occurred twice, only once where the secondary lesion was attributed a lower score
20 than the primary, and in no cases did this change the proposed management.
21 Further, in the vast majority of centres where radical treatments – rather than focal
22 – remain the standard of care, there would likely be no change in the approach to
23 curative therapy, save for planning for prostatectomy in the case of nerve-sparing
24 procedures.
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35 The cost of mpMRI has been cited as a reason for persisting with TRUSGB led
36 diagnostic pathways [47], using it instead for a second investigation in the case of a
37 negative biopsy in a patient in whom suspicion of cancer remains. Whilst mpMRI is
38 indeed useful in this scenario, recent cost effectiveness analyses have shown the
39 long term cost benefits of mpMRI led pathways when various outcomes are
40 accounted for[14,48,49] due to a reduction in overdiagnosis and higher detection
41 rates of clinically significant disease at primary biopsy. In particular, the cost-analysis
42 of the PROMIS trial cohort demonstrated that MpMRI first followed by two MRTBs
43 detects more cancer per pound spent than a TRUS first biopsy strategy[49].
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51 A major advantage of our pathway is the low time to diagnosis and treatment. At a
52 median of 8 and 20 days respectively the time a patient waits is significantly below
53 the 31 and 62-day targets set by the United Kingdom National Health Service. The
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3 meeting of these targets is a persistent challenge nationally[50]. Moreover,
4 performing an mpMRI prior to primary biopsy negates the risk of an initial false
5 negative biopsy significantly delaying a subsequent mpMRI due to post biopsy
6 haemorrhage within the prostate. This makes it difficult to localise cancer or
7 accurately determine its size or border[51]. In such circumstances, the delay in
8 diagnosis can be up to eight weeks.
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16 **Conclusions**

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18 This novel pathway offers an alternative to standard prostate cancer diagnostic
19 services. Attendance and cancer detection rates are high. The use of an mpMRI led
20 pathway allows for a significant proportion of men to avoid a biopsy and for those
21 who do, the time to diagnosis and definitive treatment is kept particularly low. The
22 integration of both mpMRI and MRTB in the prostate cancer diagnostic pathway has
23 shown cost-effectiveness in the long-term. This is especially true where rapid
24 diagnostics are mandated or desirable. Furthermore, today, where septic
25 complications are of grave concern, the transperineal route is particularly
26 advantageous. This pilot study demonstrates, that similar services can be provided in
27 appropriate centres and may be valuable to patients with a potential diagnosis of
28 prostate cancer
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41 **Contributorship statement**

42 Edward J Bass drafted the manuscript and approved the final version.

43
44 Alex Freeman contributed to the conception of the work presented, revised the
45 manuscript critically and approved the final version.
46
47

48 Charles Jameson contributed to the conception of the work presented and revised
49 the manuscript critically and approved the final version.
50
51

52 Shonit Punwani contributed to the conception of the work presented and revised
53 the manuscript critically and approved the final version.
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3 Caroline Moore contributed to the conception of the work presented and revised
4 the manuscript critically and approved the final version.
5

6
7 Manit Arya revised the manuscript critically and approved the final version.
8

9
10 Mark Emberton contributed to the conception of the work presented and revised
11 the manuscript critically and approved the final version.
12

13
14 Hashim U. Ahmed contributed to the conception of the work presented and revised
15 the manuscript critically and approved the final version.
16

17
18 All authors are accountable for all aspects of the work in terms of accuracy and
19 integrity.
20
21

22 23 24 **Competing Interests** 25

26
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31 expressed in this publication are those of the author(s) and not necessarily those of
32 the NHS, the National Institute for Health Research or the Department of Health.
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34

35
36 Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK,
37 Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed
38 is a paid medical consultant for Sophiris Biocorp for trials work.
39
40

41
42 Mark Emberton's research is supported by core funding from the United Kingdom's
43 National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research
44 Centre. He was awarded NIHR Senior Investigator in 2015.
45
46

47
48 Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer
49 Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a
50 medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging
51 and Profound Medical.
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3 Moore receives funding from the National Institute for Health Research, The
4 European Association of Urology Research Foundation, Prostate Cancer UK,
5 Movember and the Cancer Vaccine Institute, for clinical prostate cancer research.
6 She has received advisory board fees for Genomic Health.
7
8
9

10 Ahmed, Emberton, and Moore are all proctors for HIFU and are paid for training
11 other surgeons in this procedure.
12
13

14 Emberton and Freeman have loan notes/stock options in Nuada Medical Ltd (UK).
15
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19

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23 or not-for-profit sectors.
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29 **Data sharing statement**

30
31 Supplementary data is available in the reference tables in the appendix.
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Figure and Table legends

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36
37 **Figure 1:** The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

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40 **Figure 2:** A pictorial prostate mpMRI diagrammatic report, as drawn by the
41 urologist.

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44 **Figure 3:** The University College London ‘traffic light like’ system to define significant
45 prostate cancer.

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48 **Table 1A:** Baseline demographics for the cohort.

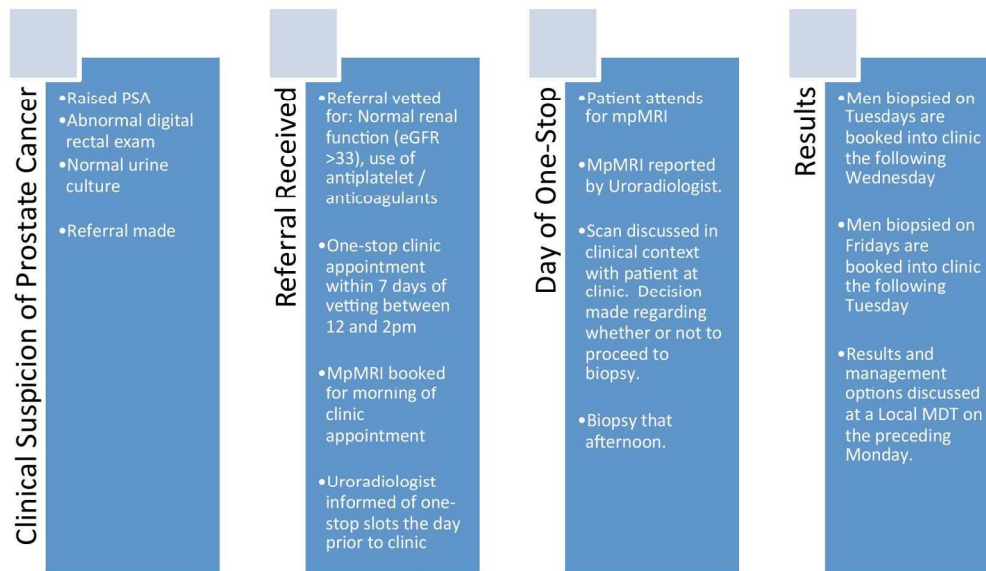
49
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51 **Table 1B:** MpMRI outcomes.

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54 **Table 1C:** Biopsy outcomes.

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57 **Table 1D:** Diagnosis and treatment outcomes.

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For peer review only

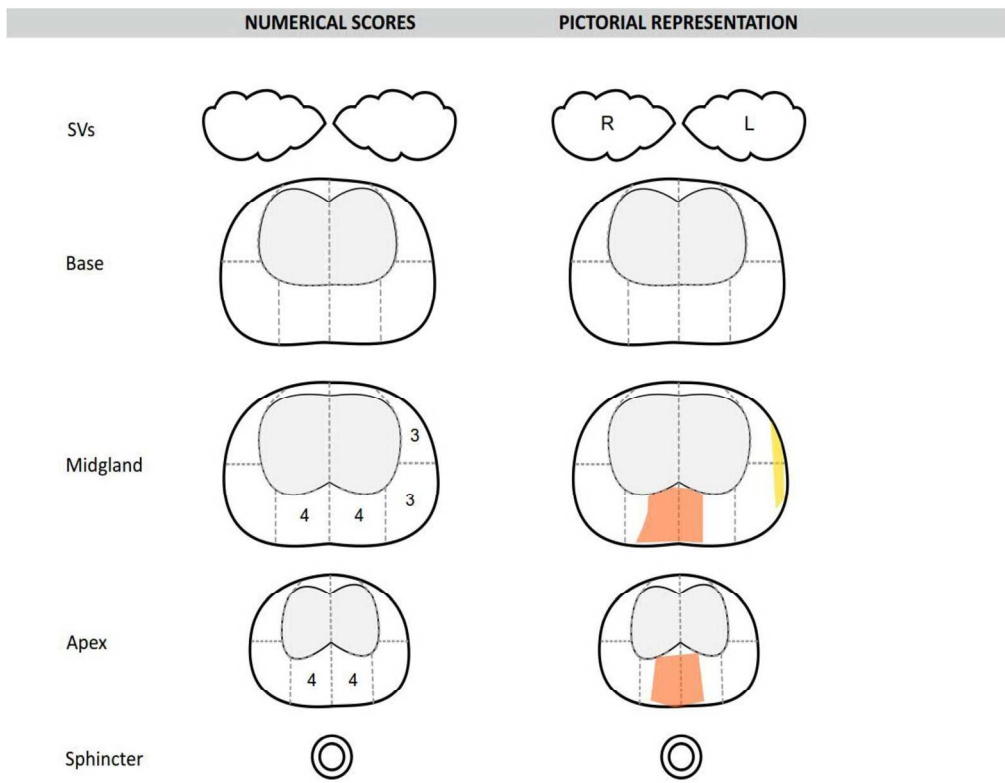


The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

168x97mm (300 x 300 DPI)

Review only

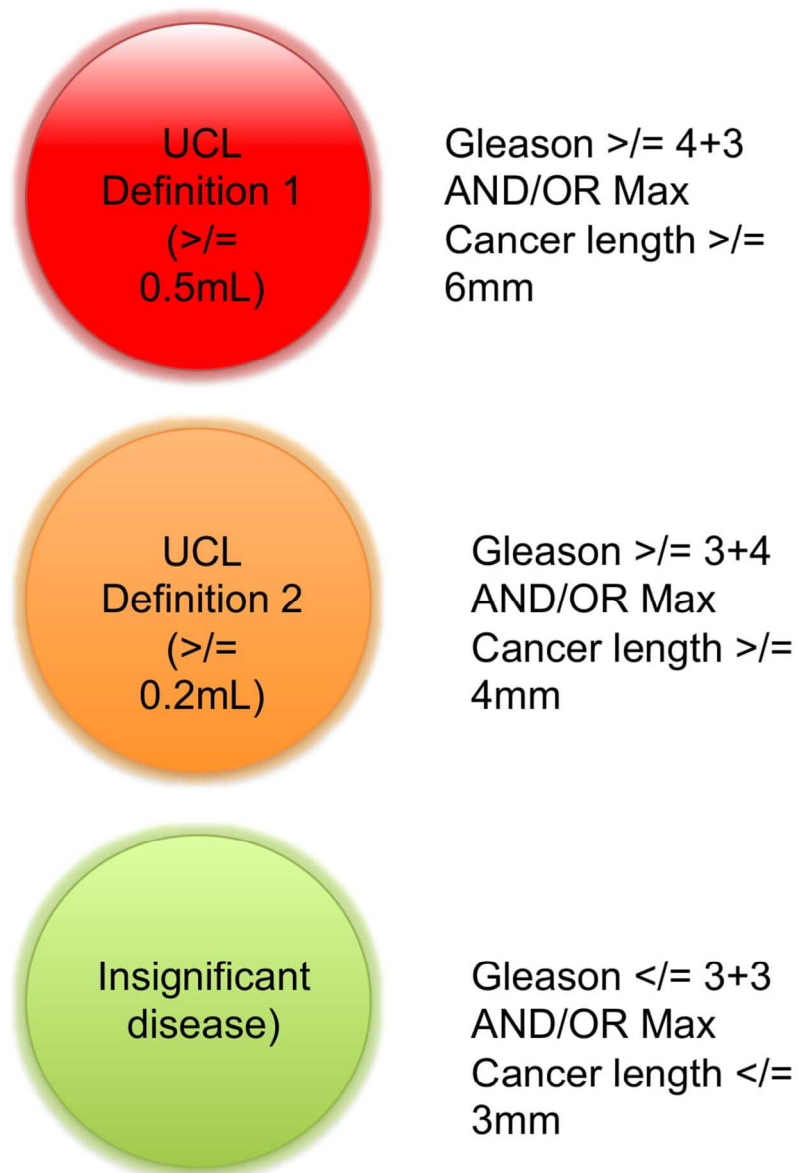
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A pictorial prostate mpMRI diagrammatic report, as drawn by the urologist.

261x230mm (300 x 300 DPI)

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The University College London 'traffic light like' system to define significant prostate cancer.

89x125mm (300 x 300 DPI)

BMJ Open

The Prostate Cancer Diagnostic Pathway: Is a One-Stop Cognitive Magnetic Resonance Imaging Targeted Biopsy Service A Realistic Goal in Everyday Practice? A pilot cohort in a Tertiary Referral Centre in the United Kingdom.

| | |
|---------------------------------|---|
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| Keywords: | Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Prostate disease < UROLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Adult urology < UROLOGY |
| | |

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Manuscripts

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3 **The Prostate Cancer Diagnostic Pathway: Is a One-Stop Cognitive**
4 **Magnetic Resonance Imaging Targeted Biopsy Service A Realistic Goal**
5 **in Everyday Practice? A pilot cohort in a Tertiary Referral Centre in the**
6 **United Kingdom.**
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Abstract**Objectives**

To evaluate the feasibility of a novel multiparametric magnetic resonance imaging (mpMRI) and cognitive fusion transperineal targeted biopsy led prostate cancer (PCa) diagnostic service with regard to cancer detection and reducing time to diagnosis and treatment.

Design

Consecutive men being investigated for possible prostate cancer under the United Kingdom two week wait guidelines.

Setting

Tertiary referral centre for prostate cancer in the United Kingdom.

Participants

Men referred with a raised prostate specific antigen (PSA) or abnormal digital rectal examination (DRE) between 02/2015 and 03/2016 under the United Kingdom two week rule guideline.

Interventions

An mpMRI was performed prior to patients attending clinic, on the same day. If required, MRTB was offered. Results were available within 48 hours and discussed at a specialist multidisciplinary team (MDT) meeting. Patients returned for counselling within 7 days

Primary and Secondary Outcome Measures

Outcome measures in this regard included the time to diagnosis and treatment of patients referred with a suspicion of prostate cancer. Quality control outcome measures included clinically significant and total cancer detection rates.

Results

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3 112 men were referred to the service. 111 (99.1%) underwent mpMRI. Median PSA
4 was 9.4ng/mL [IQR 5.6-21.0]. 87 patients had a target on mpMRI with 25 scoring
5 Likert 3/5 for likelihood of disease, 26 4/5 and 36 5/5.
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9 57 (51%) patients received a local anaesthetic, MRTB. Cancer was detected in 45
10 (79%). 43 (96%) had University College London (UCL) definition 2 disease or greater.
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12 The times to diagnosis and treatment were a median of 8 and 20 days respectively.
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14 **Conclusions**

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17 This approach greatly reduces the time to diagnosis and treatment. Detection rates
18 of significant cancer are high. Similar services may be valuable to patients with a
19 potential diagnosis of PCa.
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28 **Strengths and limitations of this study**

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31 • First prospective study demonstrating the clinical feasibility of a 'one stop',
32 rapid diagnostic prostate cancer pathway, using both multiparametric
33 magnetic resonance imaging and transperineal targeted biopsy.
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35 • Inclusion criteria reflecting 'real world' practice in the United Kingdom.
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37 • This study incorporates a standardised multiparametric MRI acquisition and a
38 validated system for defining clinically significant prostate cancer.
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40 • Cognitive targeted biopsy performed only, rather than mpMRI / ultrasound
41 fusion.
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43 • Transperineal, rather than transrectal approach offers minimal septic
44 complications post biopsy.
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Introduction

Accurate risk stratification for men presenting with localised prostate cancer is vitally important. In its absence, patient centred management cannot be offered. Men with low-risk disease can be safely managed with active surveillance, whereas men with a good life expectancy and intermediate to high-risk disease are likely to benefit from interventional treatment[1-2]. Currently, standard practice uses prostate-specific antigen (PSA) value, digital rectal examination (DRE) and transrectal ultrasound guided biopsy (TRUSGB). However, TRUSGB is inherently random. The tumour cannot be visualised with certainty, and thus leads to overdiagnosis of insignificant disease in up to 50% of men[3], and missing significant disease in 18% of men, especially if cancer is located in anterior or apical regions of the prostate[4]. This creates difficulty for urologists and adds anxiety to patients[5] who have to undergo a repetitive cascade of diagnostic tests, which inevitably has cost implications for healthcare providers.

Transperineal mapping or zonal biopsies (TPM) of the prostate offer a diagnostic alternative to TRUS biopsy with demonstrable diagnostic success. However, the burden on patients is high. Firstly, the extensive biopsies demand general anaesthesia. Secondly, the rates of urinary retention following the procedure are high, making postoperative catheterization commonplace. Thirdly, the large number of cores taken requires many hours of labour to assess. Thus, a patient may have to wait significantly longer for a result, adding to their anxiety. This may also delay necessary treatment. Whether this results in adverse outcomes is not known. However, all of these established difficulties do confer added costs. Indeed, if every patient undergoing TRUSGB instead underwent a TPM, the cost of such a move would likely be exceedingly high. Therefore, the challenge presents itself as biopsy offering superior clinically significant detection rates to the existing standard, whilst not conferring an added cost.

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has proved a useful tool in the diagnosis and risk stratification of prostate cancer. MpMRI has demonstrated its ability to detect significant cancers, whilst not detecting those

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3 which are insignificant[4]. Suspicious areas on mpMRI can be targeted with
4 subsequent transperineal biopsy (MRTB). MRTB has demonstrated greater sampling
5 efficiency and accuracy when compared with standard TRUS-guided protocols[6-8],
6 and has demonstrated accuracy when compared to the reference standard of radical
7 prostatectomy (RP)[9]. This allows for a more accurate assessment of Gleason
8 grade, and therefore an improved risk stratification and treatment plan at
9 diagnosis[10]. Furthermore, the efficiency advantage, i.e. taking fewer cores at
10 biopsy, confers significant benefits in cost, patient tolerability and post biopsy sepsis
11 rates.
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19 Three methods of transperineal MRTB currently exist. First and most common is
20 'cognitive targeting'. This approach requires the urologist to review the mpMRI
21 images and aim the needle toward the corresponding area on ultrasound (US)
22 imaging[11]. Alternatively, the reporting urologist draws a diagrammatic
23 representation of the gland and any suspicious area contained within, which guides
24 the urologist to potential cancer. Second, 'in-bore MRTB' is performed whilst the
25 patient is in the MRI scanner, allowing for real time targeting of suspicious areas
26 with MRI compatible biopsy equipment. Third, 'fusion targeting' uses specifically
27 designed software to allow combination of the mpMRI images with real time US
28 imaging[4]. The latter two methods have implications in terms of equipment
29 availability and cost, and as of yet the question of superiority of any one over
30 another remains elusive[4].
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41 Currently, prostate cancer diagnostic pathways remain built around TRUSGB.
42 MpMRI is more commonly being used prior to TRUSGB. However, the use of an
43 mpMRI and MRTB pathway remains a rarity despite the potential advantages of such
44 an approach and the novel approach of both diagnostic interventions in one day
45 exceptionally so. The reasons for this are multiple and commonly relate to the
46 techniques being in their relative infancy. The lack of standardised mpMRI
47 reporting[12], a learning curve for operators[13], mpMRI availability and cost[14]
48 and concern regarding missed diagnosis from not sampling the whole gland have all
49 been cited as reasons not to accept widespread adoption. Despite this, MRI-guided
50 targeted biopsy pathways have been utilised before, albeit via the transrectal rather
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3 than the transperineal route[15-17]. The recent findings of the PRECISION [18] trial
4 has clearly addressed concerns in regard to superiority of an MRI-targeted biopsy
5 approach over systematic TRUS biopsy, demonstrating superiority in clinically
6 significant cancer detection rate and a reduction in the detection of insignificant
7 disease.
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12 Thus, the objective of this pilot study was primarily to determine the suitability and
13 feasibility of a 'One-Stop', transperineal MRI-targeted biopsy pathway for prostate
14 cancer in 'real-world' clinical practice. Outcome measures in this regard included
15 the time to diagnosis and treatment of patients referred with a suspicion of prostate
16 cancer. Quality control outcome measures included clinically significant and total
17 cancer detection rates.
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26 **Patients and Methods**

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28 This prospective study analyses the clinical and service outcomes of an mpMRI and
29 MRTB led prostate cancer diagnostic pathway (*figure 1*) from 02/2015 to 03/2016.
30 Inclusion criteria were men presenting with a biochemical or clinical suspicion of
31 prostate cancer under the United Kingdom two week wait program and undergoing
32 mpMRI and if necessary subsequent cognitive targeted prostate biopsy. Patients
33 without negative urine cultures or with estimated glomerular filtration rates of <30
34 micromol/L were excluded. The patient was contacted on referral and an mpMRI
35 was arranged. This was reported before the patient attended clinic in the early
36 afternoon of the same day. If a targetable lesion was identified (Likert ≥ 4), a
37 transperineal-targeted biopsy was advised. If a target was rated as equivocal (Likert
38 =3), the discussion was more nuanced including risk factors for a subsequent biopsy
39 being positive such as a positive family history of prostate cancer, high PSA density
40 or concordant positive DRE findings. Further, in this group of men, those with diffuse
41 equivocal changes requiring a greater number of cores to be taken for a positive
42 result, the option of full template biopsies under general anaesthetic was discussed.
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44 Results were available within 48 hours and were discussed at a specialist MDT.
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46 Patients returned for counselling within seven days.
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3 MpMRI acquisition was performed according to the European guidelines of Uro-
4 radiology previously described by the University College London (UCL)
5 group[12,19,20]. In summary this includes the use of a 1.5 or 3.0 Tesla MRI scanner
6 acquiring T2-weighted axial and coronal, axial diffusion weighted coefficient and
7 high *b*-value as well as T1 weighted dynamic contrast enhancement (intravenous
8 Gadolinium) images. Each scan was reported by an experienced uro-radiologist as
9 previously described [21,22] and a pictorial diagrammatic map drawn (*figure 2*).
10 Regions of interest (ROIs) were scored using a Likert-like scale of 1-5[22] using the
11 overall impression of the radiologist to characterise the level of suspicion for
12 prostate cancer. ROIs scoring 4 or 5 were thought 'likely' or 'highly likely' to contain
13 a malignant lesion, which was either ≥ 0.2 mL in volume and/or had high-grade
14 components within (Gleason $\geq 3+4$)[23]. ROIs 3 were rated as indeterminate for such
15 disease and this score of 3, or higher, was chosen as the threshold for a positive
16 mpMRI. Our choice of scoring system was based on the outcomes of the 2011
17 European Consensus Meeting[12] which met prior to the Prostate Imaging and Data
18 Reporting System (PIRADS) MP-MRI reporting consensus meeting[19] and has
19 demonstrated equivalency with the PIRADS system[24].

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33 The procedure was performed as a day case under local anaesthesia and
34 antimicrobial prophylaxis in the lithotomy position, by either a consultant urologist
35 or urology clinical fellow as previously described[25]. This biopsy technique has
36 demonstrated a median procedure length of 30 minutes and good patient toleration,
37 with median visual analogue pain scores of 1.0[26].

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42 Data was collected on a case report form compliant with the Standards of Reporting
43 for MRI-targeted Biopsy Studies (START) of the prostate[11]. Included data were
44 patients demographics, indications for biopsy, PSA value, prostate volume, number
45 of targets per patient, and Likert score per target[11]. Additionally, for each biopsy
46 collected the total number of cores taken, biopsy density, number of positive cores,
47 maximum and overall Gleason scores and the maximum cancer core length (MCCL).
48 Biopsy efficiency was calculated by the number of cores demonstrating clinically
49 significant disease divided by the number of cores taken. For the purpose of this
50 study, clinically significant disease was defined using the University College London
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(UCL) classification for interpreting transperineal biopsy findings, which sets the significance threshold at Gleason score \geq to 3 + 4 and/or MCCL \geq 4 mm for definition 2 and \geq to 4 + 3 and/or MCCL \geq 6 mm for definition 1[26] (figure 3).

Finally, to assess the time to diagnosis and treatment as well as the treatments elected by men were determined by examination of the hospital trust's electronic data system.

Patient and Public Involvement

Participants were not involved in the design of the study. However, conclusions gleaned from the study are to be disseminated amongst patients newly referred to the service.

Results

Table 1

| A. Patient Demographics | | |
|--------------------------------|------------------|----------------------|
| Men included | | 112 |
| Median Age (years) | | 68 [IQR 62-78] |
| Median PSA (ng/mL) | | 9.4 (IQR 5.6 - 21.0) |
| B. MpMRI Outcomes | | |
| | n | % |
| Men undertaking mpMRI | 111 | 99% |
| Median Prostate Volume (mL) | 50 (IQR 35 - 78) | |
| Positive mpMRI (Men) | 87 | 78% |
| Negative mpMRI (Men) | 24 | 22% |
| Total ROIs | 162 | |
| 1 ROIs / man | 39 | 35% |
| 2 ROIs / man | 25 | 23% |
| 3 ROIs / man | 22 | 20% |
| 4 ROIs / man | 1 | 1% |
| Likert score per man | | |
| Likert 3 | 25 | 23% |
| Likert 4 | 26 | 23% |
| Likert 5 | 36 | 32% |
| Total ROIs | 162 | |

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|--|---------------------|------------|-------|-------|
| Median ROI volume (mL) | 0.5 (IQR 0.2 - 1.0) | | | |
| <i>Likert score per lesion</i> | | | | |
| Likert 3 | 71 | 44% | | |
| Likert 4 | 49 | 30% | | |
| Likert 5 | 42 | 26% | | |
| C. Biopsy Outcomes | | | | |
| | n | % | | |
| Men undertaking biopsy | 57 | 51% | | |
| Median cores per patient | 9 (IQR 5 - 12) | | | |
| Total cores | 514 | | | |
| Cores positive (UCL 2) | 241 | 47% | | |
| Biopsy efficiency | 47% | | | |
| Median cores per lesion | 4 (IQR 4 - 5) | | | |
| Median biopsy density (cores / ROI mL) | 10 (IQR 3.5 - 20) | | | |
| Cancer detection by man | | | | |
| Any Cancer | 45 | 79% | | |
| UCL 2 | 43 | 75% | | |
| UCL 1 | 34 | 60% | | |
| Gleason $\geq 3+4$ | 43 | 75% | | |
| Gleason $\geq 4+3$ | 23 | 40% | | |
| Median MCCL (mm) | 7 (IQR 3 - 10) | | | |
| Cancer detection by lesion | | | | |
| | | Any cancer | UCL 2 | UCL 1 |
| Likert 3 (lesions biopsied) | 40 | 13 | 10 | 4 |
| Likert 4 (lesions biopsied) | 38 | 24 | 19 | 15 |
| Likert 5 (lesions biopsied) | 35 | 35 | 35 | 28 |
| D. Diagnosis and Treatment Outcomes | | | | |
| Median time to diagnosis (days) | 8 (IQR 5 - 12) | | | |
| Median time to treatment (days) | 20 (IQR 8 - 40) | | | |
| <i>Treatment type (Post Biopsy)</i> | | | | |
| | n | % | | |
| Discharged | 4 | 7% | | |
| PSA Surveillance | 6 | 11% | | |
| Active Surveillance | 5 | 9% | | |
| Focal therapy | 6 | 11% | | |
| Robotic Prostatectomy | 9 | 16% | | |
| External Beam Radiotherapy | 10 | 18% | | |
| Brachytherapy | 2 | 4% | | |
| Androgen Deprivation Therapy | 9 | 16% | | |
| Chemotherapy | 4 | 7% | | |
| Antibiotics | 1 | 2% | | |

Repeat biopsy | 1 2%

Patient demographics

In total, 112 consecutive biopsy naive men with a median age of 68 attended the prostate cancer one stop clinic between 02/2015 and 03/2016 (*Table 1A*). All but one man (99%) received an mpMRI scan prior to clinic. The patient in question had an MRI incompatible cardiac pacemaker.

MpMRI Outcomes

The median prostate volume was 50mL. Eighty-seven men (78%) had a positive mpMRI (Likert score ≥ 3) and 24 (22%) had a negative scan (Likert score ≤ 2) and did not go on to biopsy. Twenty-five men (29%) had an mpMRI scan with an overall Likert score of 3, 26 (30%) an overall score of 4 and 36 (41%) an overall Likert score of 5. There were 162 ROIs identified on mpMRI with a median volume of 0.5mL when measured on T2 MRI sequencing. Thirty-nine men (45%) had a single ROI on mpMRI, 25 men (29%) had two, 22 men (25%) had three and a single man (1%) had four. Seventy-one lesions (30%) were Likert 3, 49 (30%) at Likert 4 and 42 (26%) and Likert 5. After mpMRI, nine with negative mpMRIs (38%) were discharged for PSA surveillance in the community, 10 (42%) remained on PSA surveillance in secondary care, four (17%) underwent investigations for lower urinary tract symptoms and one (4%) underwent a full template biopsy under general anaesthetic (*Table 1B*).

Biopsy Outcomes

Fifty-seven men (51%) underwent a local anaesthetic MRTB as described following mpMRI (*Table 1C*). Fifteen (17%) men chose not to undergo biopsy under local anaesthetic and were listed for a biopsy under sedation. Thirteen men (15%) did not have a biopsy due to clinical reasons. Any cancer was detected in 45 (79%) of men. Of these, 43 (96%) satisfied the UCL 2 criteria for clinical significance and 34 (76%) satisfying the UCL 1 criteria. The median MCCL of positive biopsies was 7mm. The calculated biopsy efficiency for UCL 2 disease was 47%. The median number of cores

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3 taken per ROI was 4, with a median calculated biopsy density of 10 cores/mL of ROI.
4 Of the 20 men who had more than one lesion on mpMRI and underwent biopsy, two
5 had a secondary lesion, which harboured either higher grade or volume disease. In
6 only one of these men was the secondary lesion a lower Likert score. Both such men
7 went on to radical prostatectomy.
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11 12 13 14 **Diagnosis and Treatment Outcomes**

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17 The median time to a man being told his diagnosis was eight days, and the median
18 time by which treatment had been started was 20 days, although in five cases this
19 time period was not clear (*Table 1D*). The treatment outcomes are shown in table
20 1D. Of note, 20 (18%) men were discharged after biopsy with 19 (17%) men starting
21 PSA surveillance. Forty-four (40%) went on to undergo treatment and nine (8%) men
22 underwent a further biopsy either due a perceived false negative or diffuse disease
23 requiring a biopsy under sedation or general anaesthetic. Eleven (10%) patients
24 underwent further assessment or treatment for benign disease.
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31 32 **Discussion**

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34 An optimal PCa diagnostic strategy should encapsulate maximal significant cancer
35 detection whilst avoiding insignificant disease or repeat biopsy. Furthermore, it
36 should convey enough information for urologists and patients to accurately devise a
37 treatment plan according to the risk of progression. However, as things stand, the
38 diagnostic pathway is still commonly led by TRUSGB, despite its accepted inaccuracy,
39 especially for disease located in the anterior or apical regions of the prostate[27]. In
40 particular the negative predictive value (NPV) of the originally described six core
41 TRUSGB is poor, with false negative rates of around 35%[28,29]. This inherent
42 disadvantage is somewhat mitigated by extending the biopsy to a 12 or even 24 core
43 technique, however increasing the number of cores past 12 leads to increased
44 numbers of insignificant cancers being detected[30,31] which is present in 40% of
45 men over the age of 50[32]. These cancers are rarely affect life expectancy or its
46 quality in any meaningful way and revealing them simply adds unnecessary burdens
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3 to patients. Furthermore, increasing the number of cores may increase incidence of
4 post TRUSGB sepsis[33] and with the incidence already on the rise alongside
5 increasing prevalence of colonisation with resistant organisms such strategies pose
6 an increasing potential for harm[34] for which our clinical options are worryingly
7 limited. As a result, transperineal zonal or mapping biopsies (TPM) have become
8 more popular. In particular, one recent series reported a 0% readmission rate for
9 infective complications after targeted transperineal biopsy[35], in comparison to
10 rates of sepsis of up to 6.3% after TRUSGB[36]. However, there are significant
11 concerns regarding its cost, need for general anaesthetic, increased complications
12 and patient burden. Such concerns have justly prevented its wider use and certainly
13 a TPM led diagnostic pathway has not been seriously suggested.
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22 However, the development and refinement of mpMRI demands that its use in
23 leading an approach to diagnosis must be contemplated. MpMRI has demonstrated
24 high levels of accuracy for the detection of clinically significant cancer when
25 compared to both TPM[37] and whole-mount prostatectomy specimens[9]. Indeed,
26 a systematic review by Fütterer et al found that mpMRI detected clinically significant
27 disease in up to 84% of men with a NPV of up to 98% where either TPM or
28 prostatectomy was used as the reference standard[20]. More recently the results of
29 the PROMIS trial demonstrate the sensitivity and negative predictive value of mpMRI
30 in detecting clinically significant disease as 93% and 89% respectively[38].
31 Furthermore, the PROMIS trial demonstrated that 27% of men could avoid a
32 biopsy[38]. Despite these findings, both the European Association of Urology
33 (EAU)[39] and National Institute of Clinical Excellence (NICE)[40] still do not
34 recommend mpMRI prior to an initial set of biopsies. In this study, leading with
35 mpMRI allowed 24 (21.6%) men to avoid a biopsy entirely. However, the majority
36 would remain on PSA surveillance due to the small – but understood - risk of a false
37 negative mpMRI. There is perhaps a concern that in less experienced centres
38 overcall images as PIRADS 3 is an issue that will expose men to unnecessary biopsies
39 and thus reducing the benefit of an image-guided pathway. However, as the PIRADS
40 v2[41] scoring system is increasingly adopted, with its ability to define a PIRADS 4
41 lesion over a 3 by utilisation of the second parameter (DCE and DWI for peripheral
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3 zone and transition zone lesions respectively), alongside its more easily understood
4 and applicable design, should reduce such an effect going forward.
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8 Clearly, there is enough evidence now to introduce an image-guided biopsy to the
9 PCa diagnostic pathway, bringing it in line with the current practice in other solid
10 organ malignancies. However, currently there is concern that targeted biopsies
11 alone risk missing areas of significant disease that appear normal on mpMRI. This
12 may be viewed as a limitation. However, our current approach to this cohort of men
13 was introduced after our paired analyses of mpMRI versus template biopsies
14 demonstrated that mpMRI cognitive biopsies had equivalent detection rates to zonal
15 mapping biopsies[37]. Furthermore, numerous centres have now reported
16 improved cancer detection rates of MRTB strategies when compared to systematic
17 approaches [42,43], as well as improved biopsy efficiency and reduced false negative
18 rates for significant cancer[8]. To underline this, another series of men who
19 underwent both fusion MRTB and systematic TPM showed a difference of clinically
20 significant cancer detection rates of 4% (28% for MRTB and 24% for systematic
21 biopsy), although combined biopsies outperformed each approach in isolation[44].
22 Naturally, such results have been reported by specialist centres and as such, concern
23 remains in regard to the level of operator dependency with targeted biopsy
24 techniques. However, authors have found no difference between cancer detection
25 rates with targeted techniques regardless of the experience of the operator, albeit
26 with TRUSGB[45]. Of course, advocating for a rapid uptake of such techniques in
27 centres with no prior experience would be optimistic. Instead, envisage a step-wise,
28 quality controlled uptake of transperineal approach biopsies, mpMRI reporting
29 before adopting targeted strategies.
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46 As with mpMRI, MRTB is not a perfect test, both can miss significant disease.
47 However, this is an improvement on our current standard diagnostic test which is
48 demonstrably poor[27-30]. As recent studies have shown, in comparison to TRUSGB,
49 MRTB is more likely to detect disease once a suspicious area has been
50 identified[6,17]. Furthermore, the recently published PRECISION randomised
51 controlled trial clearly demonstrated the superior clinically significant cancer
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3 detection rate of MRTB and a reduced insignificant cancer detection rate when
4 compared to systematic TRUS biopsy[18].
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7 A potential limitation of the MRTB technique in this study is the use of 'cognitive
8 fusion' rather than US/mpMRI fusion or 'in-bore' targeting. However, no superiority
9 of one technique over another has been clearly demonstrated, whilst 'cognitive
10 fusion' is clearly a less costly option[46]. Another potential limitation of the targeted
11 biopsy strategy is the 'satisfaction of search' bias. Essentially, this means that after
12 the primary lesion is scored, less attention to detail is given to subsequent lesions,
13 which may therefore be undercalled or undersampled. However, in this series this
14 occurred twice, only once where the secondary lesion was attributed a lower score
15 than the primary, and in no cases did this change the proposed management.
16 Further, in the vast majority of centres where radical treatments – rather than focal
17 – remain the standard of care, there would likely be no change in the approach to
18 curative therapy, save for planning for prostatectomy in the case of nerve-sparing
19 procedures.
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23 The cost of mpMRI has been cited as a reason for persisting with TRUSGB led
24 diagnostic pathways [47], using it instead for a second investigation in the case of a
25 negative biopsy in a patient in whom suspicion of cancer remains. Whilst mpMRI is
26 indeed useful in this scenario, recent cost effectiveness analyses have shown the
27 long term cost benefits of mpMRI led pathways when various outcomes are
28 accounted for[14,48,49] due to a reduction in overdiagnosis and higher detection
29 rates of clinically significant disease at primary biopsy. In particular, the cost-analysis
30 of the PROMIS trial cohort demonstrated that MpMRI first followed by two MRTBs
31 detects more cancer per pound spent than a TRUS first biopsy strategy[49].
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47 A major advantage of our pathway is the low time to diagnosis and treatment. At a
48 median of 8 and 20 days respectively the time a patient waits is significantly below
49 the 31 and 62-day targets set by the United Kingdom National Health Service. The
50 meeting of these targets is a persistent challenge nationally[50]. Moreover,
51 performing an mpMRI prior to primary biopsy negates the risk of an initial false
52 negative biopsy significantly delaying a subsequent mpMRI due to post biopsy
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3 haemorrhage within the prostate. This makes it difficult to localise cancer or
4 accurately determine its size or border[51]. In such circumstances, the delay in
5 diagnosis can be up to eight weeks.
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8 9 **Conclusions**

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11 This novel pathway offers an alternative to standard prostate cancer diagnostic
12 services. Attendance and cancer detection rates are high. The use of an mpMRI led
13 pathway allows for a significant proportion of men to avoid a biopsy and for those
14 who do, the time to diagnosis and definitive treatment is kept particularly low. The
15 integration of both mpMRI and MRTB in the prostate cancer diagnostic pathway has
16 shown cost-effectiveness in the long-term. This is especially true where rapid
17 diagnostics are mandated or desirable. Furthermore, today, where septic
18 complications are of grave concern, the transperineal route is particularly
19 advantageous. This pilot study demonstrates, that similar services can be provided in
20 appropriate centres and may be valuable to patients with a potential diagnosis of
21 prostate cancer.
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29 **Figure and Table legends**

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31 **Figure 1:** The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.
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34 **Figure 2:** A pictorial prostate mpMRI diagrammatic report, as drawn by the
35 urologist.
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38 **Figure 3:** The University College London ‘traffic light like’ system to define significant
39 prostate cancer.
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42 **Table 1A:** Baseline demographics for the cohort.
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45 **Table 1B:** MpMRI outcomes.
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48 **Table 1C:** Biopsy outcomes.
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51 **Table 1D:** Diagnosis and treatment outcomes.
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Footnotes

Contributorship statement

Edward J Bass drafted the manuscript and approved the final version.

Alex Freeman contributed to the conception of the work presented, revised the manuscript critically and approved the final version.

Charles Jameson contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Shonit Punwani contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Caroline Moore contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Manit Arya revised the manuscript critically and approved the final version.

Mark Emberton contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

Hashim U. Ahmed contributed to the conception of the work presented and revised the manuscript critically and approved the final version.

All authors are accountable for all aspects of the work in terms of accuracy and integrity.

Competing Interests

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1
2
3 Ahmed currently receives funding from the Wellcome Trust, Prostate Cancer UK,
4 Sonacare Inc., Trod Medical and Sophiris Biocorp for trials in prostate cancer. Ahmed
5 is a paid medical consultant for Sophiris Biocorp for trials work.
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8
9 Mark Emberton's research is supported by core funding from the United Kingdom's
10 National Institute of Health Research (NIHR) UCLH/UCL Biomedical Research
11 Centre. He was awarded NIHR Senior Investigator in 2015.
12
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14
15 Emberton receives funding from NIHR-i4i, MRC, Sonacare Inc., Trod Medical, Cancer
16 Vaccine Institute and Sophiris Biocorp for trials in prostate cancer. Emberton is a
17 medical consultant to Sonacare Inc., Sophiris Biocorp, Steba Biotech, Exact Imaging
18 and Profound Medical.
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22
23 Moore receives funding from the National Institute for Health Research, The
24 European Association of Urology Research Foundation, Prostate Cancer UK,
25 Movember and the Cancer Vaccine Institute, for clinical prostate cancer research.
26 She has received advisory board fees for Genomic Health.
27
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30
31 Ahmed, Emberton, and Moore are all proctors for HIFU and are paid for training
32 other surgeons in this procedure.
33
34

35 Emberton and Freeman have loan notes/stock options in Nuada Medical Ltd (UK).
36
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39

40 **Funding**

41
42 This research received no specific grant from any funding in the public, commercial
43 or not-for-profit sectors.
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49 **Data sharing statement**

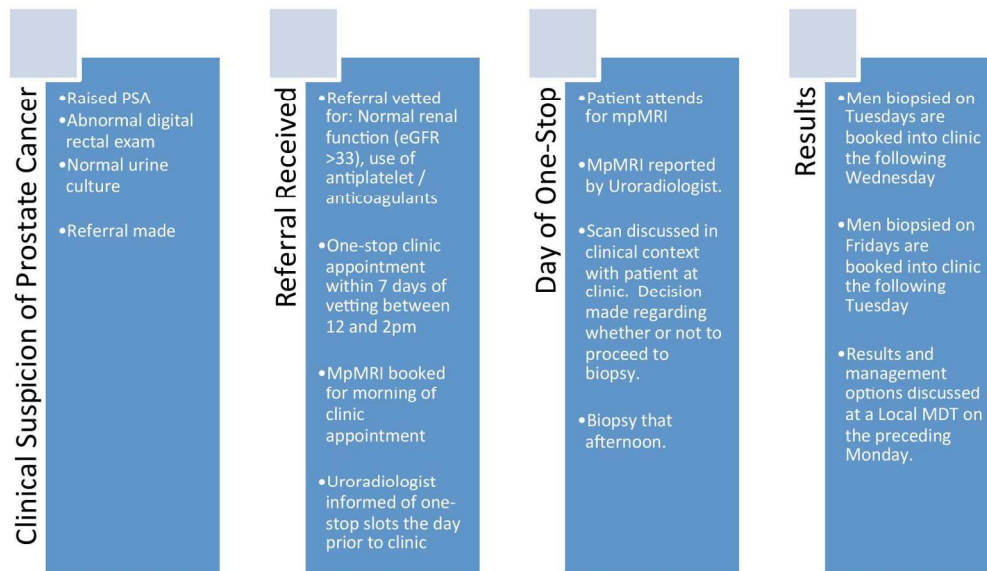
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51 We declare there is no unpublished data from etc study.
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3 **Patient Consent**
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5 Consent was obtained prior to mpMRI and biopsy.
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10 **Ethics approval**
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12 Local ethical approval was attained through the Hospital Trust's audit committee
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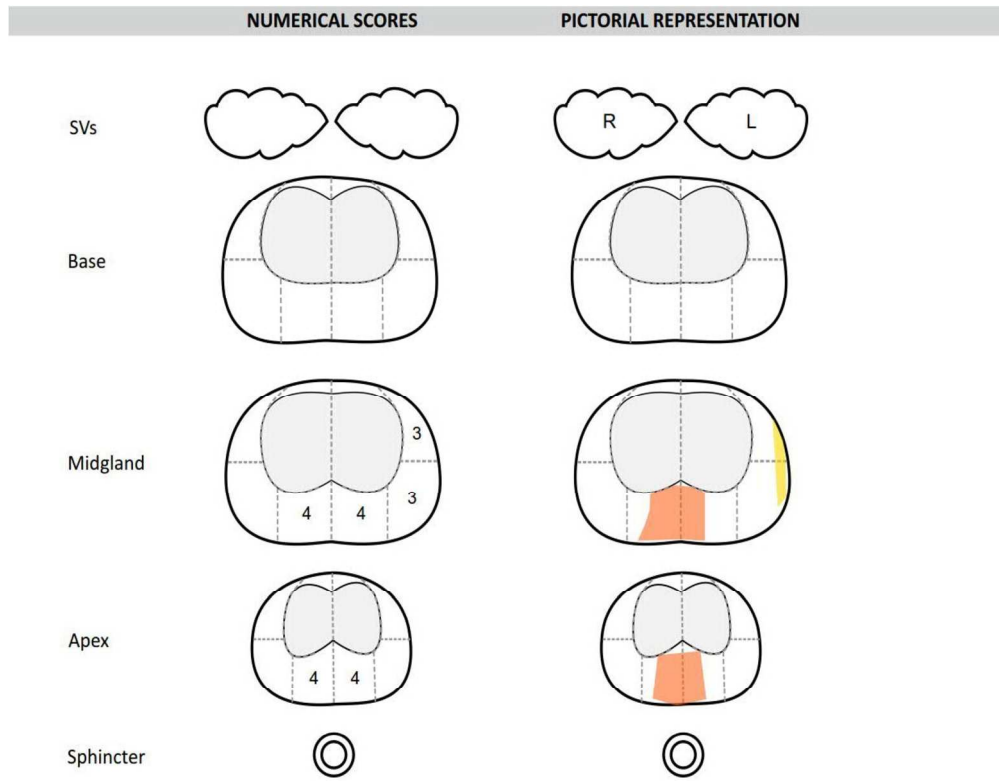


The One-Stop mpMRI led, MRTB prostate cancer diagnostic pathway.

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Review only

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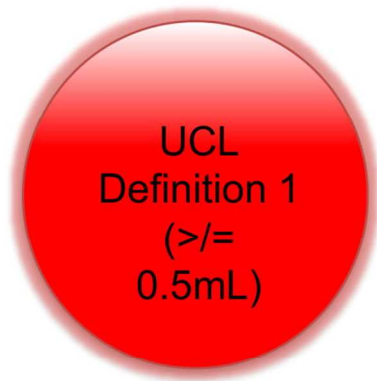


A pictorial prostate mpMRI diagrammatic report, as drawn by the urologist.

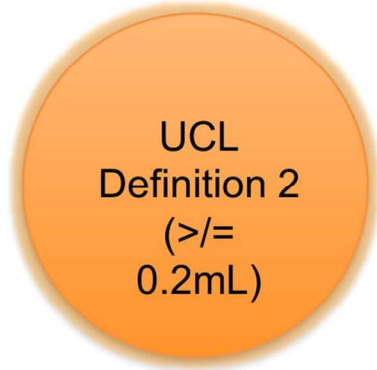
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Gleason \geq 4+3
AND/OR Max
Cancer length \geq
6mm



Gleason \geq 3+4
AND/OR Max
Cancer length \geq
4mm



Gleason \leq 3+3
AND/OR Max
Cancer length \leq
3mm

The University College London 'traffic light like' system to define significant prostate cancer.

89x125mm (300 x 300 DPI)

| Item | Extension for pilot trials | Reported | Page | Line |
|--------------------|--|----------|---------|------------------|
| Title | Identification of study as randomised pilot or feasibility trial | ✓ | 7 | 6 |
| Trial design | Description of pilot trial design (eg, parallel, cluster) | ✓ | 7 | 14 - 29 |
| Methods: | | | | |
| Participants | Eligibility criteria for participants and the settings where the pilot trial was conducted | ✓ | 7 | 17 - 20 |
| Interventions | <i>Interventions intended for each group</i> | ✓ | 8 | 1 - 22 |
| Objective | Specific objectives of the pilot trial | ✓ | 7 | 6 - 11 |
| Outcome | Prespecified assessment or measurement to address the pilot trial objectives* | ✓ | 7 | 10 - 11 |
| Randomisation | <i>How participants were allocated to interventions</i> | N / A | N / A | N / A |
| Blinding (masking) | <i>Whether or not participants, care givers, and those assessing the objectives were blinded to group assignment</i> | N / A | N / A | N / A |
| Results: | | | | |
| Numbers randomised | Number of participants screened and randomised to each group for the pilot trial objectives* | N / A | N / A | N / A |
| Recruitment | | | | |
| Numbers analysed | Number of participants analysed in each group for the pilot objectives* | ✓ | 11 | 2 - 3 |
| Outcome | Results for the pilot objectives, including any expressions of uncertainty* | ✓ | 12 & 13 | 19 - 26 & 1 - 15 |
| Harms | <i>Important adverse events or side effects</i> | ✗ | ✗ | ✗ |

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|--------------------|---|-----|-----|---------|
| Conclusions | General interpretation of the results of pilot trial and their implications for the future definitive trial | ✓ | 15 | 23 - 26 |
| Trial registration | Registration number for pilot trial and name of trial register | N/A | N/A | N/A |
| Funding | Source of funding for pilot trial | N/A | N/A | N/A |

For peer review only