



**Multi-parametric MRI followed by targeted prostate biopsy
for men with suspected prostate cancer: a clinical decision
analysis**

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5 **prostate cancer: a clinical decision analysis**
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ABSTRACT (226 words)

Objective: To compare the diagnostic outcomes of the current approach of TRUS-guided biopsy in men with suspected prostate cancer to an alternative approach using multiparametric MRI (mpMRI), followed by MRI-targeted biopsy if positive.

Design: Clinical decision analysis was used to synthesise data from recently emerging evidence in a format that is relevant for clinical decision making.

Population: A hypothetical cohort of 1000 men with suspected prostate cancer.

Interventions: mpMRI and if positive MRI-targeted biopsy compared to TRUS-guided biopsy in all men.

Outcome measures: We report the number of men expected to undergo a biopsy as well as the numbers of correctly identified patients with or without prostate cancer. A probabilistic sensitivity analysis was carried out using Monte Carlo simulation to explore the impact of statistical uncertainty in the diagnostic parameters.

Results: In 1000 men, mpMRI followed by MRI-targeted biopsy “dominates” TRUS-guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men being correctly identified as having clinically significant cancer (320 versus 250), and fewer men being falsely identified (20 versus 50). The mpMRI-based strategy dominated TRUS-guided biopsy in 90% of the simulations of the sensitivity analysis.

Conclusions: Our analysis demonstrates that mpMRI followed by MRI-targeted biopsy is likely to result in fewer and better biopsies than TRUS-guided biopsy. Future research in prostate cancer should focus on providing precise estimates of key diagnostic parameters.

STRENGTHS AND LIMITATIONS OF THE STUDY (127 words)

- There are no clinical studies that directly compare the standard diagnostic approach using TRUS biopsy in all men with suspected prostate cancer with an approach where mpMRI is used to select men for biopsy and to guide the biopsy needle towards a suspicious lesion.
- Our decision analysis brings together emerging evidence on the diagnostic accuracy of TRUS biopsy, mpMRI and MRI-targeted biopsies.
- A probabilistic sensitivity analysis demonstrates that the MRI strategy was most effective in 90% of the simulations. However this sensitivity analysis did not assess the impact of structural uncertainties.
- This analysis focuses purely on short term clinical outcomes following different testing options. Ultimately, the optimal diagnostic strategy for men with suspected prostate cancer will depend on the impact of both costs and quality-adjusted life expectancy.

INTRODUCTION

Prostate cancer is the most common male cancer in most developed countries. Incidence rates have risen rapidly over the past 15 years, in part due to the increase in prostate specific antigen (PSA) testing. PSA testing remains controversial since it does not necessarily indicate prostate cancer and many men diagnosed with prostate cancer will not die from the disease. It is increasingly accepted that a distinction should be made between prostate cancer that is unlikely to cause harm ("clinically insignificant" disease) and cancer which, if untreated, may cause symptoms or lead to death ("clinically significant" disease). Although there is no consensus on what constitutes clinically significant disease, it is usually described in terms of cancer volume and the extent of cell differentiation (cancer grade) [1-3].

The optimal strategy for diagnosing clinically significant prostate cancer is the focus of a rapidly developing body of research. The standard diagnostic approach for men with suspected prostate cancer is to offer them a transrectal ultrasound (TRUS)-guided prostate biopsy taking 10 to 12 cores [4-6]. The ultrasound guidance ensures the biopsy needles are guided to zones within the gland, but generally not to a suspicious lesion that is more likely to contain cancer. Imaging the prostate of all men before biopsy has been proposed, but it remains controversial in some centres partly due to doubts about the performance and reproducibility of multi-parametric MRI (mpMRI). This alternative diagnostic pathway, already being implemented by some NHS providers, would require all men with raised PSA to have an mpMRI but only those with a suspicious lesion to undergo an MRI-targeted biopsy. Men who are negative on mpMRI would receive no further investigation. During

1
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3 MRI-targeted biopsy, the biopsy needle is either directed by the clinician's interpretation of
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5 the mpMRI results ("cognitive registration") or by using computing technology that digitally
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7 overlays the target information derived from the mpMRI directly onto the ultrasound image
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9 ("computer-aided registration"). Irrespective of the image-registration technique, an MRI-
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11 based approach to diagnosis has two potential advantages: patients with no lesion on
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13 mpMRI would avoid a prostate biopsy and using mpMRI for targeting may improve the
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15 detection of clinically significant cancers.
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22 We summarise what can be understood from recently emerging evidence in a format that is
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24 relevant for clinical decision making. We carried out a decision analysis to compare a
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26 simplified version of the current standard diagnostic approach (TRUS-guided biopsy) with an
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28 approach where mpMRI is used to select men for biopsy and to guide the biopsy needle
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30 towards the area of suspected cancer. We estimate the number of biopsies that could be
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32 avoided with pre-biopsy mpMRI and the number of correctly identified patients with and
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34 without clinically significant prostate cancer.
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METHODS

Decision analysis

We used a decision tree to compare the standard diagnostic pathway (TRUS-guided biopsy for all) with a new pathway (mpMRI for all, then MRI-targeted biopsy if positive). The tree, presented in Figure 1, was evaluated to reveal the expected outcomes associated with each option, for a hypothetical cohort of 1000 men. The probability estimates used to populate the decision tree were derived from recent studies which reported data that reflected the conditional nature of the parameters and used an appropriate reference test [7-9]. All of these data are limited in some way, but assumptions were made so that any biases would favour the current diagnostic approach.

Target population

The target population for the decision analysis was men with increased serum PSA levels or abnormal findings on digital rectal examination who had never had a prostate biopsy.

Clinically significant disease

For our base-case analysis we defined clinically significant disease according to widely used, and arguably somewhat conservative, criteria: a minimum volume of 0.2cc or cell differentiation corresponding to a Gleason score of 3+4 or higher [10]. The prevalence of clinically significant disease in our target population is uncertain, but we estimated it to be 50% of all men with suspected prostate cancer, based on a prospective analysis of men

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3 undergoing a first prostate biopsy [11]. We varied the prevalence of clinically significant
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5 disease in a sensitivity analysis.
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8 9 10 *TRUS-guided biopsy*

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12 The gold standard used to establish the presence or absence of clinically significant disease -
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14 whole-mount pathological data - is usually only available for men who test positive and then
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16 go on to have radical surgery [7 8 12]. Therefore we used data from a study which carried
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18 out computer simulations to estimate the performance characteristics of TRUS-guided
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20 biopsy by comparing them to reconstructed whole-mount pathology obtained from patients
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22 undergoing surgery for bladder cancer, which revealed they also had prostate cancer [13].
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26 The spectrum of disease in this sample population is likely to include more early-stage
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28 disease than would be expected in an unscreened UK population, and thus this bias will
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30 favour the current diagnostic approach.
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36 The sensitivity of TRUS-guided biopsy, when criteria proposed by Epstein were used to
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38 interpret the diagnostic result, was approximately 50%[13]. According to Epstein, a biopsy
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40 result is positive for significant cancer if the maximum cancer core length from biopsy is at
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42 least 3mm or if the Gleason score is 3+4 or higher[10]. The corresponding specificity of
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44 TRUS-guided biopsy was estimated to be approximately 90%, which represents the
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46 proportion of men correctly identified with insignificant disease (men with no prostate
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48 cancer were not included in the study population).
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mpMRI and MRI-targeted biopsy

We estimated the diagnostic accuracy of the MRI-based strategy by combining the estimates for mpMRI and MRI-targeted biopsy. A recent systematic review of the literature revealed two studies on MRI in biopsy-naïve men with suspected prostate cancer [8 14 15]. The accuracy of mpMRI could only be estimated from data reported in one of these publications: a large study involving 555 men which compared pre-biopsy mpMRI results with TRUS-guided biopsy and/or MRI-targeted biopsy as a proxy for true disease status[14]. We used these data to estimate the sensitivity of mpMRI at 80% and the specificity 60%. A more recent study shows these values may in fact underestimate the performance of mpMRI[16].

The accuracy of MRI-targeted biopsy was taken from a study that compared MRI-targeted biopsy with cognitive registration to 20-sector template-prostate mapping [17]. This study was used since all men in the study population had a lesion on mpMRI and therefore allowed us to capture the sequential nature of the diagnostic approach. The study showed that when the biopsies were classified according to the Epstein criteria, the sensitivity was approximately 80% and the specificity 80%[17]. The specificity that this study reported for the MRI-targeted biopsy is lower than our estimate of the 90% specificity of TRUS-guided biopsy. However, the use of MRI-targeting instead of TRUS-guided biopsy should have no impact on men without clinically significant disease, and therefore we assumed that MRI-targeted biopsy should be as good as – but not better than – TRUS-guided biopsy at correctly identifying men without clinically significant prostate cancer. We therefore

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3 assumed that the specificity of the MRI-targeted biopsy is 90%, the same as that of TRUS-
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5 guided biopsy.
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8 9 10 *Sensitivity Analysis*

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12 We carried out a one-way sensitivity analysis by varying the prevalence of clinically
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14 significant disease from 0 to 1, keeping all other variables constant. This sensitivity analysis
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16 was intended to demonstrate the extent to which the optimal diagnostic strategy depends
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18 on the prevalence of clinically significant disease.
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24 The estimates used to describe the performance of the diagnostic tests in our decision
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26 analysis are uncertain. To assess the robustness of our results, we carried out a probabilistic
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28 sensitivity analysis using Monte Carlo simulation varying the sensitivities and specificities of
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30 the three tests (TRUS-guided biopsy, mpMRI, and MRI-targeted biopsy) simultaneously over
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32 2000 iterations, sampling from beta distributions to characterise the uncertainty in the test
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34 accuracy data [13 14 17]. We determined the beta distributions by assuming that the
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36 sensitivities and specificities were observed in populations consisting of 50 men with and 50
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38 men without clinically significant disease. We substantially widened the distributions (by
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40 assuming a small population of men) in order to increase the uncertainty associated with
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42 the test performance parameters. We ignored the correlation between sensitivity and
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44 specificity and kept the disease prevalence constant at 50%.
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RESULTS

The decision tree demonstrated that the use of TRUS-guided biopsy in a hypothetical cohort of 1000 men with suspected prostate cancer would result in 300 positive and 700 negative biopsy results, which would correctly identify 250 men with clinically significant prostate cancer and 450 men without the disease (Table 2).

The use of mpMRI and MRI-targeted biopsy in the same cohort would result in 600 men undergoing a biopsy with 340 positive and 260 negative biopsy results (Table 2). This diagnostic strategy would correctly identify 320 men as having significant prostate cancer and 480 without the disease.

Multi-parametric MRI followed by MRI-targeted biopsy can therefore be said to clinically dominate TRUS-guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men being correctly identified as having clinically significant disease (320 versus 250), and fewer men being falsely identified with the disease (20 versus 50).

Figure 2 provides a visual representation of the one-way sensitivity analysis showing the total number of people receiving the wrong diagnosis (the sum of the number of patients with a false-positive or a false-negative result) as a function of the prevalence of clinically significant disease. The MRI-based approach resulted in a lower number of patients wrongly diagnosed than with TRUS-guided biopsy for all men, at all prevalence rates. Below a

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3 prevalence of 5%, doing nothing is the “optimal” strategy as it leads to the lowest number of
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5 men with the wrong diagnosis. Above a prevalence of 70%, treating all men is optimal.
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10 When the sensitivities and specificities of the three tests were varied simultaneously in 2000
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12 simulations for the probabilistic sensitivity analysis, the diagnostic approach using mpMRI
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14 and MRI-targeted biopsy clinically dominated in 90% of the simulations, whereas TRUS-
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16 guided biopsy dominated in 0.4% of the simulations. The remaining 9.6% of simulations
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18 reveal a trade-off between correctly identifying more men with clinically significant cancer
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20 and correctly identifying more men without significant disease.
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DISCUSSION

Our decision analysis revealed that mpMRI of the prostate followed by MRI-targeted biopsy if positive would result in fewer and better biopsies than a strategy using only TRUS-guided biopsy. Indeed, the results show that this MRI-based strategy would reduce the number of biopsies by about one third (600 compared to 1000 biopsies), increase the number of men identified with clinically significant cancer by about 30% (320 compared to 250 patients), and reduce the number of men falsely identified with the disease by 60% (20 compared to 50).

When we accounted for uncertainty in the sensitivity and specificity estimates of the three diagnostic tests, we found that the dominance of the MRI strategy was robust. However, the probabilistic sensitivity analysis did not assess the impact of the inherent “structural” uncertainties. For example, the ongoing debate about the definition of clinically significant cancer, varying diagnostic thresholds used to decide whether mpMRI or biopsy results are positive or negative, and the use of imperfect gold-standard tests.

The National Institute for Health and Care Excellence (NICE), has recently updated its guidance on the diagnosis of prostate cancer patients[7]. Our estimate of the sensitivity of 50% for TRUS-guided biopsy is close to the estimate of 45% used in its analysis. However, we estimated the specificity of the TRUS-guided biopsy to be 90%, whilst NICE assumed it to be 100% [7]. While both of these specificity estimates are somewhat speculative, we felt that the specificity estimate needs to reflect that patients who have clinically insignificant

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3 prostate cancer may have biopsy results that are interpreted as suggestive of clinically
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5 significant cancer. We also assumed that this “error” is as likely with TRUS-guided as with
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7 MRI-targeted biopsies and therefore we used the same false-positive rate for TRUS-guided
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9 and for MRI-targeted biopsies. These choices were made deliberately in order to
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11 underestimate the comparative effectiveness of the proposed diagnostic strategy using
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13 mpMRI.
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19 The results of our analysis are based on a simplification of the choices facing urologists in
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21 the diagnosis of prostate cancer. In their evaluation, NICE considered a strategy of mpMRI
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23 and biopsy for all men, including targeted biopsies for all men with a lesion on MRI. This
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25 perhaps highlights the reticence of health care professionals to do ‘less’ rather than ‘more’.
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27 A major challenge therefore will be the implementation of a strategy that requires a
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29 negative diagnostic test result to be followed by no immediate further investigation.
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36 In this analysis we focussed purely on short term clinical outcomes following different
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38 testing options. Ultimately however the optimal diagnostic strategy for men with suspected
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40 prostate cancer will depend on the impact of both costs and quality-adjusted life
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42 expectancy. The cost of the diagnostic procedures alone may in fact be about the same for
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44 the two diagnostic strategies. If all men receive an mpMRI (£200 in 2011-12 UK NHS prices)
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46 and 60% of these men also receive a biopsy (£540 in 2011-12 UK NHS prices) the mpMRI-
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48 based strategy will result in an average cost of £524 per man, assuming TRUS-guided biopsy
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50 and MRI-targeted biopsy are equivalent in cost[18]. This compares to £540 per man with
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52 TRUS-guided biopsy. Of course the true costs of the two strategies include the long term
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3 costs and consequences of further investigations and treatments which need to be taken
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5 into account in future economic modelling.
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10 Despite the complexity of these downstream pathways, estimates of diagnostic
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12 performance and disease prevalence will be key drivers of the clinical and cost effectiveness
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14 of the whole of prostate cancer care. Systematic reviews of the prostate biopsy and imaging
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16 literature have revealed a large number of small studies characterised by poor reporting and
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18 important biases [7-9 12]. In our analysis we only used very recently published studies that
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20 capture the emerging evidence on how well TRUS-guided biopsy, mpMRI and MRI-targeted
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22 biopsy perform and estimate disease prevalence. Future research effort in prostate cancer
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24 need to focus on providing accurate and precise estimates of these parameters. Studies
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26 need to consistently distinguish between significant and insignificant cancer, represent the
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28 sequential nature of diagnostic tests and should adhere to high standards of reporting such
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30 as the START guidelines for MRI[19 20]. Without these studies, it will be hard to accurately
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32 evaluate the role of targeted biopsy or any new strategy for diagnosing prostate cancer.
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CONCLUSIONS

Our analysis demonstrates that mpMRI followed by MRI-targeted biopsy is likely to result in fewer and better biopsies than TRUS-guided biopsy. We found that the MRI-based strategy correctly identified more men with significant prostate cancer and correctly identified more men without the disease in 90% of the simulations in our probabilistic sensitivity analysis. Estimates of disease prevalence and diagnostic performance will be key drivers of a full economic analysis, so research efforts should focus on providing precise estimates of these crucial parameters.

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AUTHOR CONTRIBUTIONS

JvdM, SW, AM, HA, ME made substantial contributions to the conception and design of the work; SW, HA, CM and ID acquired the data; SW, JvdM, HA, CM and ID analysed and interpreted the data; SW and JvdM drafted the work and HA, CM, ID, ME, AM provided critical revision of the manuscript; ME, HA, CM, JvdM, SW and AM obtained funding and JvdM and AM provided supervision. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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29 Ethical approval was not required for this study. The data inputs and decision tree structure
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31 are explained in full so no additional data is available.
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REFERENCES

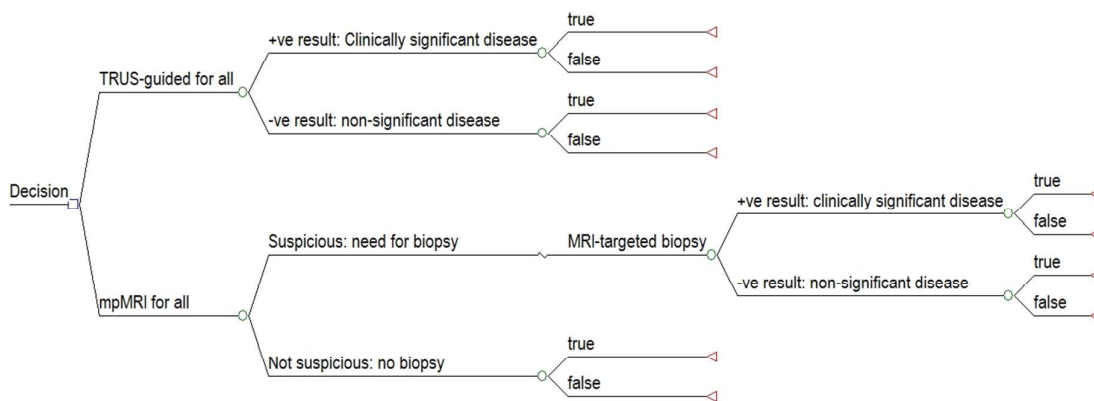
1. Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. *J Urol* 2011;**186**(2):458-64 doi: S0022-5347(11)03560-9 [pii]
2. Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993;**71**(3 Suppl):933-8
3. Goto Y, Ohori M, Arakawa A, et al. Distinguishing clinically important from unimportant prostate cancers before treatment: value of systematic biopsies. *J Urol* 1996;**156**(3):1059-63
4. Prostate Cancer Risk Management Programme. Undertaking a transrectal ultrasound guided biopsy of the prostate. Secondary Undertaking a transrectal ultrasound guided biopsy of the prostate 2006 2006. www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf.
5. National Institute for Health and Clinical Excellence. Prostate cancer diagnosis and treatment. NICE clinical guideline 58. London, 2008.
6. Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol* 2011;**59**(1):61-71
7. National Institute for Health and Care Excellence. Prostate cancer (update): guideline consultation. London: NICE, 2013.
8. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. *Eur Urol* 2013;**63**(1):125-40
9. Mowatt G, Scotland G, Boachie 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**(20):1-281
10. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage t1c) prostate cancer. *JAMA* 1994;**271**(5):368-74
11. Kuru TH, Roethke MC, Seidenader J, et al. Critical Evaluation of Magnetic Resonance Imaging Targeted, Transrectal Ultrasound Guided Transperineal Fusion Biopsy for Detection of Prostate Cancer. *J Urol* 2013;**190**(4):1380-6 doi:
12. Eichler K, Hempel S, Wilby J, et al. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006;**175**(5):1605-12

13. Lecornet E, Ahmed HU, Hu Y, et al. The accuracy of different biopsy strategies for the detection of clinically important prostate cancer: a computer simulation. *J Urol* 2012;**188**(3):974-80
14. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. *BJU Int* 2011;**108**(8 Pt 2):E171-8
15. Park BK, Park JW, Park SY, et al. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. *AJR American journal of roentgenology* 2011;**197**(5):W876-81
16. Kuru TH, Roethke MC, Seidenader J, et al. Critical Evaluation of Magnetic Resonance Imaging Targeted, Transrectal Ultrasound Guided Transperineal Fusion Biopsy for Detection of Prostate Cancer. *The Journal of Urology* 2013;**190**(4):1380-86
17. Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal Magnetic Resonance Image Targeted Prostate Biopsy Versus Transperineal Template Prostate Biopsy in the Detection of Clinically Significant Prostate Cancer. *J Urol* 2013 **189**(3):860-6
18. Department of Health. National Schedules of Reference Costs: financial year 2011 to 2012. London, 2013.
19. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;**138**(1):W1-12
20. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations from an International Working Group. *European Urology* 2013;**64**(4):544-52

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Figure 1

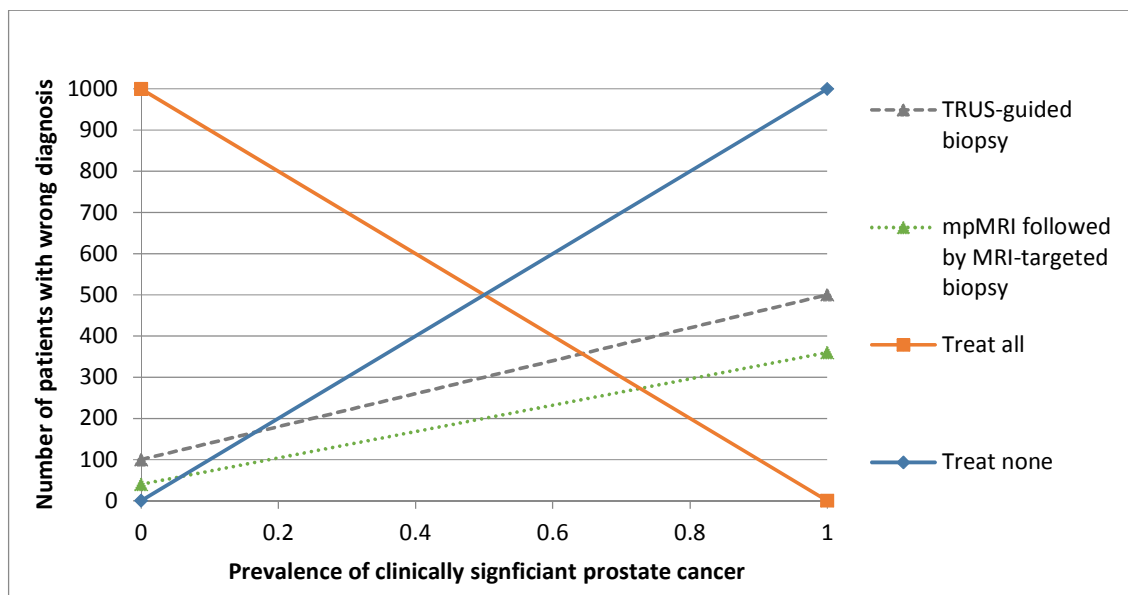
Structure of the decision tree



For review only

Figure 2

One-way sensitivity analysis showing the expected number of patients with wrong diagnoses according to the prevalence of clinically significant disease in a cohort of 1000 men. See text for further explanation.



Review only

Table 1

Diagnostic accuracy estimates of TRUS-guided biopsy, mpMRI and MRI-guided biopsy used in the base case analysis

Index Test	Sensitivity	Specificity	Reference test	Source and patient population
TRUS-guided biopsy	50% (16/34 patients, 95% CIs: 30-65)	90% (57/62 patients, 95% CIs: 82-97)	Whole-mount pathology	Lecornet 2012[13]: Simulated biopsy results on digitally reconstructed prostates of 96 men who had undergone surgery for bladder cancer which revealed prostate cancer.
mpMRI	80% (252/302, 95% CIs: 79-87)	60% (154/253 patients, 95% CIs: 45-67)	TRUS-guided extended systematic biopsies (10-12 core) plus two targeted biopsies for those with any area suspicious on MPMRI	Haffner 2011[14]: 555 men with suspected localised prostate cancer but no prior biopsy.
MRI-targeted biopsy	80% (94/121 patients, 95% CIs: 72-87)	90% <i>Assumed to be equivalent to the specificity of TRUS-guided biopsy, (57/62 patients, 95% CIs: 82-97)</i>	20 sector-TPM	Kasivisvanathan 2012 [17]: 182 men who had a suspicious lesion on MPMRI; 78 of whom were biopsy naive, 32 had a prior negative biopsy and 72 had a prior positive biopsy.

TRUS – transrectal ultrasound, TPM- template mapping biopsy, mpMRI – multi-parametric magnetic resonance imaging, MRI-TB – MRI-targeted biopsy. Data inputs were rounded to the nearest 5%.

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Table 2

Results of the decision analysis for a cohort of 1000 men comparing TRUS-guided biopsy with mpMRI and MRI-targeted biopsy.

	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy
No of biopsies	1000	600
Patients with clinically significant cancer & correctly identified (True Positive)	250	320
Patients with clinically significant cancer & wrongly identified (False Negative)	250	180
Patients with non-significant disease & correctly identified (True Negative)	450	480
Patients with non-significant disease & wrongly identified (False Positive)	50	20

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Multi-parametric MRI followed by targeted prostate biopsy for men with suspected prostate cancer: a clinical decision analysis

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1 **Multi-parametric MRI followed by targeted prostate biopsy for men with suspected**
2 **prostate cancer: a clinical decision analysis**

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21 neoplasms

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3 36 **ABSTRACT (228 words)**
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5 37 **Objective:** To compare the diagnostic outcomes of the current approach of TRUS-guided
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7 38 biopsy in men with suspected prostate cancer to an alternative approach using
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10 39 multiparametric MRI (mpMRI), followed by MRI-targeted biopsy if positive.
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12 40 **Design:** Clinical decision analysis was used to synthesise data from recently emerging
13
14
15 41 evidence in a format that is relevant for clinical decision making.
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17 42 **Population:** A hypothetical cohort of 1000 men with suspected prostate cancer.
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19 43 **Interventions:** mpMRI and if positive MRI-targeted biopsy compared to TRUS-guided biopsy
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22 44 in all men.
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24 45 **Outcome measures:** We report the number of men expected to undergo a biopsy as well as
25
26 46 the numbers of correctly identified patients with or without prostate cancer. A probabilistic
27
28 47 sensitivity analysis was carried out using Monte Carlo simulation to explore the impact of
29
30 48 statistical uncertainty in the diagnostic parameters.
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33 49 **Results:** In 1000 men, mpMRI followed by MRI-targeted biopsy “clinically dominates” TRUS-
34
35 50 guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men being
36
37 51 correctly identified as having clinically significant cancer (320 versus 250), and fewer men
38
39 52 being falsely identified (20 versus 50). The mpMRI-based strategy dominated TRUS-guided
40
41 53 biopsy in 86% of the simulations in the probabilistic sensitivity analysis.
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44 54 **Conclusions:** Our analysis suggests that mpMRI followed by MRI-targeted biopsy is likely to
45
46 55 result in fewer and better biopsies than TRUS-guided biopsy. Future research in prostate
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48 56 cancer should focus on providing precise estimates of key diagnostic parameters.
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55 58 **STRENGTHS AND LIMITATIONS OF THE STUDY (132 words)**
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3 59 • There are no clinical studies that directly compare the standard diagnostic approach
4 using TRUS-guided biopsy in all men with suspected prostate cancer with an approach
5 60 where mpMRI is used to select men for biopsy and to guide the biopsy needle towards
6 61 a suspicious lesion against an accepted gold standard.
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11 63 • Our decision analysis brings together emerging evidence on the diagnostic accuracy of
12 64 TRUS-guided biopsy, mpMRI and MRI-targeted biopsies.
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15 65 • A probabilistic sensitivity analysis demonstrates that the mpMRI-based strategy was
16 66 most effective in 86% of the simulations. However this sensitivity analysis did not assess
17 67 the impact of structural uncertainties.
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21 68 • This analysis focuses purely on short term clinical outcomes following different testing
22 69 options. Ultimately, the optimal diagnostic strategy for men with suspected prostate
23 70 cancer will depend on the impact on both costs and quality-adjusted life expectancy.
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3 72 **INTRODUCTION**
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8 74 Prostate cancer is the most common male cancer in most developed countries. Incidence
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10 75 rates have risen rapidly over the past 15 years, in part due to the increase in prostate
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12 76 specific antigen (PSA) testing. The use of PSA testing remains controversial as it lacks both
13
14 77 sensitivity and specificity for the detection of prostate cancer.^{1,2} Despite the high incidence,
15
16 78 many men diagnosed with prostate cancer will not die from the disease so it is accepted
17
18 79 that a distinction should be made between prostate cancer that is unlikely to cause harm
19
20 80 (“clinically insignificant” disease) and cancer which, if untreated, may negatively impact
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22 81 quality of life or lead to death (“clinically significant” disease). Whilst there is currently no
23
24 82 agreed threshold of significance, most commentators agree that clinically significant disease
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26 83 should be declared when disease exceeds a certain volume or is populated by histological
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28 84 patterns that exhibit poor differentiation (Gleason score).³⁻⁵
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36 86 The optimal strategy for diagnosing clinically significant prostate cancer is the focus of a
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38 87 rapidly developing body of research. The standard diagnostic approach for men with
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40 88 suspected prostate cancer is to offer them a transrectal ultrasound (TRUS)-guided prostate
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42 89 biopsy taking 10 to 12 cores.⁶⁻⁸ The ultrasound guidance ensures the biopsy needles are
43
44 90 guided to zones within the gland which are considered to have an equal probability of
45
46 91 harbouring disease. An alternative to this is to identify areas of the prostate that are more
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48 92 likely to contain cancer, and to sample from these during biopsy. The test that is currently
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50 93 gaining most favour in conferring this information is multi-parametric MRI (mpMRI).⁹
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3 95 An MRI-based approach to diagnosis would require all men with raised PSA to have an
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5 96 mpMRI. Men who are negative on mpMRI would receive no further biopsy. The men with a
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7 97 suspicious lesion on mpMRI would undergo an MRI-targeted biopsy. During MRI-targeted
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9 98 biopsy, the biopsy needle can be directed by the clinician using prior mpMR images and
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11 99 real-time ultrasound (“visual or cognitive registration”), by using assistive technology that
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13 100 digitally overlays the target information derived from the mpMRI directly onto the
14
15 101 ultrasound image (“computer-aided registration” or “image fusion”) or the biopsy can be
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17 102 performed within the MR scanner itself (“in-bore biopsy” or “MR-guided MR biopsy”).
18
19 103 Irrespective of the image-guided technique, an mpMRI-based approach to diagnosis has
20
21 104 three potential advantages. First, patients with no lesion on mpMRI could avoid a prostate
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23 105 biopsy. Second, patients with clinically insignificant disease would avoid diagnosis and
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25 106 subsequent inappropriate treatment which carries risk of side-effects and no benefit in
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27 107 terms of survival. Third, using mpMRI for targeting may improve the detection of clinically
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29 108 significant cancers and improve risk stratification.
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38 110 The UK’s National Institute of Health and Care Excellence (NICE) has recently acknowledged
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40 111 the utility of mpMRI, but stopped short of a recommendation to offer pre-biopsy mpMRI to
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42 112 all men.⁷ It remains controversial partly due to doubts about the performance and
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44 113 reproducibility of mpMRI. Despite this, many providers have adopted an image-guided
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46 114 biopsy approach in response to a man presenting with an elevated PSA.¹⁰
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52 116 We summarise what can be understood from recently emerging evidence in a format that is
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54 117 relevant for clinical decision making. We carried out a decision analysis to compare a
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3 118 simplified version of the current standard diagnostic approach (TRUS-guided biopsy) with an
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5 119 approach where mpMRI is used to select men for biopsy and to guide the biopsy needle
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8 120 towards the area of suspected cancer. We estimate the number of biopsies that could be
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10 121 avoided with pre-biopsy mpMRI and the number of correctly identified patients with and
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12 122 without clinically significant prostate cancer.
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3 124 **METHODS**
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8 126 *Decision analysis*
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10 127 We used a decision tree to compare the standard diagnostic pathway (TRUS-guided biopsy
11
12 128 for all) with a new pathway (mpMRI for all, then MRI-targeted biopsy if positive). The tree,
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14 129 presented in Figure 1, was evaluated to reveal the expected outcomes associated with each
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16 130 option, for a hypothetical cohort of 1000 men by multiplying the prevalence estimates of
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18 131 our target condition by sensitivity and specificity estimates of the diagnostic tests. The test
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20 132 accuracy estimates used to populate the decision tree were derived from recent studies
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22 133 which reported data that reflected the conditional nature of the parameters and used an
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24 134 appropriate reference test.^{11 12} All of these data are limited in some way, but assumptions
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26 135 were made so that any biases would favour the current diagnostic approach.
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34 137 *Target population*
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36 138 The target population for the decision analysis was men with increased serum PSA levels or
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38 139 abnormal findings on digital rectal examination who had never had a prostate biopsy.
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43 141 *Clinically significant disease*
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45 142 For our base-case analysis we defined clinically significant disease according to widely used,
46
47 143 and arguably somewhat conservative, criteria: a minimum volume of 0.2cc or cell
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49 144 differentiation corresponding to a Gleason score of 3+4 or higher.¹³ The prevalence of
50
51 145 clinically significant disease in our target population is uncertain, but we estimated it to be
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53 146 50% of all men with suspected prostate cancer, based on a prospective analysis of men
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3 147 undergoing a first prostate biopsy.¹⁴ The remaining 50% are assumed to have clinically
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5 148 insignificant disease or no cancer. We varied the prevalence of clinically significant disease
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8 149 in a sensitivity analysis.
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11 151 *TRUS-guided biopsy*

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15 152 The gold standard used to establish the presence or absence of clinically significant disease -
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17 153 whole-mount pathological data - is usually only available for men who test positive and then
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19 154 go on to have radical surgery.^{7 11 15} Therefore we used data from a study which carried out
20
21 155 computer simulations to estimate the performance characteristics of TRUS-guided biopsy by
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23 156 comparing them to reconstructed whole-mount pathology obtained from patients
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26 157 undergoing surgery for bladder cancer, which revealed they also had prostate cancer.¹⁶ The
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28 158 spectrum of disease in this sample population is likely to include more early-stage disease
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30 159 than would be expected in an unscreened UK population, and thus this bias will favour the
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33 160 current diagnostic approach.
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38 162 The sensitivity of TRUS-guided biopsy, when criteria proposed by Epstein were used to
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40 163 interpret the diagnostic result, was approximately 50%.¹⁶ According to Epstein, a biopsy
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42 164 result is positive for significant cancer if the maximum cancer core length from biopsy is at
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44 165 least 3mm or if the Gleason score is 3+4 or higher.¹³ The corresponding specificity of TRUS-
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46 166 guided biopsy was estimated to be approximately 90%, which represents the proportion of
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48 167 men correctly identified with insignificant disease (men with no prostate cancer were not
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50 168 included in the Lecornet et al. study population).¹⁶
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45 171 *mpMRI and MRI-targeted biopsy*
67 172 We estimated the diagnostic accuracy of the MRI-based strategy by combining the test
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10 173 accuracy estimates for mpMRI and MRI-targeted biopsy. A recent systematic review of the
1112 174 literature revealed two studies on mpMRI in biopsy-naïve men with suspected prostate
1314 175 cancer.^{11 17 18} Only one of these studies reported data at the level of detail required to
1516 176 estimate sensitivity and specificity of mpMRI: a large study involving 555 men which
1718 177 compared pre-biopsy mpMRI results with TRUS-guided biopsy and/or MRI-targeted biopsy
1920 178 as a proxy for true disease status.¹⁷ We used these data to estimate the sensitivity of
2122 179 mpMRI at 80% and the specificity, 60%. A more recent study shows these values may in
2324 180 fact underestimate the performance of mpMRI.¹⁴
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2829 181
3031 182 The accuracy of MRI-targeted biopsy was taken from a study that compared MRI-targeted
3233 183 biopsy with cognitive registration to 20-sector template-prostate mapping.¹⁹ This study was
3435 184 used since all men in the study population had a lesion on mpMRI and therefore allowed us
3637 185 to capture the sequential nature of the diagnostic approach. The study showed that when
3839 186 the biopsies were classified according to the Epstein criteria, the sensitivity was
4041 187 approximately 80% and the specificity 80%.¹⁹ The specificity that this study reported for the
4243 188 MRI-targeted biopsy is lower than our estimate of the specificity of TRUS-guided biopsy
4445 189 (90%).¹⁹ However, the use of MRI-targeting instead of TRUS-guided biopsy should have no
4647 190 impact on men without clinically significant disease, and therefore we assumed that MRI-
4849 191 targeted biopsy should be as good as – but not better than – TRUS-guided biopsy at
5051 192 correctly identifying men without clinically significant prostate cancer. We therefore used
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3 193 90% as the specificity estimate for MRI-targeted biopsy in the decision analysis, the same as
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5 194 that of TRUS-guided biopsy. We assessed the impact this had on the overall diagnostic
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7 195 results in a sensitivity analysis.
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11 12 197 *Sensitivity Analysis*

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14 198 We carried out a one-way sensitivity analysis by varying the prevalence of clinically
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16 199 significant disease from 0 to 1, keeping all other variables constant. This sensitivity analysis
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18 200 was intended to demonstrate the extent to which the optimal diagnostic strategy depends
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20 201 on the prevalence of clinically significant disease. We also carried out two sensitivity
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22 202 analyses to assess the impact of specific test performance estimates of the mpMRI-based
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24 203 strategy on overall diagnostic outcomes. In the first scenario (scenario i) we used a pooled
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26 204 estimate of mpMRI test performance from a recent meta-analysis (mpMRI sensitivity 74%,
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28 205 mpMRI specificity 88%).²⁰ In the second scenario (scenario ii) we investigated the impact of
29
30 206 our assumption that MRI-targeting has no impact on men without clinically significant
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32 207 disease (by using a specificity of 80% for MRI-targeted biopsy as reported by
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34 208 Kasivisvanathan and colleagues rather than our base case estimate of 90%).¹⁹
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43 210 Although these sensitivity analyses provide some insight into the specific impact of
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45 211 individual parameters, the estimates used to describe the performance of all the diagnostic
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47 212 tests are associated with significant uncertainties. Therefore, to assess the robustness of our
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49 213 results, we performed a probabilistic sensitivity analysis using Monte Carlo simulation
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51 214 varying the sensitivities and specificities of the three tests (TRUS-guided biopsy, mpMRI, and
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53 215 MRI-targeted biopsy) simultaneously over 2000 iterations, sampling from beta distributions
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3 216 to characterise the uncertainty in the test accuracy data (see table 1). We determined the
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5 217 beta distributions by assuming that the sensitivities and specificities were observed in
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7 218 populations consisting of 50 men with and 50 men without clinically significant disease. We
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10 219 substantially widened the distributions (by assuming a small population of men) in order to
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12 220 increase the uncertainty associated with the test performance parameters. We ignored the
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15 221 correlation between sensitivity and specificity and kept the disease prevalence constant at
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17 222 50%.
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226 **RESULTS**

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228 The decision tree estimated that the use of TRUS-guided biopsy in a hypothetical cohort of
229 1000 men with suspected prostate cancer – and an estimated 50% prevalence of clinically
230 significant disease – would result in 300 positive and 700 negative biopsy results, which
231 would correctly identify 250 men with clinically significant prostate cancer and 450 men
232 without the disease (Table 2). It follows that 250 men with significant prostate cancer would
233 be missed by TRUS-guided biopsy and 50 men who do not have significant prostate cancer
234 would wrongly receive a diagnosis.

235

236 The use of mpMRI and MRI-targeted biopsy in the same cohort would result in 600 men
237 undergoing a prostate biopsy with 340 positive and 260 negative biopsy results (Table 2).
238 This strategy would correctly identify 320 men as having significant prostate cancer and 480
239 without the disease. In other words, the use of the mpMRI-based strategy would fail to
240 diagnose significant cancer in 180 men ($= 500 - 320$), which is the result of significant
241 prostate cancer that were missed by mpMRI in addition to significant cancers that were
242 identified on the mpMRI but were missed by MRI-targeted biopsy. 20 men ($= 500 - 480$) who
243 do not have clinically significant prostate cancer would wrongly receive a diagnosis.

244

245 Multi-parametric MRI followed by MRI-targeted biopsy can be said to “clinically dominate”
246 TRUS-guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men
247 being correctly identified as having clinically significant disease (320 versus 250), and fewer
248 men being falsely identified with the disease (20 versus 50).

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5 250 Figure 2 provides a visual representation of the one-way sensitivity analysis showing the
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8 251 total number of people receiving the wrong diagnosis (the sum of the number of patients
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10 252 with a false-positive or a false-negative result) as a function of the prevalence of clinically
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12 253 significant disease. The mpMRI-based approach resulted in a lower number of patients
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14 254 wrongly diagnosed than with TRUS-guided biopsy for all men, at all prevalence rates. Below
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16 255 a prevalence of 5%, doing nothing is the “optimal” strategy as it leads to the lowest number
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19 256 of men with the wrong diagnosis. Above a prevalence of 70%, treating all men is optimal.
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24 258 Table 3 demonstrates that assuming a sensitivity of 74% and a specificity of 88% as
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26 259 estimates of the test performance of mpMRI (instead of a sensitivity of 80% and a specificity
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29 260 of 60% used in the base case analysis) found that the mpMRI-based strategy resulted in far
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31 261 fewer biopsies than our base case estimation (430 instead of 600), but slightly worse
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33 262 diagnostic outcomes for men with significant disease (296 correctly identified instead of
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35 263 320), which was still better than the current standard of care (250 correctly identified).

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38 264 Table 3 also shows that using a lower specificity for MRI-targeted biopsy (80% instead of
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40 265 90%) resulted in 40 men (instead of 20) without clinically significant disease wrongly
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42 266 identified as having significant cancer, but this is still less than the 50 men that would be
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44 267 wrongly identified using the standard diagnostic approach using TRUS-guided biopsy alone.
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49 269 When the sensitivities and specificities of the three tests were varied simultaneously in 2000
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51 270 simulations for the probabilistic sensitivity analysis, the diagnostic approach using mpMRI
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53 271 and MRI-targeted biopsy clinically dominated in 86% of the simulations, whereas TRUS-

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3 272 guided biopsy dominated in 0.8% of the simulations. Within the remaining 13.2% of
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5 273 simulations, the choice between the mpMRI-based strategy and TRUS-guided biopsy is not
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8 274 clear as there was a 'trade-off' between outcomes. That is, either the mpMRI-based strategy
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10 275 correctly identified more men with clinically significant cancer but fewer men without
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12 276 clinically significant disease than TRUS-guided biopsy, or vice-versa.
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3 278 **DISCUSSION**
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7
8 280 Our decision analysis suggests that mpMRI of the prostate followed by MRI-targeted biopsy
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10 281 if positive could result in fewer and better biopsies than a strategy using only TRUS-guided
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12 282 biopsy. The results suggest that the mpMRI-based strategy could reduce the number of
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14 283 biopsies by about one third (600 compared to 1000 biopsies), increase the number of men
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16 284 identified with clinically significant cancer by about 30% (320 compared to 250 patients),
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18 285 and reduce the number of men falsely identified with the disease by 60% (20 compared to
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20 286 50). These results are in line with those of recent clinical studies comparing similar
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22 287 strategies, albeit not against a gold standard of pathology or template biopsy.^{21 22}
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29 289 When we accounted for uncertainty in the sensitivity and specificity estimates of the three
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31 290 diagnostic tests, we found that the dominance of the mpMRI-based strategy was robust.
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33 291 However, the probabilistic sensitivity analysis did not assess the impact of inherent
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35 292 “structural” uncertainties, such as the ongoing debate about the definition of clinically
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37 293 significant cancer, various diagnostic thresholds used to decide whether mpMRI or biopsy
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39 294 results are positive or negative, and the use of imperfect gold-standard tests.
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45 296 The National Institute for Health and Care Excellence (NICE), has recently updated its
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47 297 guidance on the diagnosis and management of men with prostate cancer.⁷ Our estimate of
48
49 298 the sensitivity of 50% for TRUS-guided biopsy is close to the estimate of 45% used in its
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51 299 analysis.⁷ However, we estimated the specificity of the TRUS-guided biopsy to be 90%,
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53 300 whilst NICE assumed it to be 100%. While both of these specificity estimates are somewhat
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3 301 speculative, we believed that the specificity estimate needed to reflect that patients who
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5 302 have clinically insignificant prostate cancer may have biopsy results that are interpreted as
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7 303 suggestive of clinically significant cancer. We also assumed that this “error” is as likely with
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9 304 TRUS-guided as with MRI-targeted biopsies and therefore we used the same false-positive
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11 305 rate for TRUS-guided and for MRI-targeted biopsies. ~~These choices were made deliberately~~
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13 306 ~~in order to underestimate the comparative effectiveness of the proposed diagnostic~~
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15 307 ~~strategy using mpMRI.~~ In addition we used data on the test accuracy of MRI-targeted biopsy
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17 308 from a study which used visual registration techniques. It has been suggested that
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19 309 computer-aided registration techniques may be more accurate,⁷ although recent RCT data
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21 310 showed no statistically significant difference in detection rates.²³
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29 312 The results of our analysis are based on a simplification of the choices facing urologists in
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31 313 the diagnosis of prostate cancer. In their evaluation, NICE considered a strategy of mpMRI
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33 314 and biopsy for all men, including targeted biopsies for all men with a lesion on mpMRI. This
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35 315 perhaps highlights the reticence of health care professionals to do ‘less’ rather than ‘more’,
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37 316 which may be influenced by concern over medical liability. A major challenge therefore will
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39 317 be the implementation of a strategy that requires a negative diagnostic test result to be
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41 318 established and then followed by no immediate further investigation. New guidelines based
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43 319 on the results of forthcoming randomised controlled trials (such as PROMIS) and expert
44
45 320 consensus may be required to avoid a “creep” in the numbers of unnecessary biopsies.²⁴
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52 322 In this analysis we focussed purely on short term clinical outcomes following different
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54 323 testing options. Ultimately however the optimal diagnostic strategy for men with suspected
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3 324 prostate cancer will depend on the impact on both costs and quality-adjusted life
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5 325 expectancy. The cost of the diagnostic procedures may in fact be about the same for the
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7
8 326 two diagnostic strategies. If all men receive an mpMRI (£200 in 2011-12 UK NHS prices) and
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10 327 60% of these men also receive a biopsy (£540 in 2011-12 UK NHS prices) the mpMRI-based
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12 328 strategy will result in an average cost of £524 per man, assuming TRUS-guided biopsy and
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15 329 MRI-targeted biopsy are equivalent in cost.²⁵ This compares to £540 per man with TRUS-
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17 330 guided biopsy. Of course the true costs of the two strategies include the long term costs and
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19 331 consequences of further investigations and treatments which need to be taken into account
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21 332 in future economic modelling. Initial estimates from a published economic evaluation
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23 333 suggest a mpMRI-based strategy is likely to be highly cost-effective in the Netherlands²⁶
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25 334 although uncertainties, particularly around long term health outcomes, remain.²⁷
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31 336 Despite the complexity of the downstream pathways, estimates of diagnostic performance
32
33 337 and disease prevalence will be key drivers of the clinical and cost effectiveness of the whole
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35 338 of prostate cancer care. Systematic reviews of the prostate biopsy and imaging literature
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37 339 have revealed a large number of small studies characterised by poor reporting and
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39 340 important biases.^{7 11 12 15} In our analysis we only used very recently published studies that
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41 341 capture the emerging evidence on how well TRUS-guided biopsy, mpMRI and MRI-targeted
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43 342 biopsy perform and estimate disease prevalence. Future research efforts in prostate cancer
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45 343 need to focus on providing accurate and precise estimates of these parameters. Studies
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47 344 need to consistently distinguish between significant and insignificant cancer, represent the
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49 345 sequential nature of diagnostic tests and should adhere to high standards of reporting such
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51 346 as the START guidelines for MRI.^{28 29} Without these studies, it will be hard to accurately
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347 evaluate the role of targeted biopsy or any new strategy for diagnosing prostate cancer in
348 future.
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3 350 **CONCLUSIONS**

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5 352 Our analysis suggests that mpMRI followed by MRI-targeted biopsy may result in fewer and

6
7 353 better biopsies than TRUS-guided biopsy. We found that the mpMRI-based strategy

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9 354 correctly identified more men with significant prostate cancer and correctly identified more

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11 355 men without the disease in 86% of the simulations in our probabilistic sensitivity analysis.

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13 356 Estimates of disease prevalence and diagnostic performance will be key drivers of a full

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15 357 economic analysis, so research efforts should focus on providing precise estimates of these

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17 358 crucial parameters.
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35 373
36 374 JvdM, SW, AM, HA, ME made substantial contributions to the conception and design of the
37
38 375 work; SW, HA, CM and ID acquired the data; SW, JvdM, HA, CM and ID analysed and
39
40 376 interpreted the data; SW and JvdM drafted the work and HA, CM, ID, ME, AM provided
41
42 377 critical revision of the manuscript; ME, HA, CM, JvdM, SW and AM obtained funding and
43
44 378 JvdM and AM provided supervision. All authors have read and approved the final
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46 379 manuscript and agree to be accountable for all aspects of the work.
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3 383 **COMPETING INTERESTS**
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20 395 Ethical approval was not required for this study. The data inputs, the decision tree structure
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22 396 and the calculations are given in full so no additional data are available
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24 397 **DATA SHARING STATEMENT**
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26 398 The data inputs, the decision tree structure and the calculations are given in full so no
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28 399 additional data are available.
29

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31 400 **FIGURE LEGENDS**
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34 401 **Figure 1:** Structure of the decision tree
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36 402 **Figure 2:** One-way sensitivity analysis showing the expected number of patients with wrong
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38 403 diagnoses according to the prevalence of clinically significant disease in a cohort of 1000
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40 404 men. See text for further explanation.
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42
43 405 **Table 1:** Diagnostic accuracy estimates of TRUS-guided biopsy, mpMRI and MRI-targeted
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45 406 biopsy used in the base case analysis. *TRUS – transrectal ultrasound, TPM- template*
46
47 407 *mapping biopsy, mpMRI – multi-parametric magnetic resonance imaging, MRI-TB – MRI-*
48
49 408 *targeted biopsy. Data inputs were rounded to the nearest 5%. Beta distributions were*
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51 409 *estimated using the integer form in Excel according to the parameters α and β .*
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3 410 **Table 2:** Details of calculations and results of the decision analysis for a cohort of 1000 men
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5 411 comparing TRUS-guided biopsy with mpMRI and MRI-targeted biopsy. *'prev'* – prevalence;
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7 412 *'no_in_cohort'* – number of men in cohort; *'sensTRUS'* – sensitivity of TRUS-guided biopsy; *'specTRUS'* –
8
9 413 specificity of TRUS-guided biopsy; *'sensMRI'* – sensitivity of mpMRI; *'specMRI'* – specificity of mpMRI;
10
11 414 *'sensMRITB'* – sensitivity of MRI-targeted biopsy; *'specMRITB'* – specificity of MRI-targeted biopsy.
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13
14 415 **Table 3:** Results of sensitivity analyses in a cohort of 1000 men
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418 **REFERENCES**

- 419
- 420 1. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early
421 detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010;**60**(2):70-98.
- 422 2. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate
423 cancer. *JAMA* 2009;**302**(15):1685-92.
- 424 3. Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using
425 template prostate mapping biopsy. *J Urol* 2011;**186**(2):458-64.
- 426 4. Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor
427 volume to clinical significance for treatment of prostate cancer. *Cancer* 1993;**71**(3
428 Suppl):933-8.
- 429 5. Goto Y, Ohori M, Arakawa A, et al. Distinguishing clinically important from unimportant
430 prostate cancers before treatment: value of systematic biopsies. *J Urol*
431 1996;**156**(3):1059-63.
- 432 6. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1:
433 screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol*
434 2014;**65**(1):124-37.
- 435 7. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and
436 treatment (CG 175). London, 2014.
- 437 8. Prostate Cancer Risk Management Programme. Undertaking a transrectal ultrasound
438 guided biopsy of the prostate. 2006.
439 www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf.
- 440 9. Lee DJ, Ahmed HU, Moore CM, et al. Multiparametric magnetic resonance imaging in the
441 management and diagnosis of prostate cancer: current applications and strategies.
442 *Curr Urol Rep* 2014;**15**(3):390.
- 443 10. Emberton M. Has magnetic resonance-guided biopsy of the prostate become the
444 standard of care? *Eur Urol* 2013;**64**(5):720-1.
- 445 11. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using
446 magnetic resonance imaging-derived targets: a systematic review. *Eur Urol*
447 2013;**63**(1):125-40.
- 448 12. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness
449 of magnetic resonance spectroscopy and enhanced magnetic resonance imaging
450 techniques in aiding the localisation of prostate abnormalities for biopsy: a
451 systematic review and economic evaluation. *Health Technol Assess* 2013;**17**(20):1-
452 281.

- 1
2
3 453 13. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict
4 454 tumor extent of nonpalpable (stage t1c) prostate cancer. JAMA 1994;**271**(5):368-74.
5
6 455 14. Kuru TH, Roethke MC, Seidenader J, et al. Critical Evaluation of Magnetic Resonance
7 456 Imaging Targeted, Transrectal Ultrasound Guided Transperineal Fusion Biopsy for
8 457 Detection of Prostate Cancer. J Urol 2013;**190**(4):1380-6.
9
10
11 458 15. Eichler K, Hempel S, Wilby J, et al. Diagnostic value of systematic biopsy methods in the
12 459 investigation of prostate cancer: a systematic review. J Urol 2006;**175**(5):1605-12.
13
14 460 16. Lecornet E, Ahmed HU, Hu Y, et al. The accuracy of different biopsy strategies for the
15 461 detection of clinically important prostate cancer: a computer simulation. J Urol
16 462 2012;**188**(3):974-80.
17
18
19 463 17. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial
20 464 biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy
21 465 for significant prostate cancer detection. BJU Int 2011;**108**(8 Pt 2):E171-8.
22
23 466 18. Park BK, Park JW, Park SY, et al. Prospective evaluation of 3-T MRI performed before
24 467 initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-
25 468 specific antigen and no previous biopsy. AJR American journal of roentgenology
26 469 2011;**197**(5):W876-81.
27
28
29 470 19. Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal Magnetic Resonance Image
30 471 Targeted Prostate Biopsy Versus Transperineal Template Prostate Biopsy in the
31 472 Detection of Clinically Significant Prostate Cancer. J Urol 2013 **189**(3):860-6.
32
33 473 20. de Rooij M, Hamoen EH, Futterer JJ, et al. Accuracy of multiparametric MRI for prostate
34 474 cancer detection: a meta-analysis. AJR American journal of roentgenology
35 475 2014;**202**(2):343-51.
36
37
38 476 21. Pokorny MR, de Rooij M, Duncan E, et al. Prospective Study of Diagnostic Accuracy
39 477 Comparing Prostate Cancer Detection by Transrectal Ultrasound-Guided Biopsy
40 478 Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in
41 479 Men Without Previous Prostate Biopsies. Eur Urol 2014.
42
43
44 480 22. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-
45 481 fusion biopsy significantly upgrades prostate cancer versus systematic 12-core
46 482 transrectal ultrasound biopsy. Eur Urol 2013;**64**(5):713-9.
47
48
483 483 23. Wysock JS, Rosenkrantz AB, Huang WC, et al. A Prospective, Blinded Comparison of
49 484 Magnetic Resonance (MR) Imaging-Ultrasound Fusion and Visual Estimation in the
50 485 Performance of MR-targeted Prostate Biopsy: The PROFUS Trial. Eur Urol 2013.
51
52
53 486 24. PROstate MRI Imaging Study (PROMIS). Current Controlled Trials Web site.
54 487 ISRCTN16082556/16082556. <http://www.controlled-trials.com/>
55
56 488

- 1
2
3 489 25. Department of Health. National Schedules of Reference Costs: financial year 2011 to
4 490 2012. London, 2013.
5
6 491 26. de Rooij M, Crienen S, Witjes JA, et al. Cost-effectiveness of Magnetic Resonance (MR)
7 492 Imaging and MR-guided Targeted Biopsy Versus Systematic Transrectal Ultrasound-
8 493 Guided Biopsy in Diagnosing Prostate Cancer: A Modelling Study from a Health Care
9 494 Perspective. *Eur Urol* 2013.
10
11 495 27. Willis S, Miners A, van der Meulen J. Re: de Rooij M, et al. Cost-effectiveness of Magnetic
12 496 Resonance (MR) Imaging and MR-guided Targeted Biopsy Versus Systematic
13 497 Transrectal Ultrasound-Guided Biopsy in Diagnosing Prostate Cancer: A Modelling
14 498 Study from a Health Care Perspective. [eLetter]. *European Urology*, April 22 2014.
15
16 499 28. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of
17 500 diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;**138**(1):W1-
18 501 12.
19
20 502 29. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of Reporting for MRI-targeted
21 503 Biopsy Studies (START) of the Prostate: Recommendations from an International
22 504 Working Group. *European Urology* 2013;**64**(4):544-52.
23
24 505
25
26
27
28
29 506
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509 **Table 3**

510 Diagnostic accuracy estimates of TRUS-guided biopsy, mpMRI and MRI-targeted biopsy used
 511 in the base case analysis

Index Test	Sensitivity	Specificity	Reference test	Source and patient population
TRUS-guided biopsy	50% (16/34 patients, 95% CIs: 27-73) $\alpha = 25, \beta = 25$	90% (57/62 patients, 95% CIs: 78-97) $\alpha = 45, \beta = 5$	Whole-mount pathology	Lecornet 2012 ¹⁶ : Simulated biopsy results on digitally reconstructed prostates of 96 men who had undergone surgery for bladder cancer which revealed prostate cancer.
mpMRI	80% (252/302, 95% CIs: 66-90) $\alpha = 40, \beta = 5$	60% (154/253 patients, 95% CIs: 45-76) $\alpha = 30, \beta = 20$	TRUS-guided extended systematic biopsies (10-12 core) plus two targeted biopsies for those with any area suspicious on mpMRI (score ≥ 3)	Haffner 2011 ¹⁷ : 555 men with suspected localised prostate defined as raised PSA of >3-4ng/ml and/or abnormal DRE with no clinical or biological suspicion of stage T>3 or mets and had no prior biopsy.
MRI-targeted biopsy	80% (94/121 patients, 95% CIs: 66-90) $\alpha = 40, \beta = 10$	90% <i>Assumed to be equivalent to the specificity of TRUS-guided biopsy,</i> (57/62 patients, 95% CIs: 78-97) $\alpha = 45, \beta = 5$	20 sector-TPM	Kasivisvanathan 2013 ¹⁹ : 182 men who had a suspicious lesion on mpMRI; 78 of whom were biopsy naive, 32 had a prior negative biopsy and 72 had a prior positive biopsy.

512

513 *TRUS – transrectal ultrasound, TPM- template mapping biopsy, mpMRI – multi-parametric*514 *magnetic resonance imaging, MRI-TB – MRI-targeted biopsy. Data inputs were rounded to*

515 the nearest 5%. Beta distributions were estimated using the integer form in Excel according
 516 to the parameters α and β .

517 **Table 4**

518 Details of calculations and results of the decision analysis for a cohort of 1000 men
 519 comparing TRUS-guided biopsy with mpMRI and MRI-targeted biopsy.

	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy
No of biopsies	1000 (all men)	600 $= P(\text{MRI+} \text{D+}) + P(\text{MRI+} \text{D-})$ $= (\text{sensMRI} * \text{prev} * \text{no_in_cohort}) +$ $((1 - \text{specMRI}) * (1 - \text{prev}) * \text{no_in_cohort})$ $= (0.8 * 0.5 * 1000) + ((1 - 0.6) * (1 - 0.5) * 1000)$
Patients with clinically significant cancer & correctly identified (True Positive)	250 $= P(\text{TRUS+} \text{D+})$ $= \text{sensTRUS} * \text{prev} * \text{no_in_cohort}$ $= 0.5 * 0.5 * 1000$	320 $= P(\text{MRI+} \text{D+}) * P(\text{MRITB+} \text{D+})$ $= \text{sensMRI} * \text{sensMRITB} * \text{prev} * \text{no_in_cohort}$ $= 0.8 * 0.8 * 0.5 * 1000$
Patients with clinically significant cancer & wrongly identified (False Negative)	250 $= P(\text{TRUS+} \text{D-})$ $= (1 - \text{sensTRUS}) * \text{prev} * \text{no_in_cohort}$ $= (1 - 0.5) * 0.5 * 1000$	180 $= P(\text{MRI-} \text{D+}) + P(\text{MRI+} \text{D+}) * P(\text{MRITB-} \text{D+})$ $= ((1 - \text{sensMRI}) * \text{prev} * \text{no_in_cohort}) +$ $(\text{sensMRI} * (1 - \text{sensMRITB}) * \text{prev} * \text{no_in_cohort})$ $= ((1 - 0.8) * 0.5 * 1000) + (0.8 * (1 - 0.8) * 0.5 * 1000)$
Patients with insignificant prostate cancer or no prostate cancer & correctly identified (True Negative)	450 $= P(\text{TRUS-} \text{D-})$ $= \text{specTRUS} * (1 - \text{prev}) * \text{no_in_cohort}$ $= 0.9 * (1 - 0.5) * 1000$	480 $= P(\text{MRI-} \text{D-}) + P(\text{MRI+} \text{D-}) * P(\text{MRITB-} \text{D-})$ $= (\text{specMRI} * (1 - \text{prev}) * \text{no_in_cohort}) +$ $((1 - \text{specMRI}) * \text{specMRITB} * (1 - \text{prev}) * \text{no_in_cohort})$ $= (0.6 * (1 - 0.5) * 1000) + ((1 - 0.6) * 0.9 * (1 - 0.5) * 1000)$
Patients with insignificant prostate cancer or no prostate cancer & wrongly identified (False Positive)	50 $= P(\text{TRUS+} \text{D-})$ $= (1 - \text{specTRUS}) * (1 - \text{prev}) * \text{no_in_cohort}$ $= (1 - 0.9) * 0.5 * 1000$	20 $= P(\text{MRI+} \text{D-}) * P(\text{MRITB+} \text{D-})$ $= (1 - \text{specMRI}) * (1 - \text{specMRITB}) * (1 - \text{prev}) * \text{no_in_cohort}$ $= (1 - 0.6) * (1 - 0.9) * (1 - 0.5) * 1000$

520

521 'prev' – prevalence; 'no_in_cohort' – number of men in cohort; 'sensTRUS' – sensitivity of TRUS-guided biopsy;

522 'specTRUS' – specificity of TRUS-guided biopsy; 'sensMRI' – sensitivity of mpMRI; 'specMRI' – specificity of

523 mpMRI; 'sensMRITB' – sensitivity of MRI-targeted biopsy; 'specMRITB' – specificity of MRI-targeted biopsy.

524 **Table 3**

525 Results of sensitivity analyses in a cohort of 1000 men

Scenario	Base case analysis		Scenario i: (mpMRI sensitivity 74%, specificity 88%)		Scenario ii: (MRI-targeted biopsy sensitivity 80%, specificity 80%)	
	TRUS- guided biopsy	mpMRI then MRI- targeted biopsy	TRUS- guided biopsy	mpMRI then MRI- targeted biopsy	TRUS- guided biopsy	mpMRI then MRI- targeted biopsy
No of biopsies	1000	600	1000	430	1000	600
Patients with clinically significant cancer & correctly identified (True Positive)	250	320	250	296	250	320
Patients with clinically significant cancer & wrongly identified (False Negative)	250	180	250	204	250	180
Patients with insignificant prostate cancer or no prostate cancer & correctly identified (True Negative)	450	480	450	494	450	460
Patients with insignificant prostate cancer or no prostate cancer & wrongly identified (False Positive)	50	20	50	6	50	40

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1 **Multi-parametric MRI followed by targeted prostate biopsy for men with suspected**
2 **prostate cancer: a clinical decision analysis**

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37 39 Emberton is a consultant/investigator for USHIFU, STEBA Biotech, Sanofi Aventis,
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39 40 GlaxoSmithKline and Angiodynamics, is a consultant for Sophiris and is a director of
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47 44 consultant/investigator for STEBA Biotech and has been paid for lecturing by Sanofi. Prof.
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47 Ethical approval was not required for this study. The data inputs, the decision tree structure
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2
3 49 **ABSTRACT (228 words)**
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8 51 **Objective:** To compare the diagnostic outcomes of the current approach of TRUS-guided
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10 52 biopsy in men with suspected prostate cancer to an alternative approach using
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12 53 multiparametric MRI (mpMRI), followed by MRI-targeted biopsy if positive.

14 54 **Design:** Clinical decision analysis was used to synthesise data from recently emerging
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16 55 evidence in a format that is relevant for clinical decision making.
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19 56 **Population:** A hypothetical cohort of 1000 men with suspected prostate cancer.
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22 57 **Interventions:** mpMRI and if positive MRI-targeted biopsy compared to TRUS-guided biopsy
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24 58 in all men.
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26 59 **Outcome measures:** We report the number of men expected to undergo a biopsy as well as
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28 60 the numbers of correctly identified patients with or without prostate cancer. A probabilistic
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30 61 sensitivity analysis was carried out using Monte Carlo simulation to explore the impact of
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32 62 statistical uncertainty in the diagnostic parameters.
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35 63 **Results:** In 1000 men, mpMRI followed by MRI-targeted biopsy “clinically dominates” TRUS-
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37 64 guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men being
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39 65 correctly identified as having clinically significant cancer (320 versus 250), and fewer men
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41 66 being falsely identified (20 versus 50). The mpMRI-based strategy dominated TRUS-guided
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43 67 biopsy in 86% of the simulations in the probabilistic sensitivity analysis.
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47 68 **Conclusions:** Our analysis suggests that mpMRI followed by MRI-targeted biopsy is likely to
48
49 69 result in fewer and better biopsies than TRUS-guided biopsy. Future research in prostate
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51 70 cancer should focus on providing precise estimates of key diagnostic parameters.
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3 72 **STRENGTHS AND LIMITATIONS OF THE STUDY (132 words)**
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- 5 73 • There are no clinical studies that directly compare the standard diagnostic approach
6 using TRUS-guided biopsy in all men with suspected prostate cancer with an approach
7 74 where mpMRI is used to select men for biopsy and to guide the biopsy needle towards
8 a suspicious lesion against an accepted gold standard.
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13 77 • Our decision analysis brings together emerging evidence on the diagnostic accuracy of
14 TRUS-guided biopsy, mpMRI and MRI-targeted biopsies.
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18 79 • A probabilistic sensitivity analysis demonstrates that the mpMRI-based strategy was
19 most effective in 86% of the simulations. However this sensitivity analysis did not assess
20 80 the impact of structural uncertainties.
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24 82 • This analysis focuses purely on short term clinical outcomes following different testing
25 options. Ultimately, the optimal diagnostic strategy for men with suspected prostate
26 83 cancer will depend on the impact on both costs and quality-adjusted life expectancy.
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3 86 **INTRODUCTION**
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88 Prostate cancer is the most common male cancer in most developed countries. Incidence
89 rates have risen rapidly over the past 15 years, in part due to the increase in prostate
90 specific antigen (PSA) testing. The use of PSA testing remains controversial as it lacks both
91 sensitivity and specificity for the detection of prostate cancer.^{1,2} Despite the high incidence,
92 many men diagnosed with prostate cancer will not die from the disease so it is accepted
93 that a distinction should be made between prostate cancer that is unlikely to cause harm
94 (“clinically insignificant” disease) and cancer which, if untreated, may negatively impact
95 quality of life or lead to death (“clinically significant” disease). Whilst there is currently no
96 agreed threshold of significance, most commentators agree that clinically significant disease
97 should be declared when disease exceeds a certain volume or is populated by histological
98 patterns that exhibit poor differentiation (Gleason score).³⁻⁵
99

100

101 The optimal strategy for diagnosing clinically significant prostate cancer is the focus of a
102 rapidly developing body of research. The standard diagnostic approach for men with
103 suspected prostate cancer is to offer them a transrectal ultrasound (TRUS)-guided prostate
104 biopsy taking 10 to 12 cores.⁶⁻⁸ The ultrasound guidance ensures the biopsy needles are
105 guided to zones within the gland which are considered to have an equal probability of
106 harbouring disease. An alternative to this is to identify areas of the prostate that are more
107 likely to contain cancer, and to sample from these during biopsy. The test that is currently
108 gaining most favour in conferring this information is multi-parametric MRI (mpMRI).⁹

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3 109 An MRI-based approach to diagnosis would require all men with raised PSA to have an
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5 110 mpMRI. Men who are negative on mpMRI would receive no further biopsy. The men with a
6
7 111 suspicious lesion on mpMRI would undergo an MRI-targeted biopsy. During MRI-targeted
8
9 112 biopsy, the biopsy needle can be directed by the clinician using prior mpMR images and
10
11 113 real-time ultrasound (“visual or cognitive registration”), by using assistive technology that
12
13 114 digitally overlays the target information derived from the mpMRI directly onto the
14
15 115 ultrasound image (“computer-aided registration” or “image fusion”) or the biopsy can be
16
17 116 performed within the MR scanner itself (“in-bore biopsy” or “MR-guided MR biopsy”).
18
19 117 Irrespective of the image-guided technique, an mpMRI-based approach to diagnosis has
20
21 118 three potential advantages. First, patients with no lesion on mpMRI could avoid a prostate
22
23 119 biopsy. Second, patients with clinically insignificant disease would avoid diagnosis and
24
25 120 subsequent inappropriate treatment which carries risk of side-effects and no benefit in
26
27 121 terms of survival. Third, using mpMRI for targeting may improve the detection of clinically
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29 122 significant cancers and improve risk stratification.
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38 124 The UK’s National Institute of Health and Care Excellence (NICE) has recently acknowledged
39
40 125 the utility of mpMRI, but stopped short of a recommendation to offer pre-biopsy mpMRI to
41
42 126 all men.⁷ It remains controversial partly due to doubts about the performance and
43
44 127 reproducibility of mpMRI. Despite this, many providers have adopted an image-guided
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46 128 biopsy approach in response to a man presenting with an elevated PSA.¹⁰
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52 130 We summarise what can be understood from recently emerging evidence in a format that is
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54 131 relevant for clinical decision making. We carried out a decision analysis to compare a
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3 132 simplified version of the current standard diagnostic approach (TRUS-guided biopsy) with an
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5 133 approach where mpMRI is used to select men for biopsy and to guide the biopsy needle
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7 134 towards the area of suspected cancer. We estimate the number of biopsies that could be
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10 135 avoided with pre-biopsy mpMRI and the number of correctly identified patients with and
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12 136 without clinically significant prostate cancer.
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3 138 **METHODS**
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8 140 *Decision analysis*
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10 141 We used a decision tree to compare the standard diagnostic pathway (TRUS-guided biopsy
11
12 142 for all) with a new pathway (mpMRI for all, then MRI-targeted biopsy if positive). The tree,
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14
15 143 presented in Figure 1, was evaluated to reveal the expected outcomes associated with each
16
17 144 option, for a hypothetical cohort of 1000 men by multiplying the prevalence estimates of
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19
20 145 our target condition by sensitivity and specificity estimates of the diagnostic tests. The test
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22 146 accuracy estimates used to populate the decision tree were derived from recent studies
23
24 147 which reported data that reflected the conditional nature of the parameters and used an
25
26 148 appropriate reference test.^{11 12} All of these data are limited in some way, but assumptions
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28
29 149 were made so that any biases would favour the current diagnostic approach.
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34 151 *Target population*
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36 152 The target population for the decision analysis was men with increased serum PSA levels or
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38 153 abnormal findings on digital rectal examination who had never had a prostate biopsy.
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43 155 *Clinically significant disease*
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45 156 For our base-case analysis we defined clinically significant disease according to widely used,
46
47 157 and arguably somewhat conservative, criteria: a minimum volume of 0.2cc or cell
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50 158 differentiation corresponding to a Gleason score of 3+4 or higher.¹³ The prevalence of
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53 159 clinically significant disease in our target population is uncertain, but we estimated it to be
54
55 160 50% of all men with suspected prostate cancer, based on a prospective analysis of men
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3 161 undergoing a first prostate biopsy.¹⁴ The remaining 50% are assumed to have clinically
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5 162 insignificant disease or no cancer. We varied the prevalence of clinically significant disease
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8 163 in a sensitivity analysis.
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11 165 *TRUS-guided biopsy*

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15 166 The gold standard used to establish the presence or absence of clinically significant disease -
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17 167 whole-mount pathological data - is usually only available for men who test positive and then
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19 168 go on to have radical surgery.^{7 11 15} Therefore we used data from a study which carried out
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21 169 computer simulations to estimate the performance characteristics of TRUS-guided biopsy by
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23 170 comparing them to reconstructed whole-mount pathology obtained from patients
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25 171 undergoing surgery for bladder cancer, which revealed they also had prostate cancer.¹⁶ The
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27 172 spectrum of disease in this sample population is likely to include more early-stage disease
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29 173 than would be expected in an unscreened UK population, and thus this bias will favour the
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31 174 current diagnostic approach.
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38 176 The sensitivity of TRUS-guided biopsy, when criteria proposed by Epstein were used to
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40 177 interpret the diagnostic result, was approximately 50%.¹⁶ According to Epstein, a biopsy
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42 178 result is positive for significant cancer if the maximum cancer core length from biopsy is at
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44 179 least 3mm or if the Gleason score is 3+4 or higher.¹³ The corresponding specificity of TRUS-
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46 180 guided biopsy was estimated to be approximately 90%, which represents the proportion of
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48 181 men correctly identified with insignificant disease (men with no prostate cancer were not
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50 182 included in the Lecornet et al. study population).¹⁶
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185 *mpMRI and MRI-targeted biopsy*186 We estimated the diagnostic accuracy of the MRI-based strategy by combining the **test**187 **accuracy** estimates for mpMRI and MRI-targeted biopsy. A recent systematic review of the

188 literature revealed two studies on mpMRI in biopsy-naïve men with suspected prostate

189 cancer.^{11 17 18} **Only one of these studies reported data at the level of detail required to**190 **estimate sensitivity and specificity of mpMRI:** a large study involving 555 men which

191 compared pre-biopsy mpMRI results with TRUS-guided biopsy and/or MRI-targeted biopsy

192 as a proxy for true disease status.¹⁷ We used these data to estimate the sensitivity of

193 mpMRI at 80% and the specificity, 60%. A more recent study shows these values may in

194 fact underestimate the performance of mpMRI.¹⁴

195

196 The accuracy of MRI-targeted biopsy was taken from a study that compared MRI-targeted

197 biopsy with cognitive registration to 20-sector template-prostate mapping.¹⁹ This study was

198 used since all men in the study population had a lesion on mpMRI and therefore allowed us

199 to capture the sequential nature of the diagnostic approach. The study showed that when

200 the biopsies were classified according to the Epstein criteria, the sensitivity was

201 approximately 80% and the specificity 80%.¹⁹ The specificity that this study reported for the

202 MRI-targeted biopsy is lower than our estimate of the specificity of TRUS-guided biopsy

203 **(90%).¹⁹** However, the use of MRI-targeting instead of TRUS-guided biopsy should have no

204 impact on men without clinically significant disease, and therefore we assumed that MRI-

205 targeted biopsy should be as good as – but not better than – TRUS-guided biopsy at

206 correctly identifying men without clinically significant prostate cancer. We therefore **used**

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2
3 207 90% as the specificity estimate for MRI-targeted biopsy in the decision analysis, the same as
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5 208 that of TRUS-guided biopsy. We assessed the impact this had on the overall diagnostic
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7 209 results in a sensitivity analysis.
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11 211 *Sensitivity Analysis*

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14 212 We carried out a one-way sensitivity analysis by varying the prevalence of clinically
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17 213 significant disease from 0 to 1, keeping all other variables constant. This sensitivity analysis
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19 214 was intended to demonstrate the extent to which the optimal diagnostic strategy depends
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21
22 215 on the prevalence of clinically significant disease. We also carried out two sensitivity
23
24 216 analyses to assess the impact of specific test performance estimates of the mpMRI-based
25
26 217 strategy on overall diagnostic outcomes. In the first scenario (scenario i) we used a pooled
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28 218 estimate of mpMRI test performance from a recent meta-analysis (mpMRI sensitivity 74%,
29
30 219 mpMRI specificity 88%).²⁰ In the second scenario (scenario ii) we investigated the impact of
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32
33 220 our assumption that MRI-targeting has no impact on men without clinically significant
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35 221 disease (by using a specificity of 80% for MRI-targeted biopsy as reported by
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37 222 Kasivisvanathan and colleagues rather than our base case estimate of 90%).¹⁹
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43 224 Although these sensitivity analyses provide some insight into the specific impact of
44
45 225 individual parameters, the estimates used to describe the performance of all the diagnostic
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47 226 tests are associated with significant uncertainties. Therefore, to assess the robustness of our
48
49 227 results, we performed a probabilistic sensitivity analysis using Monte Carlo simulation
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51
52 228 varying the sensitivities and specificities of the three tests (TRUS-guided biopsy, mpMRI, and
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54 229 MRI-targeted biopsy) simultaneously over 2000 iterations, sampling from beta distributions
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3 230 to characterise the uncertainty in the test accuracy data (see table 1). We determined the
4
5 231 beta distributions by assuming that the sensitivities and specificities were observed in
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7 232 populations consisting of 50 men with and 50 men without clinically significant disease. We
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10 233 substantially widened the distributions (by assuming a small population of men) in order to
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12 234 increase the uncertainty associated with the test performance parameters. We ignored the
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15 235 correlation between sensitivity and specificity and kept the disease prevalence constant at
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17 236 50%.

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3 240 **RESULTS**
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7 242 The decision tree **estimated** that the use of TRUS-guided biopsy in a hypothetical cohort of
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10 243 1000 men with suspected prostate cancer – **and an estimated 50% prevalence of clinically**
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12 244 **significant disease** – would result in 300 positive and 700 negative biopsy results, which
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14 245 would correctly identify 250 men with clinically significant prostate cancer and 450 men
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16 246 without the disease (Table 2). **It follows that 250 men with significant prostate cancer would**
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18 247 **be missed by TRUS-guided biopsy and 50 men who do not have significant prostate cancer**
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20
21 248 **would wrongly receive a diagnosis.**
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26 250 The use of mpMRI and MRI-targeted biopsy in the same cohort would result in 600 men
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28 251 undergoing a **prostate** biopsy with 340 positive and 260 negative biopsy results (Table 2).
29
30 252 This strategy would correctly identify 320 men as having significant prostate cancer and 480
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32 253 without the disease. **In other words, the use of the mpMRI-based strategy would fail to**
33
34 254 **diagnose significant cancer in 180 men (= 500 - 320), which is the result of significant**
35
36 255 **prostate cancer that were missed by mpMRI in addition to significant cancers that were**
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38 256 **identified on the mpMRI but were missed by MRI-targeted biopsy. 20 men (= 500 - 480) who**
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40 257 **do not have clinically significant prostate cancer would wrongly receive a diagnosis.**
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47 259 Multi-parametric MRI followed by MRI-targeted biopsy can be said to “clinically dominate”
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49 260 TRUS-guided biopsy as it results in fewer expected biopsies (600 versus 1000), more men
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51 261 being correctly identified as having clinically significant disease (320 versus 250), and fewer
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53 262 men being falsely identified with the disease (20 versus 50).
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Figure 2 provides a visual representation of the one-way sensitivity analysis showing the total number of people receiving the wrong diagnosis (the sum of the number of patients with a false-positive or a false-negative result) as a function of the prevalence of clinically significant disease. The mpMRI-based approach resulted in a lower number of patients wrongly diagnosed than with TRUS-guided biopsy for all men, at all prevalence rates. Below a prevalence of 5%, doing nothing is the “optimal” strategy as it leads to the lowest number of men with the wrong diagnosis. Above a prevalence of 70%, treating all men is optimal.

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Table 3 demonstrates that assuming a sensitivity of 74% and a specificity of 88% as estimates of the test performance of mpMRI (instead of a sensitivity of 80% and a specificity of 60% used in the base case analysis) found that the mpMRI-based strategy resulted in far fewer biopsies than our base case estimation (430 instead of 600), but slightly worse diagnostic outcomes for men with significant disease (296 correctly identified instead of 320), which was still better than the current standard of care (250 correctly identified).

Table 3 also shows that using a lower specificity for MRI-targeted biopsy (80% instead of 90%) resulted in 40 men (instead of 20) without clinically significant disease wrongly identified as having significant cancer, but this is still less than the 50 men that would be wrongly identified using the standard diagnostic approach using TRUS-guided biopsy alone.

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When the sensitivities and specificities of the three tests were varied simultaneously in 2000 simulations for the probabilistic sensitivity analysis, the diagnostic approach using mpMRI and MRI-targeted biopsy clinically dominated in 86% of the simulations, whereas TRUS-

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3 286 guided biopsy dominated in 0.8% of the simulations. Within the remaining 13.2% of
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5 287 simulations, the choice between the mpMRI-based strategy and TRUS-guided biopsy is not
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8 288 clear as there was a 'trade-off' between outcomes. That is, either the mpMRI-based strategy
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10 289 correctly identified more men with clinically significant cancer but fewer men without
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12 290 clinically significant disease than TRUS-guided biopsy, or vice-versa.
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292 **DISCUSSION**

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294 Our decision analysis suggests that mpMRI of the prostate followed by MRI-targeted biopsy
295 if positive could result in fewer and better biopsies than a strategy using only TRUS-guided
296 biopsy. The results suggest that the mpMRI-based strategy could reduce the number of
297 biopsies by about one third (600 compared to 1000 biopsies), increase the number of men
298 identified with clinically significant cancer by about 30% (320 compared to 250 patients),
299 and reduce the number of men falsely identified with the disease by 60% (20 compared to
300 50). These results are in line with those of recent clinical studies comparing similar
301 strategies, albeit not against a gold standard of pathology or template biopsy.^{21 22}

302

303 When we accounted for uncertainty in the sensitivity and specificity estimates of the three
304 diagnostic tests, we found that the dominance of the mpMRI-based strategy was robust.
305 However, the probabilistic sensitivity analysis did not assess the impact of inherent
306 “structural” uncertainties, such as the ongoing debate about the definition of clinically
307 significant cancer, various diagnostic thresholds used to decide whether mpMRI or biopsy
308 results are positive or negative, and the use of imperfect gold-standard tests.

309

310 The National Institute for Health and Care Excellence (NICE), has recently updated its
311 guidance on the diagnosis and management of men with prostate cancer.⁷ Our estimate of
312 the sensitivity of 50% for TRUS-guided biopsy is close to the estimate of 45% used in its
313 analysis.⁷ However, we estimated the specificity of the TRUS-guided biopsy to be 90%,
314 whilst NICE assumed it to be 100%. While both of these specificity estimates are somewhat

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3 315 speculative, we believed that the specificity estimate needed to reflect that patients who
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5 316 have clinically insignificant prostate cancer may have biopsy results that are interpreted as
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7 317 suggestive of clinically significant cancer. We also assumed that this “error” is as likely with
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9 318 TRUS-guided as with MRI-targeted biopsies and therefore we used the same false-positive
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11 319 rate for TRUS-guided and for MRI-targeted biopsies. These choices were made deliberately
12
13 320 in order to underestimate the comparative effectiveness of the proposed diagnostic
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15 321 strategy using mpMRI. In addition we used data on the test accuracy of MRI-targeted biopsy
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17 322 from a study which used visual registration techniques. It has been suggested that
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19 323 computer-aided registration techniques may be more accurate,⁷ although recent RCT data
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21 324 showed no statistically significant difference in detection rates.²³
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29 326 The results of our analysis are based on a simplification of the choices facing urologists in
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31 327 the diagnosis of prostate cancer. In their evaluation, NICE considered a strategy of mpMRI
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33 328 and biopsy for all men, including targeted biopsies for all men with a lesion on mpMRI. This
34
35 329 perhaps highlights the reticence of health care professionals to do ‘less’ rather than ‘more’,
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37 330 which may be influenced by concern over medical liability. A major challenge therefore will
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39 331 be the implementation of a strategy that requires a negative diagnostic test result to be
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41 332 established and then followed by no immediate further investigation. New guidelines based
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43 333 on the results of forthcoming randomised controlled trials (such as PROMIS) and expert
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45 334 consensus may be required to avoid a “creep” in the numbers of unnecessary biopsies.²⁴
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52 336 In this analysis we focussed purely on short term clinical outcomes following different
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54 337 testing options. Ultimately however the optimal diagnostic strategy for men with suspected
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3 338 prostate cancer will depend on the impact on both costs and quality-adjusted life
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5 339 expectancy. The cost of the diagnostic procedures may in fact be about the same for the
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8 340 two diagnostic strategies. If all men receive an mpMRI (£200 in 2011-12 UK NHS prices) and
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10 341 60% of these men also receive a biopsy (£540 in 2011-12 UK NHS prices) the mpMRI-based
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12 342 strategy will result in an average cost of £524 per man, assuming TRUS-guided biopsy and
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14
15 343 MRI-targeted biopsy are equivalent in cost.²⁵ This compares to £540 per man with TRUS-
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17 344 guided biopsy. Of course the true costs of the two strategies include the long term costs and
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19 345 consequences of further investigations and treatments which need to be taken into account
20
21
22 346 in future economic modelling. Initial estimates from a published economic evaluation
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24 347 suggest a mpMRI-based strategy is likely to be highly cost-effective in the Netherlands²⁶
25
26 348 although uncertainties, particularly around long term health outcomes, remain.²⁷
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31 350 Despite the complexity of the downstream pathways, estimates of diagnostic performance
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33 351 and disease prevalence will be key drivers of the clinical and cost effectiveness of the whole
34
35 352 of prostate cancer care. Systematic reviews of the prostate biopsy and imaging literature
36
37 353 have revealed a large number of small studies characterised by poor reporting and
38
39 354 important biases.^{7 11 12 15} In our analysis we only used very recently published studies that
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41 355 capture the emerging evidence on how well TRUS-guided biopsy, mpMRI and MRI-targeted
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43 356 biopsy perform and estimate disease prevalence. Future research efforts in prostate cancer
44
45 357 need to focus on providing accurate and precise estimates of these parameters. Studies
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47 358 need to consistently distinguish between significant and insignificant cancer, represent the
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49 359 sequential nature of diagnostic tests and should adhere to high standards of reporting such
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51 360 as the START guidelines for MRI.^{28 29} Without these studies, it will be hard to accurately
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3 361 evaluate the role of targeted biopsy or any new strategy for diagnosing prostate cancer in

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3 364 **CONCLUSIONS**

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5 366 Our analysis suggests that mpMRI followed by MRI-targeted biopsy may result in fewer and

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7 367 better biopsies than TRUS-guided biopsy. We found that the mpMRI-based strategy

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9 368 correctly identified more men with significant prostate cancer and correctly identified more

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11 369 men without the disease in 86% of the simulations in our probabilistic sensitivity analysis.

12
13 370 Estimates of disease prevalence and diagnostic performance will be key drivers of a full

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15 371 economic analysis, so research efforts should focus on providing precise estimates of these

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17 372 crucial parameters.
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3 373 **AUTHOR CONTRIBUTIONS**
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5 374 JvdM, SW, AM, HA, ME made substantial contributions to the conception and design of the
6
7 375 work; SW, HA, CM and ID acquired the data; SW, JvdM, HA, CM and ID analysed and
8
9 376 interpreted the data; SW and JvdM drafted the work and HA, CM, ID, ME, AM provided
10
11 377 critical revision of the manuscript; ME, HA, CM, JvdM, SW and AM obtained funding and
12
13 378 JvdM and AM provided supervision. All authors have read and approved the final
14
15 379 manuscript and agree to be accountable for all aspects of the work.
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23

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40 389 and the Department of Health. The views expressed in this publication are those of the
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42 390 authors and not necessarily those of the Wellcome Trust or the Department of Health.
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3 393 **DATA SHARING STATEMENT**

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5 394 The data inputs, the decision tree structure and the calculations are given in full so no
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7 395 additional data are available.
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12 397 **FIGURE LEGENDS**

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15 398 **Figure 1: Structure of the decision tree**

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17 399 **Figure 2: One-way sensitivity analysis showing the expected number of patients with wrong**
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19 400 diagnoses according to the prevalence of clinically significant disease in a cohort of 1000
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21 401 men. See text for further explanation.
22

23
24 402 **Table 1: Diagnostic accuracy estimates of TRUS-guided biopsy, mpMRI and MRI-targeted**

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26 403 biopsy used in the base case analysis. *TRUS – transrectal ultrasound, TPM- template*

27
28 404 *mapping biopsy, mpMRI – multi-parametric magnetic resonance imaging, MRI-TB – MRI-*

29
30 405 *targeted biopsy. Data inputs were rounded to the nearest 5%. Beta distributions were*

31
32 406 *estimated using the integer form in Excel according to the parameters α and β .*

33
34 407 **Table 2: Details of calculations and** results of the decision analysis for a cohort of 1000 men

35
36 408 comparing TRUS-guided biopsy with mpMRI and MRI-targeted biopsy. *'prev' – prevalence;*

37
38 409 *'no_in_cohort' – number of men in cohort; 'sensTRUS' – sensitivity of TRUS-guided biopsy; 'specTRUS' –*

39
40 410 *specificity of TRUS-guided biopsy; 'sensMRI' – sensitivity of mpMRI; 'specMRI' – specificity of mpMRI;*

41
42 411 *'sensMRITB' – sensitivity of MRI-targeted biopsy; 'specMRITB' – specificity of MRI-targeted biopsy.*

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44 412 **Table 3: Results of sensitivity analyses in a cohort of 1000 men**

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415 REFERENCES

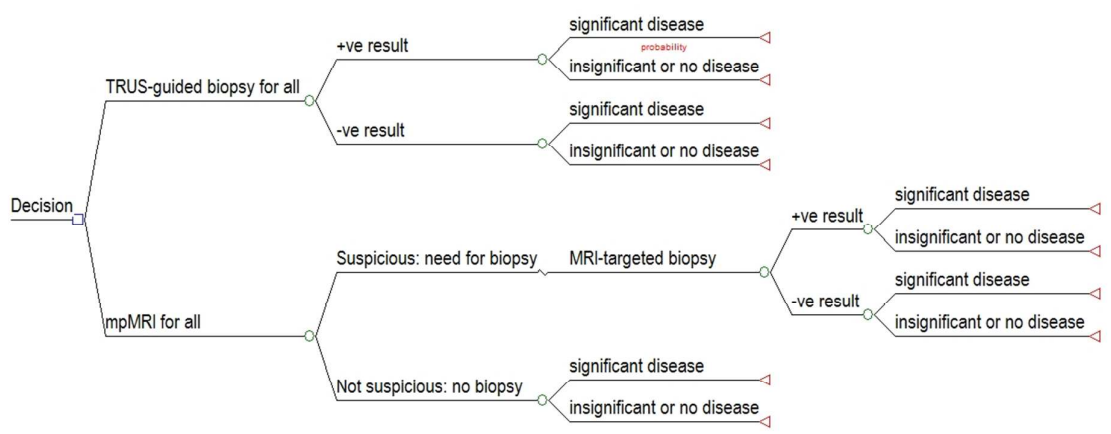
- 416
- 417 1. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early
418 detection of prostate cancer: update 2010. *CA Cancer J Clin* 2010;**60**(2):70-98.
- 419 2. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate
420 cancer. *JAMA* 2009;**302**(15):1685-92.
- 421 3. Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using
422 template prostate mapping biopsy. *J Urol* 2011;**186**(2):458-64.
- 423 4. Stamey TA, Freiha FS, McNeal JE, et al. Localized prostate cancer. Relationship of tumor
424 volume to clinical significance for treatment of prostate cancer. *Cancer* 1993;**71**(3
425 Suppl):933-8.
- 426 5. Goto Y, Ohori M, Arakawa A, et al. Distinguishing clinically important from unimportant
427 prostate cancers before treatment: value of systematic biopsies. *J Urol*
428 1996;**156**(3):1059-63.
- 429 6. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1:
430 screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol*
431 2014;**65**(1):124-37.
- 432 7. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and
433 treatment (CG 175). London, 2014.
- 434 8. Prostate Cancer Risk Management Programme. Undertaking a transrectal ultrasound
435 guided biopsy of the prostate. 2006.
436 www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf.
- 437 9. Lee DJ, Ahmed HU, Moore CM, et al. Multiparametric magnetic resonance imaging in the
438 management and diagnosis of prostate cancer: current applications and strategies.
439 *Curr Urol Rep* 2014;**15**(3):390.
- 440 10. Emberton M. Has magnetic resonance-guided biopsy of the prostate become the
441 standard of care? *Eur Urol* 2013;**64**(5):720-1.
- 442 11. Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using
443 magnetic resonance imaging-derived targets: a systematic review. *Eur Urol*
444 2013;**63**(1):125-40.
- 445 12. Mowatt G, Scotland G, Boachie C, et al. The diagnostic accuracy and cost-effectiveness
446 of magnetic resonance spectroscopy and enhanced magnetic resonance imaging
447 techniques in aiding the localisation of prostate abnormalities for biopsy: a
448 systematic review and economic evaluation. *Health Technol Assess* 2013;**17**(20):1-
449 281.

- 1
2
3 450 13. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict
4 451 tumor extent of nonpalpable (stage t1c) prostate cancer. JAMA 1994;**271**(5):368-74.
5
6 452 14. Kuru TH, Roethke MC, Seidenader J, et al. Critical Evaluation of Magnetic Resonance
7 453 Imaging Targeted, Transrectal Ultrasound Guided Transperineal Fusion Biopsy for
8 454 Detection of Prostate Cancer. J Urol 2013;**190**(4):1380-6.
9
10 455 15. Eichler K, Hempel S, Wilby J, et al. Diagnostic value of systematic biopsy methods in the
11 456 investigation of prostate cancer: a systematic review. J Urol 2006;**175**(5):1605-12.
12
13 457 16. Lecornet E, Ahmed HU, Hu Y, et al. The accuracy of different biopsy strategies for the
14 458 detection of clinically important prostate cancer: a computer simulation. J Urol
15 459 2012;**188**(3):974-80.
16
17 460 17. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial
18 461 biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy
19 462 for significant prostate cancer detection. BJU Int 2011;**108**(8 Pt 2):E171-8.
20
21 463 18. Park BK, Park JW, Park SY, et al. Prospective evaluation of 3-T MRI performed before
22 464 initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-
23 465 specific antigen and no previous biopsy. AJR American journal of roentgenology
24 466 2011;**197**(5):W876-81.
25
26 467 19. Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal Magnetic Resonance Image
27 468 Targeted Prostate Biopsy Versus Transperineal Template Prostate Biopsy in the
28 469 Detection of Clinically Significant Prostate Cancer. J Urol 2013 **189**(3):860-6.
29
30 470 20. de Rooij M, Hamoen EH, Futterer JJ, et al. Accuracy of multiparametric MRI for prostate
31 471 cancer detection: a meta-analysis. AJR American journal of roentgenology
32 472 2014;**202**(2):343-51.
33
34 473 21. Pokorny MR, de Rooij M, Duncan E, et al. Prospective Study of Diagnostic Accuracy
35 474 Comparing Prostate Cancer Detection by Transrectal Ultrasound-Guided Biopsy
36 475 Versus Magnetic Resonance (MR) Imaging with Subsequent MR-guided Biopsy in
37 476 Men Without Previous Prostate Biopsies. Eur Urol 2014.
38
39 477 22. Siddiqui MM, Rais-Bahrami S, Truong H, et al. Magnetic resonance imaging/ultrasound-
40 478 fusion biopsy significantly upgrades prostate cancer versus systematic 12-core
41 479 transrectal ultrasound biopsy. Eur Urol 2013;**64**(5):713-9.
42
43 480 23. Wysock JS, Rosenkrantz AB, Huang WC, et al. A Prospective, Blinded Comparison of
44 481 Magnetic Resonance (MR) Imaging-Ultrasound Fusion and Visual Estimation in the
45 482 Performance of MR-targeted Prostate Biopsy: The PROFUS Trial. Eur Urol 2013.
46
47 483 24. PROstate MRI Imaging Study (PROMIS). Current Controlled Trials Web site.
48 484 [http://www.controlled-trials.com/](http://www.controlled-trials.com/ISRCTN16082556/16082556)
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3 486 25. Department of Health. National Schedules of Reference Costs: financial year 2011 to
4 487 2012. London, 2013.
5
6 488 26. de Rooij M, Crienen S, Witjes JA, et al. Cost-effectiveness of Magnetic Resonance (MR)
7 489 Imaging and MR-guided Targeted Biopsy Versus Systematic Transrectal Ultrasound-
8 490 Guided Biopsy in Diagnosing Prostate Cancer: A Modelling Study from a Health Care
9 491 Perspective. *Eur Urol* 2013.
10
11 492 27. Willis S, Miners A, van der Meulen J. Re: de Rooij M, et al. Cost-effectiveness of Magnetic
12 493 Resonance (MR) Imaging and MR-guided Targeted Biopsy Versus Systematic
13 494 Transrectal Ultrasound-Guided Biopsy in Diagnosing Prostate Cancer: A Modelling
14 495 Study from a Health Care Perspective. [eLetter]. *European Urology*, April 22 2014.
15
16 496 28. Bossuyt PM, Reitsma JB, Bruns DE, et al. The STARD statement for reporting studies of
17 497 diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003;**138**(1):W1-
18 498 12.
19
20 499 29. Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of Reporting for MRI-targeted
21 500 Biopsy Studies (START) of the Prostate: Recommendations from an International
22 501 Working Group. *European Urology* 2013;**64**(4):544-52.
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504 **Figure 3**
505 **Structure of the decision tree**

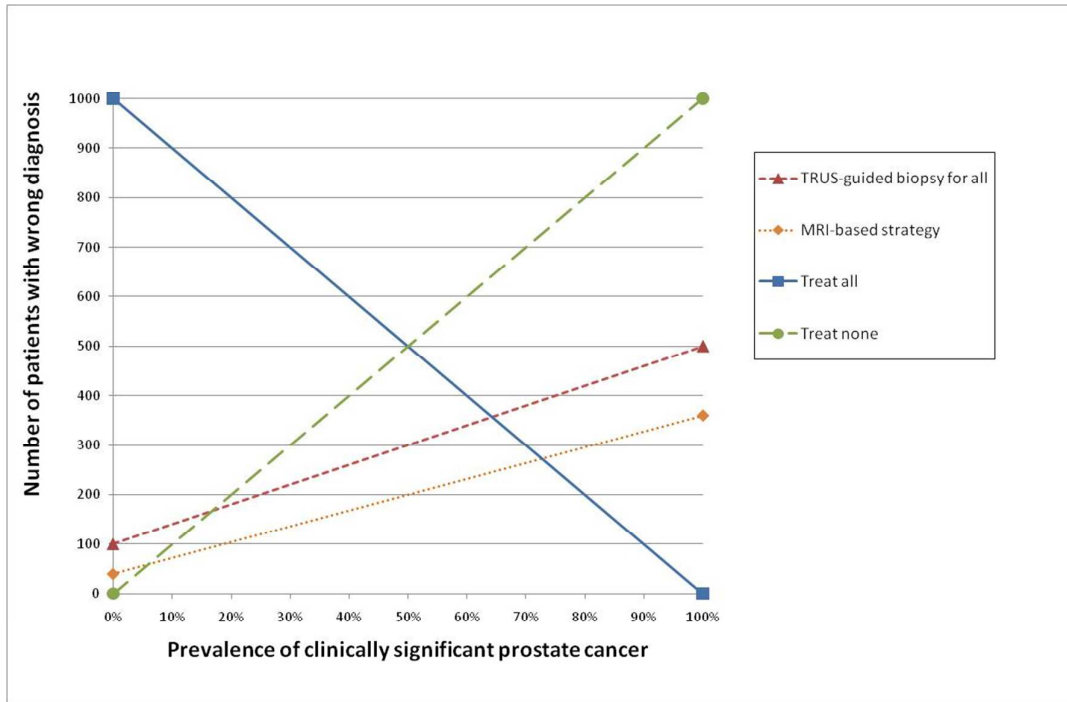


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512 **Figure 4**

513 One-way sensitivity analysis showing the expected number of patients with wrong
 514 diagnoses according to the prevalence of clinically significant disease in a cohort of 1000
 515 men. See text for further explanation.



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519 **Table 3**

520 Diagnostic accuracy estimates of TRUS-guided biopsy, mpMRI and MRI-targeted biopsy used
 521 in the base case analysis

Index Test	Sensitivity	Specificity	Reference test	Source and patient population
TRUS-guided biopsy	50% (16/34 patients, 95% CIs: 27-73) $\alpha = 25, \beta = 25$	90% (57/62 patients, 95% CIs: 78-97) $\alpha = 45, \beta = 5$	Whole-mount pathology	Lecornet 2012 ¹⁶ : Simulated biopsy results on digitally reconstructed prostates of 96 men who had undergone surgery for bladder cancer which revealed prostate cancer.
mpMRI	80% (252/302, 95% CIs: 66-90) $\alpha = 40, \beta = 5$	60% (154/253 patients, 95% CIs: 45-76) $\alpha = 30, \beta = 20$	TRUS-guided extended systematic biopsies (10-12 core) plus two targeted biopsies for those with any area suspicious on mpMRI (score ≥ 3)	Haffner 2011 ¹⁷ : 555 men with suspected localised prostate defined as raised PSA of >3-4ng/ml and/or abnormal DRE with no clinical or biological suspicion of stage T>3 or mets and had no prior biopsy.
MRI-targeted biopsy	80% (94/121 patients, 95% CIs: 66-90) $\alpha = 40, \beta = 10$	90% <i>Assumed to be equivalent to the specificity of TRUS-guided biopsy,</i> (57/62 patients, 95% CIs: 78-97) $\alpha = 45, \beta = 5$	20 sector-TPM	Kasivisvanathan 2013 ¹⁹ : 182 men who had a suspicious lesion on mpMRI; 78 of whom were biopsy naive, 32 had a prior negative biopsy and 72 had a prior positive biopsy.

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523 *TRUS – transrectal ultrasound, TPM- template mapping biopsy, mpMRI – multi-parametric*524 *magnetic resonance imaging, MRI-TB – MRI-targeted biopsy. Data inputs were rounded to*

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3 525 the nearest 5%. Beta distributions were estimated using the integer form in Excel according

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5 526 to the parameters α and β .

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528 **Table 4**529 **Details of calculations and** results of the decision analysis for a cohort of 1000 men

530 comparing TRUS-guided biopsy with mpMRI and MRI-targeted biopsy.

	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy
No of biopsies	1000 (all men)	600 $= P(\text{MRI+ D+}) + P(\text{MRI+ D-})$ $= (\text{sensMRI} * \text{prev} * \text{no_in_cohort}) +$ $((1 - \text{specMRI}) * (1 - \text{prev}) * \text{no_in_cohort})$ $= (0.8 * 0.5 * 1000) + ((1 - 0.6) * (1 - 0.5) * 1000)$
Patients with clinically significant cancer & correctly identified (True Positive)	250 $= P(\text{TRUS+ D+})$ $= \text{sensTRUS} * \text{prev} * \text{no_in_cohort}$ $= 0.5 * 0.5 * 1000$	320 $= P(\text{MRI+ D+}) * P(\text{MRITB+ D+})$ $= \text{sensMRI} * \text{sensMRITB} * \text{prev} * \text{no_in_cohort}$ $= 0.8 * 0.8 * 0.5 * 1000$
Patients with clinically significant cancer & wrongly identified (False Negative)	250 $= P(\text{TRUS+ D-})$ $= (1 - \text{sensTRUS}) * \text{prev} * \text{no_in_cohort}$ $= (1 - 0.5) * 0.5 * 1000$	180 $= P(\text{MRI- D+}) + P(\text{MRI+ D+}) * P(\text{MRITB- D+})$ $= ((1 - \text{sensMRI}) * \text{prev} * \text{no_in_cohort}) +$ $(\text{sensMRI} * (1 - \text{sensMRITB}) * \text{prev} * \text{no_in_cohort})$ $= ((1 - 0.8) * 0.5 * 1000) + (0.8 * (1 - 0.8) * 0.5 * 1000)$
Patients with insignificant prostate cancer or no prostate cancer & correctly identified (True Negative)	450 $= P(\text{TRUS- D-})$ $= \text{specTRUS} * (1 - \text{prev}) * \text{no_in_cohort}$ $= 0.9 * (1 - 0.5) * 1000$	480 $= P(\text{MRI- D-}) + P(\text{MRI+ D-}) * P(\text{MRITB- D-})$ $= (\text{specMRI} * (1 - \text{prev}) * \text{no_in_cohort}) +$ $((1 - \text{specMRI}) * \text{specMRITB} * (1 - \text{prev}) * \text{no_in_cohort})$ $= (0.6 * (1 - 0.5) * 1000) + ((1 - 0.6) * 0.9 * (1 - 0.5) * 1000)$
Patients with insignificant prostate cancer or no prostate cancer & wrongly identified (False Positive)	50 $= P(\text{TRUS+ D-})$ $= (1 - \text{specTRUS}) * (1 - \text{prev}) * \text{no_in_cohort}$ $= (1 - 0.9) * 0.5 * 1000$	20 $= P(\text{MRI+ D-}) * P(\text{MRITB+ D-})$ $= (1 - \text{specMRI}) * (1 - \text{specMRITB}) * (1 - \text{prev}) * \text{no_in_cohort}$ $= (1 - 0.6) * (1 - 0.9) * (1 - 0.5) * 1000$

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532 '*prev*' – prevalence; '*no_in_cohort*' – number of men in cohort; '*sensTRUS*' – sensitivity of TRUS-guided biopsy;533 '*specTRUS*' – specificity of TRUS-guided biopsy; '*sensMRI*' – sensitivity of mpMRI; '*specMRI*' – specificity of534 mpMRI; '*sensMRITB*' – sensitivity of MRI-targeted biopsy; '*specMRITB*' – specificity of MRI-targeted biopsy.

535 **Table 3**

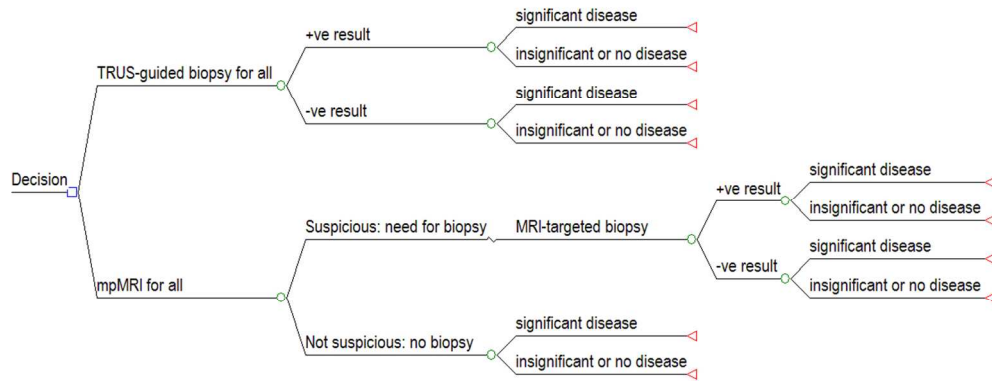
536 Results of sensitivity analyses in a cohort of 1000 men

Scenario	Base case analysis		Scenario i: (mpMRI sensitivity 74%, specificity 88%)		Scenario ii: (MRI-targeted biopsy sensitivity 80%, specificity 80%)	
Strategy	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy	TRUS-guided biopsy	mpMRI then MRI-targeted biopsy
No of biopsies	1000	600	1000	430	1000	600
Patients with clinically significant cancer & correctly identified (True Positive)	250	320	250	296	250	320
Patients with clinically significant cancer & wrongly identified (False Negative)	250	180	250	204	250	180
Patients with insignificant prostate cancer or no prostate cancer & correctly identified (True Negative)	450	480	450	494	450	460
Patients with insignificant prostate cancer or no prostate cancer & wrongly identified (False Positive)	50	20	50	6	50	40

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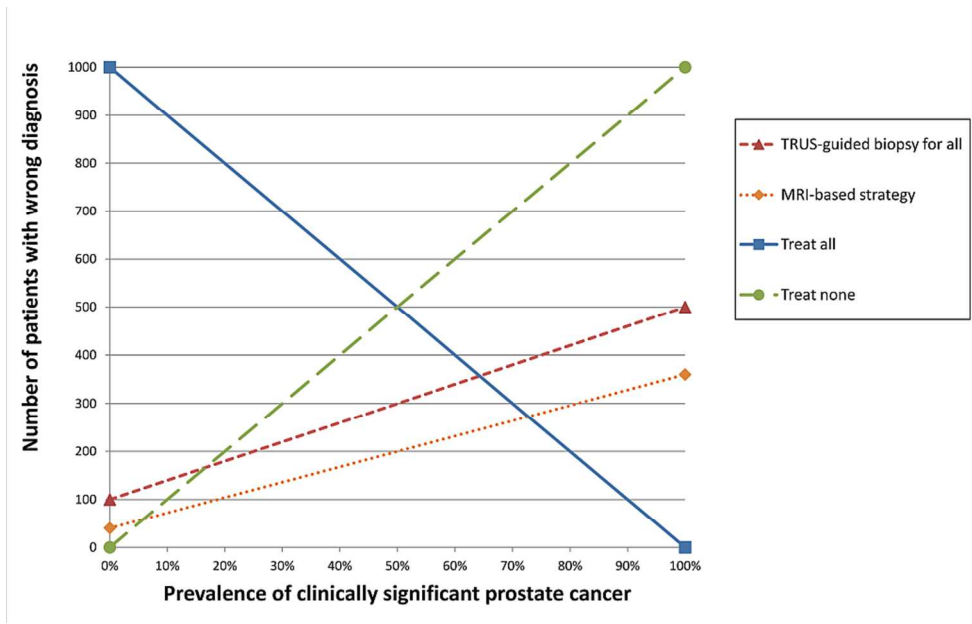
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One-way sensitivity analysis showing the expected number of patients with wrong diagnoses according to the prevalence of clinically significant disease in a cohort of 1000 men. See text for further explanation. 90x55mm (300 x 300 DPI)

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