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Optimising the diagnosis of prostate cancer in the era of multi-parametric magnetic resonance imaging: a cost-effectiveness analysis based on the PROMIS study

How to optimise the diagnosis of prostate cancer

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Abstract

Background: The current recommendation of using transrectal ultrasound guided biopsy (TRUSB) to diagnose prostate cancer misses clinically significant (CS) cancers. More sensitive biopsies (e.g. template mapping biopsy (TPMB)) are too resource intensive for routine use and there is little evidence on multiparametric magnetic resonance imaging (MPMRI).

Objective: To identify the most effective and cost-effective way of using these tests to detect CS prostate cancer.

Design, setting, and participants: Cost-effectiveness modelling of health outcomes and costs of men referred to secondary care with suspicion of prostate cancer prior to any biopsy in the UK National Health Service using information from the PROMIS diagnostic study.

Intervention(s): Combinations of MPMRI, TRUSB and TPMB, using different definitions and diagnostic cut-offs for CS cancer.

Outcome Measurements and Statistical Analysis: Strategies that detect the most CS cancers given testing costs; incremental cost-effectiveness ratios (ICERs) in quality adjusted life years (QALYs), given the long-term costs.

Results and Limitations:

Using MPMRI first then up to two MPMRI-targeted TRUSB detects more CS cancers per pound spent than a strategy using TRUSB first (sensitivity=0.95 (95% confidence interval (CI) 0.92 to 0.98 vs. 0.91 (95% CI 0.86 to 0.94)) and is cost-effective (ICER=£7,076(€8,350/QALY gained). The limitations stem from the evidence base in the accuracy of MRI-targeted biopsy and the long-term outcomes of men with CS prostate cancer.

Conclusions: An MPMRI first strategy is effective and cost-effective for the diagnosis of CS prostate cancer. These findings are sensitive to the test costs, the sensitivity of MPMRI-

targeted TRUSB and the long-term outcomes of men with cancer, which warrant more empirical research. This analysis can inform the development of clinical guidelines.

Patient summary: We found that, under certain assumptions, using MPMRI first then up to two TRUSB is better than the current clinical standard and is good value for money.

Introduction

Multiparametric magnetic resonance imaging (MPMRI) is increasingly recommended for the diagnosis of clinically significant (CS) prostate cancer, if the initial biopsy proves negative.[1, 2] An alternative approach is to begin with MPMRI imaging to inform who needs a biopsy and, in those who do need it, how it might be best conducted.[3] Recent studies have reported encouraging results on the performance of MPMRI in detecting CS prostate cancer.[3-5] The PROMIS study was the largest accuracy study on the use of MPMRI and transrectal ultrasound guided biopsy (TRUSB) in the diagnosis of prostate cancer.[4] Using template mapping biopsy (TPMB) as the reference standard, it found that MPMRI had better sensitivity for CS prostate cancer compared to TRUSB but worse specificity.[4] It is therefore necessary to explore how best to combine these tests and the consequences of incorrect diagnosis on health outcomes. This study aims to identify the combinations of tests - diagnostic strategies - that detect the most CS cancers per spent in testing and achieve the maximum health given their cost to the health care service.

Methods

The target population was men at risk of prostate cancer referred to secondary care for further investigation.[4, 6] The perspective was the UK National Health Service (NHS). Costs were expressed in pound sterling from a 2015 price base. The time horizon is the population's predicted lifetime. Costs incurred and health outcomes attained in the future were discounted to present values at 3.5% per annum.[7]

Diagnostic strategies

The diagnostic strategies consisted of clinically feasible combinations of MPMRI, TRUSB and TPMB, in addition to the use of TRUSB and TPMB in isolation (Table 1; details in Supplementary material S1.1). These included strategies using MPMRI to decide whether a TRUSB or TPMB is necessary, and strategies starting with TRUSB and using MPMRI to

decide whether a repeat biopsy is warranted. To inform the decision whether to have radical treatment, strategies were defined to always end with a confirmatory biopsy. Within each test combination, there are alternative ways each test can be used, following the definitions used in the PROMIS study (see Tables 2 and 3). Each of the 32 test combinations were tested for the alternative classifications and cut-offs, returning a total of 383 strategies.

Model structure

The model had a diagnosis and a long-term component (eFigure 1 in the Supplementary material). For diagnosis, a decision tree combined the information on diagnostic accuracy of the tests to determine the accuracy of the test combinations (Figure 1). The long-term outcomes component calculated the long-term health outcomes and costs of men with CS cancer, non-CS cancer and no cancer, by whether they were correctly diagnosed or missed. Their diagnosis determined their clinical management, as either immediate radical treatment if CS cancer is diagnosed or surveillance if not. The long-term outcomes component was a cohort Markov, with two health states for men with no cancer (alive and dead) and three states for men with cancer: localised cancer, metastatic and death. The decision model was developed in Microsoft Excel™.

Diagnostic performance

The model explicitly reflects the sensitivity and specificity of TRUSB and MPMRI in detecting prostate cancer. Tables 2 and 3 show the diagnostic performance of the tests, calculated from the individual level data collected in the PROMIS study[4] (details in Supplementary material S2). The men's true disease status was classified in four subgroups, according to the TPMB results and their serum PSA level:[1]

- No cancer
- Low risk: PSA ≤ 10 ng/ml and Gleason score ≤ 6 , who should be classified as non-CS cancer.

- Intermediate risk: PSA 10-15ng/ml or Gleason score=7, who should be classified as CS cancer.
- High risk: Gleason score ≥ 8 , who should be classified as CS cancer.

Management post-diagnosis

The long-term outcomes of men with cancer were based on the PIVOT study,[8] a randomised controlled trial comparing radical prostatectomy and watchful waiting in men with localised prostate cancer, by risk subgroup as defined above.[8] The information from PIVOT was combined with that from the STAMPEDE study (metastatic subgroup) [9] in a calibration model in order to estimate the probability of transition between the Markov model health states. Since the diagnostic strategies are perfectly specific, only men with intermediate or high risk cancer are classified as having CS cancer and receive treatment. Details are provided in Supplementary material S3.

Health-related quality of life (HRQoL) and costs

For HRQoL, the model considers the direct impact of TPMB, obtained from the patient-reported EQ-5D collected in the PROMIS study.[4] TRUSB is assumed to have no impact on HRQoL given that no effect was found in a large European screening study.[10] For costs, the model included the direct cost of the tests and the costs associated with managing their related complications.[11, 12]

In the long-term, the model considers the reduction in HRQoL from any metastatic disease[13] and ageing.[14] The model included the direct cost of radical prostatectomy and surveillance, the costs of their complications, and the costs of metastatic disease.[8] Details are provided in Supplementary material S4 (HRQOL) and S5 (Costs).

Main outcomes and measures

The main outcomes were cost-effectiveness of diagnosis, defined as the strategies that detect the most CS cancers for a given spend in testing; and long-term cost-effectiveness,

defined as the strategies that achieve the most health outcomes given their costs, for alternative cost-effectiveness thresholds: £13,000 (€15,398), £20,000 (€23,689) and £30,000 (€35,534)/QALY gained.[7, 15] The results are probabilistic in that they are the average over 1,000 Monte Carlo simulations. A number of sensitivity analyses were conducted on aspects of the short- and long-term components of the model (Supplementary material S6 for details).

Results

Base-case analysis

Detection of CS cancers per pound spend in diagnosis

Figure 2A plots the detection of CS cancers and cost of testing for each of the 383 strategies defined (Supplementary material S8 for details, including costs in euro). Out of all the 383 strategies, the figure highlights the 14 strategies that are expected to detect the most CS cancers per pound spent in testing (red circles). These define a frontier of valuable diagnostic options. The remaining strategies are not expected to represent good value. Due to the uncertainty around diagnostic accuracy and costs, some of these retain the possibility of being in the frontier, i.e. of being valuable (black circles).

Five of 14 red strategies detect at least 80% of the CS cancers: M7 223, T7 223, T7 222, M7 222 and P4 2 (strategies 10-14 in Figure 2A). In M7, all men receive MPMRI and men with suspicion of CS cancer receive a MPMRI-targeted TRUSB. Men in whom MPMRI-targeted TRUSB did not detect CS cancer receive a second MRI-targeted TRUSB. M7 223 detects 85% (95%CI 81% to 89%) of CS cancers and costs £628 (95%CI £597 to £660); M7 222 detects 95% (95%CI 92% to 0.98%) and costs £807 (95%CI £777 to £833). This MPMRI definition and cut-off refers to MRI-targeted TRUSB 96% of men: all men with high risk CS cancer; 98% of men with intermediate risk CS cancer; 92% of men with low risk non-CS cancer; and 93% of men with no cancer. T7 consists of testing all men with TRUSB, followed by MPMRI in men in whom CS cancer was not detected, and a repeat MRI-targeted TRUSB

in men with negative TRUSB if there is suspicion of CS cancer at the MPMRI. T7 223 detects 91% (95%CI 86% to 94%) CS cancers and costs £709 (95%CI £688 to £730); T7 222 detects 95% (95%CI 90% to 98%) CS cancers and costs £792 (95%CI £769 to £816). P4 2 consists of TRUSB for all men and TPMB for those in whom TRUSB did not detect CS cancer. It has perfect sensitivity but costs £1332 (95% CI £1278 to £1385).

Quality-adjusted life years (QALYs) per NHS spend

Figure 2B shows the expected lifetime health outcomes and costs achieved by each strategy per man referred for testing (Supplementary material S9 for details, including costs in euro). The line linking the cost-effective strategies (in red) is the cost-effectiveness frontier and its slope corresponds to the ICER of a strategy versus the next best (to its left); the strategies on the frontier and their ICERs are shown in Table 4. The strategy attaining the greatest expected health outcomes was P4 2, and the next best strategy is M7 222. The incremental cost-effectiveness ratio (ICER) of P4 2 vs. M7 222 was £30,084/QALY. Next best to M7 222 is T7 223, and the ICER of M7 222 vs. T7 223 is £7,076/QALY gained, making it the cost-effective strategy in the UK setting. These results are consistent with the cost-effectiveness acceptability frontier (eFigure 1), in which M7 222 is the strategy most likely to be cost-effective for cost-effectiveness thresholds between £7,250-£30,000/QALY.

Sensitivity Analysis

The cost-effective strategy changed from M7 222 to T7 222, T9 222 or P4 2 in response to a reduction in the sensitivity of MRI-targeted TRUSB and an increase in the sensitivity of MRI-targeted 2nd TRUSB. The cost-effective strategy changes to P4 2 if the sensitivity of MRI-targeted 2nd TRUSB reduces, as this reduces the CS cancer detection rates of M7 222, to T7 222 and T9 222, but not P4 2. Increases in the cost of MPMRI coupled with reductions in the cost of TRUSB results in strategies starting with TRUSB becoming cost-effective, while reductions in the cost of TPMB favour strategies involving TPMB for all or a large proportion of men. The cost-effective strategy changed to less costly less sensitive strategies (T7 223, T6 222) if radical prostatectomy is less cost-effective, for example due to reduced

effectiveness, higher HRoQL burden or greater costs. Conversely, the cost-effective strategy changed to more sensitive strategies (P4 2) is men incorrectly classified as no cancer have worse health outcomes. For full results see Supplementary material S9.

Discussion

A diagnostic strategy consisting of MPMRI first and up to two MRI-targeted TRUSB at the more sensitive definitions (definitions 2) and cut-offs is more likely to be cost-effective at cost-effectiveness thresholds at and below £30,000. For MPMRI, this is lesion volume $\geq 0.2\text{cc}$ and/or Gleason score $\geq 3+4$ (likely benign or above); for TRUSB this is any Gleason pattern ≥ 4 and/or cancer core length $\geq 4\text{mm}$. The most clinically effective strategy is testing all men with TRUSB at definition 2 and re-testing men in whom CS cancer was not detected with TPMB; however this is not cost-effective at current cost-effectiveness thresholds and will not be clinically feasible to deliver across the board in any healthcare setting. These findings can directly inform UK policy, but they can also be generalised to similar, international, settings. The extent to which the cost-effectiveness results can be generalised to other jurisdictions depends on the similarities of the population, outcomes, health systems, and pricing.

The sensitivity of MPMRI and TRUSB depends on their definitions and cut-offs. A MPMRI cut-off of 2 and above refers 96% of men to biopsy, but ensures that only 2% of men with intermediate risk cancer and none of the men with high risk cancer are missed. Furthermore, it means that most men receive a more sensitive TRUSB, since MRI-targeted TRUSB is thought to be more sensitive than standard [16]. The recent guidance based on the Prostate Imaging Reporting and Data System (PI-RADS) suggests that men with PI-RADS 1 or 2 should not be referred for biopsy given concerns about over-diagnosis.[17] This may not be equivalent to the cut-off recommended here since the PROMIS diagnostic study did not use PI-RADS, which is a limitation. Nonetheless, higher MPMRI cut-offs, whilst reducing the proportion of men receiving biopsy, also reduce the proportion of CS cancers detected and treated.

This is the first study comparing all possible ways of using MPMRI, TRUSB, and TPMB to diagnose CS prostate cancer, using data from PROMIS, the largest study on MPMRI and TRUSB.[4] A limitation of PROMIS, and of this study, is that it did not include other tests, such as transperineal biopsies, nor the combination of additional clinical and genetic characteristics for the diagnosis and risk stratification. This is an area for future research. Another area for future research is on the sensitivity of 1st and 2nd MPMRI-targeted TRUSB, since these parameters were key cost-effectiveness driver. Previous cost-effectiveness studies compared up to two ways of using MPMRI, either as a first test to determine which men should receive MPMRI-targeted TRUSB, [1, 18] as MPMRI-targeted TRUSB for all men, [1] or for men with previous negative biopsy.[19] For these reasons, this study is the most comprehensive cost-effectiveness analysis to date of alternative diagnostic strategies for prostate cancer.

The appropriate MPMRI cut-off, and ultimately the optimal diagnostic strategy, depends on the cost-effectiveness of early diagnosis and treatment. Although this study did not include radiotherapy, it did test the impact of changes to the cost-effectiveness of treatment. If radiotherapy has similar or more favourable cost-effectiveness as radical prostatectomy, highly sensitive strategies such as M7 222 are cost-effective. Highly sensitive diagnostic strategies may not be cost-effective if radical treatment is not as cost-effective in the manner modelled here. The cost-effectiveness of treatment is less favourable if i) treatment is less effective, ii) it impacts negatively on HRQoL or iii) it is more costly than it was assumed for this study.

The management of men classified as having no cancer or non-CS cancer also has an impact on the scope for investment in diagnosis. More sensitive monitoring protocols improve the cost-effectiveness of less sensitive less costly diagnostic strategies. There is a dearth of evidence on the effectiveness of repeated testing protocols, which constitutes an important limitation of the current evidence base in support of policy, and meant that these analyses could not formally evaluate the use of such protocols.

In order to evaluate the cost-effectiveness of diagnostic tests, evidence is required on the long-term outcomes of patients who are correctly diagnosed and of patients who are misclassified, given their true disease status. The extensive literature searches conducted for this study did not identify evidence on the outcomes of patients and the effectiveness of treatments when true disease status is known (for example, using TPMB to identify and risk stratify patients). The existing studies used TRUSB to diagnose and risk-stratify patients [8, 20, 21], hence some individuals may have been underdiagnosed. As a consequence, their long-term quality-adjusted survival may have been overestimated, and the cost-effectiveness of treatment may have been underestimated. This issue can only be resolved with better quality evidence on the outcomes of men with prostate cancer, based on a perfect test such as TPMB for their diagnosis and classification.

Conclusions

MPMRI is cost-effective as the first test for the diagnosis of prostate cancer, when followed by MPMRI-targeted TRUSB in men in whom the MPMRI suggests suspicion for CS cancer, and a second TRUSB if no CS cancer is found, under the most sensitive CS cancer definitions and cut-offs. These findings are sensitive to the cost of each test, the sensitivity of MPMRI-targeted TRUSB and the long-term outcomes of men with cancer, which warrant more empirical research.

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Data sharing statement

Data sharing: the technical appendix is available at [doi]. No additional data were used as part of this research.

Role of the Funder/Sponsor:

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RF had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

Transparency declaration

RF affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Author contributions

Concept and design: All authors

Acquisition, analysis, or interpretation of the data: All authors

Drafting of the manuscript: RF

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: RF, MOS, ES.

Obtaining funding: HUA, RK, ME, MJS

Study supervision: MJS, MOS.

All authors approved the final version of the work for publication.

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Declaration of interests

RF, MOS, ES, LB, RK, and MJS have no conflict of interests.

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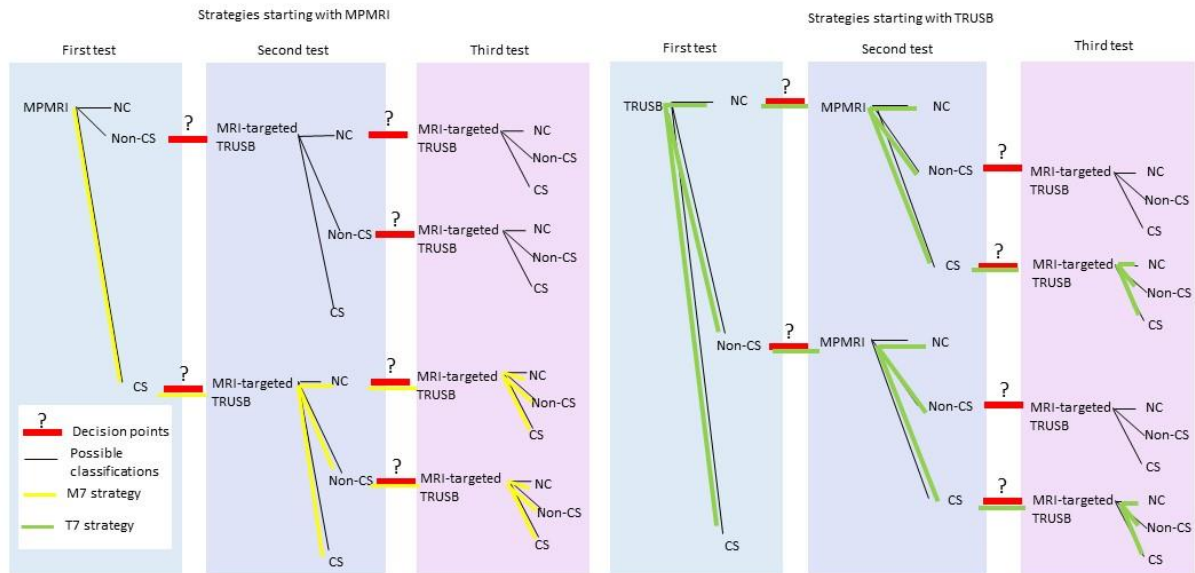
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Figures

FIGURE 1: SCHEMATIC OF DECISION TREE



The diagram represents the decision tree used to predict the outcomes of the diagnostic strategies. The diagram shows only the general structure of the tree for diagnostic strategies composed of MPMRI and TRUSB; a similar tree was used for strategies including TPMB. In the model, men can have a sequence of up to 3 tests. The black lines represent the possible test classifications. The red lines with a question mark represent decisions. Different decisions constitute different sequences of tests and hence different strategies. The diagram highlights strategies M7 (left side) and T7 (right side). In M7, men receive MPMRI and are classified as having no suspicion of cancer (no cancer; NC), suspicion of non-CS cancer or suspicion of CS cancer. Men with suspicion of CS cancer receive an MRI-targeted TRUSB, and are classified as having no cancer (NC), non-CS cancer and CS cancer. Men in whom CS cancer was not detected, but had suspicion of CS cancer at the MPMRI, receive a second MRI-targeted biopsy. In T7, men receive a TRUSB, and are classified as having no cancer (NC), non-CS cancer and CS cancer. Men in whom CS cancer was not detected receive an MPMRI, and are classified as having no suspicion of cancer (NC), suspicion of non-CS cancer or suspicion of CS cancer. Men in whom the MPMRI classified as having

suspicion of CS cancer receive a second TRUSB, this time MRI-targeted TRUSB since there is now information from the MPMRI.

Figure 2A: Detection of CS cancers per spend in diagnosis

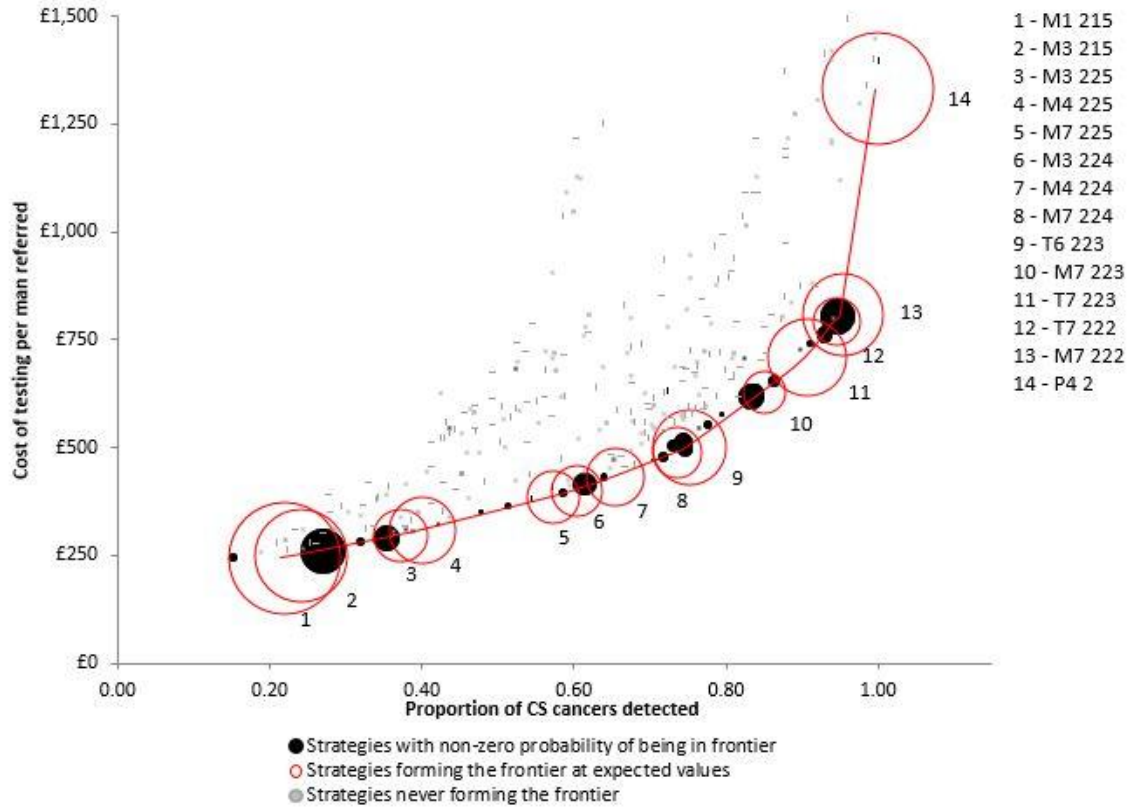
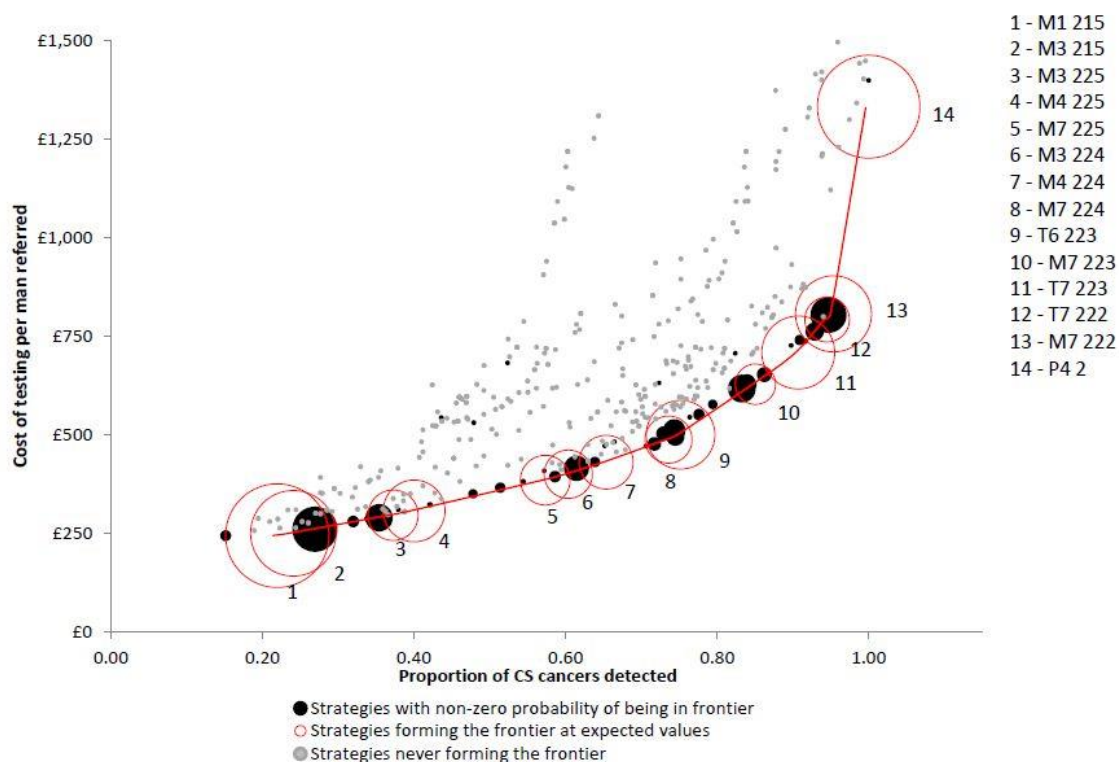


Figure 2B: Quality-adjusted life years (QALY) per NHS spend



Each bubble represents one of the 383 diagnostic strategies evaluated; their size is directly related to the probability that the strategy is cost-effective and therefore forms the frontier (i.e. forms the red line). The red bubbles represent the 14 diagnostic strategies that form the frontier at expected values. This means that, on average, these are the best strategies per pound spent. The black bubbles represent the strategies that do not form the frontier at expected values, but that have some probability of being in the frontier given their distribution of costs and outcomes. The grey bubbles represent the strategies that do not form the efficiency frontier at any simulation. Given the distribution of parameter inputs, these strategies are never efficient or cost-effective.

Tables

Table 1: Diagnostic strategies

The diagnostic strategies were labelled according to their test combination first (M1 to M7; N1 to N7; T1 to T9; P1 to P9, then their biopsy TRUSB definition (1 or 2), MPMRI definition (1 or 2), and cut-off (2 to 5). T-strategies start with TRUSB, M-strategies start with MPMRI; P-strategies are the same as T-strategies, and N-strategies are the same as M-strategies, but have TPMB as the last biopsy. For example, strategy M1 125 refers to test combination M1, in which all men were first assessed using MPMRI definition 2 and cut-off 5 and then followed up with biopsy definition 1 for those with a suspicion of CS cancer. See Supplementary material S1 for full details on the test sequences for each diagnostic strategy.

Test	Strategies
MRMRI	
First test	M1 to M7. N1 to N7.
Second test after TRUSB	T5, T6, T7, T8, T9
TRUSB	
First test	T1 to T9. P2 to P9.
Repeat TRUSB in men with no cancer detected	T2, T4
Repeat TRUSB in men with non-CS cancer detected	T3, T4
Second test after MPMRI: MRI-targeted TRUSB, in men with lesions visible at the MPMRI	M1 to M7.
Repeat MRI-targeted TRUSB in men with previous no cancer or non-CS cancer at 1 st MRI-targeted TRUSB but with lesions visible at MRI	M3-M7. T5-T9.

TPMB	
First test	P1
Second test	P2-P4; N1-N4;
Third test	P5-P9; N3-N7.

Key:

MPMRI: Multiparametric magnetic resonance imaging.

TRUSB: Transrectal ultrasound guided biopsy.

TPMB: Transperineal template mapping biopsy.

CS: Clinically significant

Table 2: Diagnostic performance of TRUSB

The diagnostic performance of first TRUSB was obtained from the individual patient data of the PROMIS study [4]. For TRUSB and TPMB, the histological CS cancer definitions were (1) dominant Gleason pattern ≥ 4 and/or any Gleason pattern ≥ 5 and/or cancer core length ≥ 6 mm (Histology definition 1) and (2) any Gleason pattern ≥ 4 and/or cancer core length ≥ 4 mm (Histology definition 2). Since the PROMIS study collected information on blind first TRUSB, external evidence was used on the sensitivity of repeat TRUSB and MPMRI-targeted TRUSB, either as first or second TRUSB [16, 22, 23].

Type	Subgroups: Definition	Low risk cancer			Intermediate risk cancer			High risk cancer			Source
		NC	CNS	CS	NC	CNS	CS	NC	CNS	CS	
1	1	0.65	0.35	0.00	0.24	0.42	0.34	0.00	0.00	1.00	PROMIS study [4]
	2	0.65	0.35	0.00	0.24	0.17	0.59	0.00	0.00	1.00	
2	1	0.55	0.45	0.00	0.55	0.25	0.20	0.55	0.00	0.45	[22]
	2	0.55	0.45	0.00	0.55	0.10	0.35	0.55	0.00	0.45	
3	1	0.00	1.00	0.00	0.00	0.75	0.25	0.00	0.75	0.25	[23]
	2	0.00	1.00	0.00	0.00	0.75	0.25	0.00	0.75	0.25	
4	1	0.80	0.20	0.00	0.20	0.37	0.43	0.00	0.00	1.00	PROMIS study [4] combined with [16]
	2	0.79	0.21	0.00	0.15	0.11	0.74	0.00	0.00	1.00	
5	1 & 2	0.68	0.32	0.00	0.05	0.08	0.87	0.05	0.08	0.87	[16]

Parameter inputs presented as point estimates (mean). See Supplementary material S2 for 95% confidence intervals and details on the data sources.

Key:

1: TRUS-guided biopsy before MP-MRI

2: TRUS-guided biopsy after a TRUS-guided biopsy that did not detect cancer

3: TRUS-guided biopsy after a TRUS-guided biopsy that detected CNS cancer

4: TRUS-guided biopsy after a suspicious MP-MRI.

5: TRUS-guided biopsy after a TRUS-guided biopsy that did not detect cancer and a suspicious MP-MRI

CS: Clinically significant

CNS: Clinically non-significant.

NC: No cancer

Table 3: Diagnostic performance of MPMRI

The diagnostic performance of MPMRI was obtained from the individual patient data of PROMIS study [4]. For interpretation of MPMRI, the definitions for CS cancer were a radiologist estimation of: (1) lesion volume $\geq 0.5\text{cc}$ and/or Gleason score $\geq 4+3$; and (2) lesion volume $\geq 0.2\text{cc}$ and/or Gleason score $\geq 3+4$. Suspicion of a lesion meeting these definitions was scored on a Likert-scale on 1-5, 1 being highly likely benign and 5 being highly likely malignant. This scale was also used to score the image for whether any cancer (whether considered CS or not) is present.

Cut-off	Subgroups: Definition	No cancer			Low risk cancer			Intermediate risk cancer			High risk cancer		
		NC	CNS	CS	NC	CNS	CS	NC	CNS	CS	NC	CNS	CS
≥ 2	1	0.00	0.23	0.77	0.00	0.20	0.80	0.01	0.06	0.93	0.00	0.00	1.00
	2	0.00	0.07	0.93	0.00	0.08	0.92	0.01	0.01	0.98	0.00	0.00	1.00
≥ 3	1	0.33	0.41	0.26	0.28	0.40	0.32	0.08	0.18	0.74	0.00	0.00	1.00
	2	0.33	0.17	0.50	0.28	0.16	0.56	0.08	0.05	0.87	0.00	0.00	1.00
≥ 4	1	0.86	0.08	0.06	0.75	0.14	0.11	0.30	0.24	0.46	0.00	0.06	0.94
	2	0.86	0.03	0.11	0.75	0.04	0.21	0.30	0.04	0.65	0.00	0.00	1.00
=5	1	0.96	0.02	0.02	0.98	0.01	0.01	0.60	0.17	0.23	0.23	0.16	0.61
	2	0.96	0.01	0.03	0.98	0.00	0.02	0.60	0.03	0.38	0.23	0.00	0.77

Parameter inputs presented as point estimates (mean). See Supplementary material S2 for 95% confidence intervals.

CS: Clinically significant

CNS: Clinically non-significant.

NC: No cancer

Table 4: Cost-effectiveness results

The strategies in the cost-effectiveness frontier are shown, together with their ICERs vs the next best strategy.

Strategy	ICER, /QALY
M1 115: MPMRI for all men definition 1 cut-off 5; TRUSB in men suspicious of CS cancer definition 1	Reference
M1 215: MPMRI for all men definition 2 cut-off 5; TRUSB in men suspicious of CS cancer definition 1	£3,081
M3 215: MPMRI for all men definition 2 cut-off 5; TRUSB in men with suspicion on CS cancer definition 2; Men with CNS at 1st biopsy receive 2nd TRUSB definition 2.	£3,630
M4 225: MPMRI for all men definition 2 cut-off 5; TRUS-guided in men with suspicion of any cancer definition 2. Men with suspicion of CS cancer at MPMRI and in whom CNS cancer was detected at the 1st biopsy receive 2nd TRUSB definition 2.	£3,738
M7 225: MPMRI for all men definition 2 cut-off 5; TRUSB definition 2 in men with suspicion of CS cancer. Re-biopsy with TRUSB definition 2 those in whom CS cancer was not detected	£3,867
M3 224: MPMRI for all men definition 2 cut-off 4; TRUSB definition 2 in men with suspicion on CS cancer; Men with CNS at 1st biopsy receive 2nd TRUSB definition 2.	£3,921
M4 224: MPMRI for all men definition 2 cut-off 4; TRUSB definition 2 in men with suspicion of any cancer. Men with suspicion of CS cancer at MPMRI and in whom CNS cancer was detected at the 1st biopsy receive 2nd TRUSB definition 2.	£4,031
M7 224: MPMRI for all men definition 2 cut-off 4; TRUSB definition 2 in men with suspicion of CS cancer. Re-biopsy with TRUSB definition 2 those in whom CS cancer was not detected but MPMRI had suspicion of CS cancer	£4,250
T6 223: TRUSB definition 2 for all men; Men classified as CNS receive a MRI definition 2 cut-off 3. Men with suspicion of CS cancer receive a 2nd TRUSB definition 2.	£4,393

T6 222: TRUSB definition 2 for all men; Men classified as CNS receive a MRI definition 2 cut-off 2. Men with suspicion of CS cancer receive a 2nd TRUSB definition 2.	£4,633
M7 223: MPMRI for all men definition 2 cut-off 3; TRUSB definition 2 in men with suspicion of CS cancer. Re-biopsy with TRUSB definition 2 those in whom CS cancer was not detected	£5,501
T7 223: TRUSB definition 2 for all men; Men classified as NC or CNS receive a MPMRI definition 2 cut-off 3. Men with suspicion of CS cancer receive a 2nd TRUSB definition 2.	£5,778
M7 222: MPMRI definition 2 cut-off 2 for all men; TRUSB definition 2 in men with suspicion of CS cancer. Re-biopsy with TRUSB definition 2 those in whom CS cancer was not detected but MPMRI had suspicion of CS cancer.	£7,076
P4 2: TRUSB definition 2 in all men and TPMB in men in whom CS cancer was not detected.	£30,084