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Review – Prostate Cancer

Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis

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Abstract

Context: Magnetic resonance imaging (MRI), with or without MRI-targeted biopsy (MRI pathway), is an alternative test to systematic transrectal ultrasonography-guided biopsy in men suspected of having prostate cancer. At present, evidence on which test to use is insufficient to inform detailed evidence-based decision making.
Objective: To determine the diagnostic accuracy of the index tests MRI only, MRI-targeted biopsy, MRI pathway, and systematic biopsy, as compared with template-guided biopsy (reference standard), in detecting clinically significant prostate cancer, defined as International Society of Urological Pathology grade 2 or higher, in biopsy-naive men or those with a prior-negative biopsy (or mix of both).
Evidence acquisition: We systematically searched the literature and considered for inclusion any cross-sectional study if it investigated (1) one or more index tests verified by the reference standard, and (2) paired testing of the MRI pathway with systematic biopsy. Quality and certainty of evidence were assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) and Grading of Recommendations Assessment, Development and Evaluation, respectively.
Evidence synthesis: *Accuracy analyses:* Using a baseline cancer prevalence of 30%, MRI pathway (sensitivity 0.72 [95% confidence interval {CI}: 0.60–0.82]; specificity 0.96 [0.94–0.98]; eight studies) may result in 216 (180–246) true positives, 28 (14–42) false positives, 672 (658–686) true negatives, and 84 (54–120) false negatives per 1000 men. Systematic biopsy (sensitivity 0.63 [0.19–0.93]; specificity 1.00 [0.91–1.00];

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four studies) may result in 189 (57–279) true positives, 0 (0–63) false positives, 700 (637–700) true negatives, and 111 (21–243) false negatives per 1000 men. *Agreement analyses:* With a direct comparison of the MRI pathway with systematic biopsy concerning significant disease, we found pooled detection ratios of 1.05 (95% CI: 0.95–1.16; 20 studies) in biopsy-naive men and 1.44 (1.19–1.75; 10 studies) in men with a prior-negative biopsy. Concerning insignificant disease, we found detection ratios of 0.63 (95% CI: 0.54–0.74), and 0.62 (95% CI: 0.44–0.88), respectively.
Conclusions: MRI pathway had the most favourable outcome in significant and insignificant prostate cancer detection compared with systematic biopsy. The certainty in our findings was reduced by study limitations.
Patient summary: We reviewed recent advances in prostate biopsy by magnetic resonance imaging (MRI) guidance and targeting for prostate cancer detection in comparison with standard diagnosis by systematic biopsies. The findings of this Cochrane review suggest that MRI pathway is better than systematic biopsies in making a correct diagnosis of clinically important prostate cancer and reducing redundant biopsies and the detection of unimportant cancers substantially. However, MRI pathway still misses some men with important prostate cancer. Therefore, further research in this area is important.

1. Introduction

To reduce overdiagnosis and overtreatment of indolent prostate cancer, while improving the detection of clinically significant prostate cancer and reducing the number of biopsy procedures, we need more accurate diagnostic methods and better risk stratification [1]. In a recent international multicentre randomised controlled trial, magnetic resonance imaging (MRI) in combination with MRI-targeted biopsy (MRI pathway) detected an absolute 12% more clinically significant prostate cancer and 13% less indolent prostate cancer than systematic biopsy in biopsy-naive men, and achieved 28% reduction of biopsies, because men with negative MRI did not receive prostate biopsy [2]. These results indicate that prebiopsy MRI and MRI-targeted biopsy in the presence of an MRI-suspicious lesion would be superior to a systematic biopsy. If this is confirmed by other studies and longer follow-up of men who were not biopsied, it may initiate a change to guidelines.

Previous systematic reviews on diagnostic performances of the MRI pathway or prebiopsy MRI approach [3–11] have been based on study designs that did not accurately capture target conditions and index or reference test definitions, leading to a number of biases and inaccurate findings. Studies in these reviews included mainly men with positive MRI and disregarded men with negative MRI, inevitably leading to inaccurate true- and false-negative values of the MRI pathway. In addition, these reviews used systematic biopsy or radical whole-mount surgical specimens as reference standards, which inherently have a number of biases. Furthermore, the established definitions of clinically significant prostate cancer, based on histology from systematic biopsy and possibly additional nonhistological parameters, cannot be applied to results from the MRI pathway [12]. In this (copublished) Cochrane review and meta-analysis [13] we have largely overcome these limitations.

2. Evidence acquisition

For further detailed information on methods, we refer to the original Cochrane review [13].

2.1. Objectives

We aimed to determine the diagnostic accuracy of the index tests MRI only, MRI-targeted biopsy, MRI pathway (MRI with or without MRI-targeted biopsy), and systematic biopsy, as compared with template-guided biopsy as the reference standard, in detecting International Society of Urological Pathology (ISUP) grade 2 or higher (primary target condition), grade 3 or higher, and grade 1 prostate cancer (secondary target condition). Furthermore, we aimed to determine the agreement and disagreement, and the potential change in the number of biopsy procedures between the two index tests, MRI pathway, and systematic biopsy, for detecting the primary and secondary target conditions.

2.2. Inclusion criteria

2.2.1. Types of studies

We considered any cross-sectional study, if it investigated (Fig. 1) the following: (1) diagnostic test accuracy of one or more of the index tests (MRI, MRI pathway;including MRI-targeted biopsy], or systematic biopsy) verified by the reference standard (template-guided biopsy), with each index test and reference standard performed in the same men or compared as in a randomised trial of test accuracy; or (2) agreement evidence between the MRI pathway and systematic biopsy, with each test performed in the same men.

Studies involving MRI had to report on both MRI-positive and MRI-negative men. The primary target condition had to be reported on a per-participant basis for all studies (Fig. 2).

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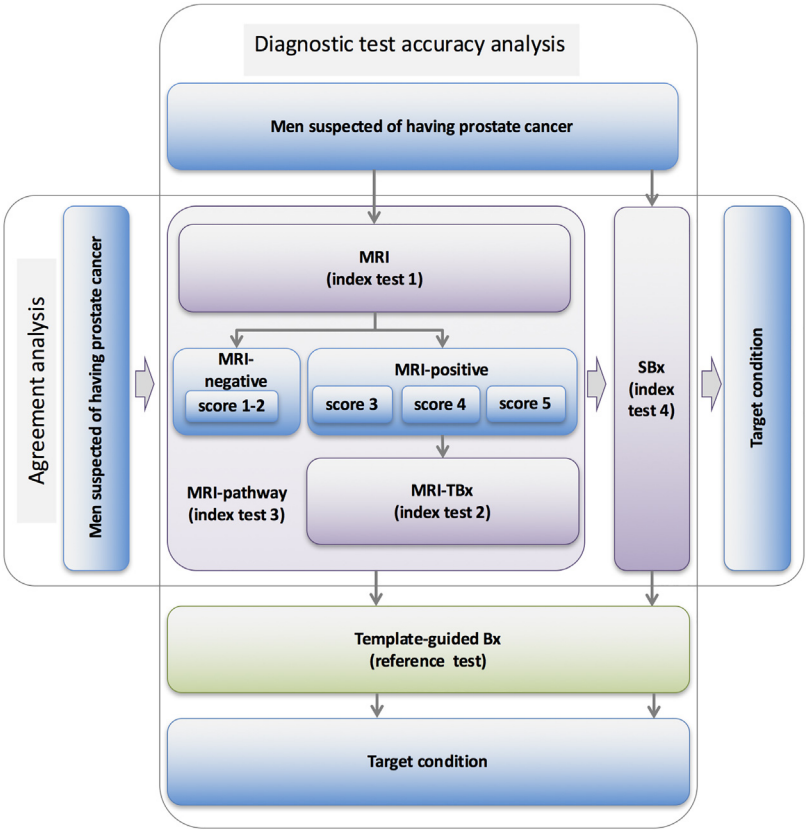

Fig. 1 – Clinical pathway flow diagram and study design.

2.2.2. *Study population*

The study population consisted of men with a clinical suspicion of prostate cancer (based on prostate-specific antigen or digital rectal examination outcome) in the biopsy-naive or prior-negative biopsy setting (or a mix of both).

2.2.3. *Index tests*

MRI (index test 1) comprised at least T2-weighted imaging and one functional imaging technique (diffusion-weighted imaging or dynamic contrast-enhanced imaging), reported according to any MRI-scoring system, mainly based on a five-point scale (Likert or Prostate Imaging Reporting and Data System) [14,15]. We defined the default threshold for MRI-positivity as 3/5 or more where possible. MRI-targeted biopsy (index test 2) included only MRI-positive men. The MRI pathway (index test 3) included MRI-positive men (in whom MRI-targeted biopsy was performed) and MRI-negative men (in whom no MRI-targeted biopsy was performed). Systematic biopsy (index test 4) included either systematic transrectal or transperineal ultrasound-guided biopsies. We defined the MRI pathway and systematic biopsy as positive when histopathology of one of the target conditions in the biopsy cores was confirmed.

2.2.4. *Reference standard*

Template-guided biopsy, including transperineal template-guided mapping biopsy and the template-guided saturation biopsy, served as the reference standard [16,17]. We defined a positive template-guided biopsy as histopathological confirmation of one of the target conditions within the biopsy cores.

2.2.5. *Target conditions*

We solely focused on target conditions based on histological definitions according to the ISUP grading, as was recommended by International Working Group on Standards of Reporting for MRI-targeted biopsy studies (START) in order to overcome differences between definitions and biopsy methods [18]. The primary target condition was clinically significant prostate cancer, defined as ISUP grade 2 or higher based on histopathology findings, and scored as Gleason score (GS) 3 + 4 or higher [19]. Secondary target conditions were grade 1 (GS 3 + 3, indolent prostate cancer) and grade 3 or higher (GS 4 + 3 or higher).

2.3. *Search strategy*

We performed a comprehensive search with no restriction on language or status of publication (including on-going studies), in electronic databases (CENTRAL, MEDLINE, Embase, and nine other databases), and updated to 31 July 2018 (Supplementary material, Appendix 1).

2.4. *Data collection and analysis*

2.4.1. *Selection of studies, data extraction, and management*

Two reviewers independently screened all abstracts and full-text articles for eligibility, and extracted data using a

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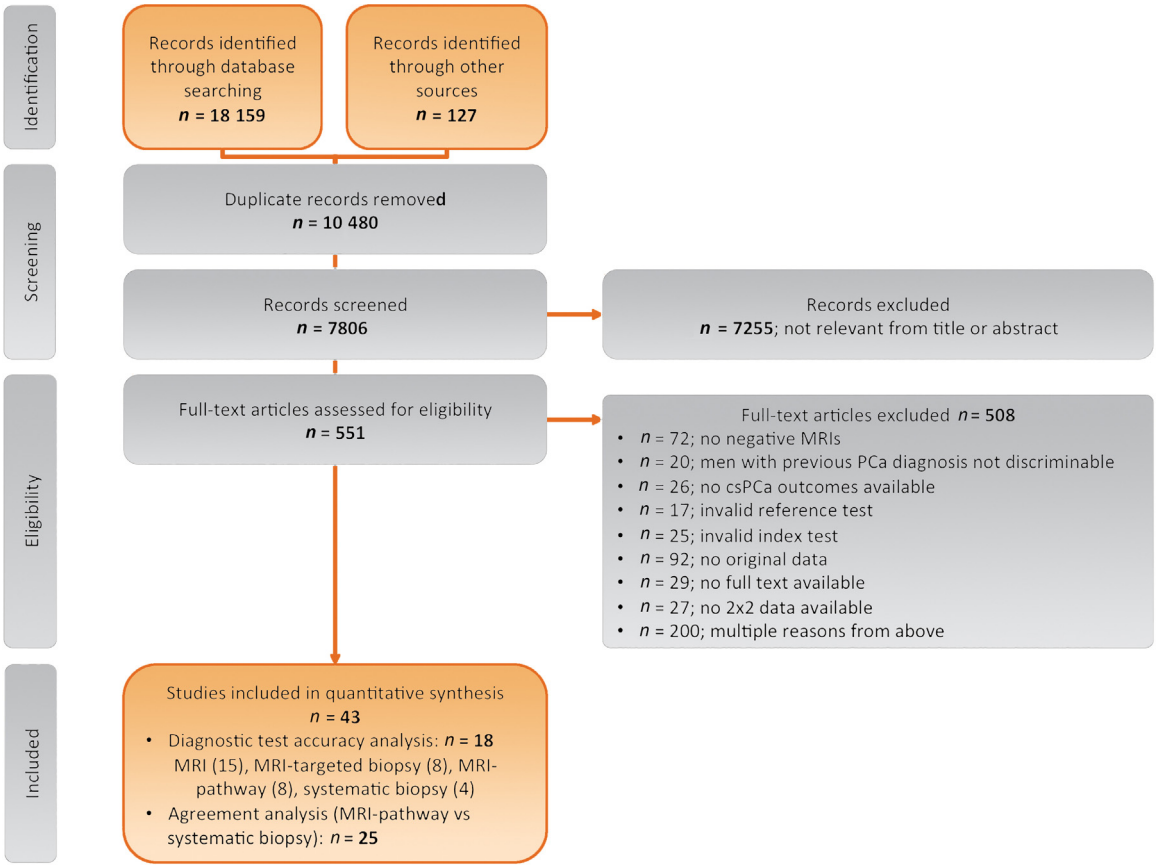

Fig. 2 – Study flowchart. csPCa = clinically significant prostate cancer; MRI = magnetic resonance imaging; MRI pathway = magnetic resonance imaging with subsequent magnetic resonance imaging-targeted biopsy; PCa = prostate cancer.

predefined data-extraction form. We constructed two-by-two tables for cross-classification of the index tests versus reference standard for test accuracy data and the MRI pathway versus systematic biopsy for agreement data, based on per-participant data (Supplementary material, Appendix 2).

2.4.2. *Assessment of methodological quality*

Two reviewers independently assessed all included studies for methodological quality using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool [20], tailored to this Cochrane review [13].

2.4.3. *Statistical analysis and data synthesis*

For the test accuracy analysis, we calculated pooled estimates of sensitivity and specificity using the bivariate model [21]. For the agreement analysis (MRI pathway vs systematic biopsy), we calculated the proportion of detected cases (total number of cancers) as the number of concordant positive results plus the number of discordant positive results of both tests (Supplementary material, Appendix 2). We calculated the detection rate of either test as the number of positive results of that test divided by the total number of cancers detected. We synthesised pooled estimates of detection ratios (detection rate of MRI pathway/detection rate of systematic biopsy) by performing random-effect meta-analyses. We used mixed models (multinomial logistic regression models with a random intercept for study effects) to calculate pooled proportions of concordance and discordance between tests (Cochrane review [13]). Added value (discordance) data were constructed such that we assessed the tests as add-on tests (ie, considering reclassification by each test; Supplementary material, Appendix 3). We used Statistical Analysis Software (SAS), version 9.3, for Windows and R version 3.5.0 to perform all statistical analyses.

2.4.4. *Investigations of heterogeneity and sensitivity analyses*

To explore sources of heterogeneity, we assessed covariates by adding them one by one in our bivariate model: population setting, MRI magnet strength, MRI sequences, MRI-positivity threshold, endorectal coil, MRI-targeted biopsy method, biopsy approach, and radiologists' experience. We tested the same covariates using meta-regression techniques for the detection ratio in the agreement analysis.

2.4.5. *Certainty of evidence*

We rated the certainty of evidence on a per-outcome basis according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance for studies of diagnostic accuracy [22]. For the four main

comparisons, we rated the certainty of evidence using GRADEpro GDT.

3. Evidence synthesis

For further detailed information on results, we refer to the original Cochrane review [13].

3.1. Results of the search

A total of 43 studies were eligible for inclusion in this review (Fig. 1) and provided data for multiple tests (Supplementary material, Appendix 4). Eighteen studies addressed the test accuracy analysis (index tests vs reference standard): 15 studies on MRI, eight studies on MRI, MRI-targeted biopsy, and MRI pathway in the same men and four studies on systematic biopsy (Table 1). These studies included 6871 men, of whom 5075 were biopsy naive, and 1796 had a history of at least one prior-negative biopsy. Twenty-five studies addressed the agreement analysis between MRI pathway and systematic biopsy in detecting prostate cancer with 6944 men, of whom 5353 were biopsy naive and 1591 had a history of at least one prior-negative biopsy (Table 1).

3.2. Methodological quality of included studies

As a result of QUADAS-2 assessment (Supplementary Fig. 2), we acknowledge overall concerns about the independence and applicability of tests in both test accuracy and agreement analyses, for which we performed sensitivity analyses to exclude studies with such quality concerns.

3.3. Findings

3.3.1. Test accuracy analysis (index tests verified by reference standard)

3.3.1.1. Detection of grade 2 or higher prostate cancer. MRI (pooled sensitivity of 0.91 [95% confidence interval {CI} 0.83–0.95], specificity of 0.37 [0.29–0.46]; 12 studies, 3091 men; Table 2) at a baseline prevalence of 30% (300/1000) may result in 273 (249–285) true positives, 441 (378–497) false positives, 259 (203–322) true negatives, and 27 (15–51) false negatives per 1000 men (Table 3). Hence, MRI did not identify 9% (27/300) of men with grade 2 or higher prostate cancer.

These accuracy and predictive metrics are also presented for the index tests MRI-targeted biopsy, MRI pathway, and systematic biopsy (Tables 2 and 3). MRI-targeted biopsy, MRI pathway, and systematic biopsy missed, respectively, 20% (60/300), 28% (84/300), and 37% (111/300) of men with grade 2 or higher prostate cancer at the prevalence of 30% (300/1000), identified by the reference standard. Implications of these results, taking into account each step in the MRI pathway (MRI with subsequent MRI-targeted biopsy in MRI-positive men only) and systematic biopsy, are shown in Fig. 3.

A comparison of MRI with MRI pathway showed a substantial decrease in sensitivity (from 0.91 to 0.72; Fig. 4) and an increase in specificity (from 0.37 to 0.96), which were both statistically significant ($p < 0.01$; Table 2). Comparing MRI pathway with systematic biopsy showed a substantial decrease in sensitivity (0.72 vs 0.63; $p = 0.06$; Table 2) and similar specificities (Fig. 4).

At a baseline prevalence of 30% grade 2 or higher prostate cancer, the negative predictive values for MRI, MRI-targeted biopsy, MRI pathway, and systematic biopsy are 91% (86–94%), 92 (88–94%), 89% (85–92%), and 86% (65–95%), respectively (Table 2). Consequently, in the MRI pathway, negative MRI falsely predicts the absence of grade 2 or higher prostate cancer in 9% of men, while a negative systematic biopsy falsely predicts the absence of grade 2 or higher prostate cancer in 14% of men.

3.3.1.2. Detection of grade 1 prostate cancer. The pooled sensitivity and specificity for detecting grade 1 prostate cancer of all index tests are shown in Table 2. Comparing the sensitivity of the MRI pathway and systematic biopsy, the MRI pathway potentially avoided the detection of 66% of men with grade 1 prostate cancer, whereas systematic biopsy potentially avoided 45% of men with grade 1 prostate cancer ($p = 0.52$).

3.3.1.3. Detection of grade 2 or higher prostate cancer at a higher MRI-positive threshold. In clinical practice, lesions with an MRI suspicion score of 3 (likelihood for clinically significant cancer is equivocal [23]) might or might not be targeted with biopsies. By increasing the threshold of MRI positivity from 3/5 to 4/5, the proportion of negative MRI increased from 30% (23–38%) to 59% (43–74%). The pooled sensitivity of MRI for detecting grade 2 or higher prostate cancer decreased from 0.89 (0.82–0.94) to 0.72 (0.52–0.86). The pooled specificity increased from 0.39 (0.32–0.47) to 0.78 (0.68–0.86). Consequently, with a threshold 4/5 for MRI positivity, negative MRI missed identifying 28% of men with grade 2 or higher prostate cancer.

3.3.2. Agreement analysis between MRI pathway and systematic biopsy

In this section, we focused on agreement and disagreement (concordance and discordance) in the number of target conditions identified by the MRI pathway and systematic biopsy.

3.3.2.1. Detection of grade 2 or higher prostate cancer. In a mixed population (of biopsy-naive and prior-negative biopsy men), the pooled detection ratio of grade 2 or higher prostate cancer was 1.12 (1.02–1.23; 25 studies, 6944 men), meaning that the MRI pathway increased the detection rate of grade 2 or higher prostate cancer by 12% compared with systematic biopsy.

For men in the biopsy-naive setting, cancer proportion (total prostate cancer detected by both tests) was 27.7% (23.7–32.6%; 20 studies, 5219 men) versus prior-negative biopsy setting of 22.8% (20.0–26.2%; 10 studies, 1564 men; Table 4). The pooled detection ratios for grade 2 or higher prostate cancer were 1.05 (0.95–1.16), and 1.44 (1.19–1.75), respectively ($p < 0.01$; Fig. 5). When focusing on only MRI-positive men in both subgroups, the pooled detection ratio

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Table 1 – Characteristic of the diagnostic test accuracy and agreement studies

Study	Tests						Target condition	Recruitment			Patient characteristics			
	Index tests				Reference standard									
Author (year)	Index tests analysed	MRI scale; threshold	MRI TBx, technique	Route	Technique	Independence	ISUP grade (G)	Study design[a]	Consecutive enrolment	Population	No. of participants	Median age (range/SD)	Median PSA ng/ml (range)	Median prostate volume cm^3 (range)
Diagnostic test accuracy studies														
Abd-Alazeez (2014)	MRI	1–5; ≥3	Cognitive	Transperineal	TTMB	No	G = 1, ≥1, ≥2, ≥3	Retrospective	No	Prior-negative Bx	54	64 (39–75)	10 (2–23)	53 (19–136)
Ahmed (2017)	MRI, SBx	1–5; ≥3	NA	Transrectal	TTMB	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	576	63 (7.6)[b]	7.1 (2.9)[b]	NR
Dal Moro (2019)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Cognitive	Transrectal	TSB[c]	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Prior-negative Bx	123	62 (57–68[d])	6.3 (4.8–8.9[d])	55 (20–149)[b]
Distler (2017)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Software	Transperineal	TSB[e]	No	G ≥ 2	Prospective	Yes	Mixed[f]	1040 (597/443)	65 (60–71[d])	7.2 (5.3–10.4[d])	45 (34–64[d])
Grey (2015)	MRI	1–5; ≥3	Cognitive	Transperineal	TSB[e]	No	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Mixed [f]	83	64 (6.8)[b]	13.3 (12.1)[b]	68 (35)[b]
											103	65 (7.6)[a]	12.6 (13.7)[a]	54 (31)[a]
Hansen (2016)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Software/ transperineal	Transperineal	TSB[e]	Unclear	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Prior-negative Bx	295	65 (59–69[d])	7.8 (6.0–12[d])	65 (44–83[d])
Hansen (2018)	MRI	1–5; ≥3	Software	Transperineal	TSB[e]	No	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive (centre 1)	163	64 (57–69[d])	6.6 (4.6–9.0[d])	44 (33–55[d])
			Cognitive							Bx naive (centre 3)	242	65 (60–70[d])	5.9 (4.6–8.0 [d])	25 (24–47[d])
Hansen (2017)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Software/ transperineal	Transperineal	TSB[e]	Unclear	G ≥ 2	Prospective	Unclear	Prior-negative Bx	287	66 (61–72[d])	9.7 (7.1–13.9[d])	52 (36–75[d])
Kesch (2017)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Software/ transperineal	Transperineal	TSB[g]	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Unclear	Mixed [f]	146 (95/51)	65 (58–71[d])	7.2 (5.4–10.2[d])	46 (36–60[d])
Lawrence (2014)	MRI, MRI TBx, MRI pathway	1–4; ≥2	Software	Transperineal	TSB[e]	No	G = 1, ≥1, ≥2	Retrospective	No	Prior-negative Bx	39	64 (47–77)[b]	10 (1.2–36)	NR
Mortezavi (2018)	MRI, MRI TBx, MRI pathway	1–5; ≥3	Software	Transrectal	TSB	No	G = 1, ≥1, ≥2, ≥3	Retrospective	Yes	Bx naive	163	63 (57–68[d])	5.8 (4.4–8.9[d])	44 (34–60[d])
										Prior-negative Bx	86	64 (60–69[d])	8.6 (5.7–13[d])	54 (41–70[d])
Muthuveloe (2016)	MRI	1–5; ≥3	NA	NA	TSB[h]	Unclear	G = 1, ≥1, ≥2, ≥3	Retrospective	Unclear	Bx naive	9	68 (46–81)	11.5 (1.2–92.5)	NR
										Prior-negative Bx	162	65 (47–78)	10 (2.7–61)	NR
Pepe (2013)	MRI, MRI TBx, MRI pathway	0–1: ≥1	Cognitive	Transrectal	TSB[h]	No	G = 1, ≥1, ≥2	Prospective	Unclear	Prior-negative Bx	78	63 (49–72)	11 (3.7–45)	NR
Thompson (2016)	MRI	1–5; ≥3	Software, cognitive	Transperineal	TTMB	No	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	344	63 (56–67[d])	5.2 (3.7–7.1[d])	40 (30–54[d])
Tsivian (2017)	MRI	1–5; ≥3	NA	NA	TTMB	Yes	G = 1, ≥1, ≥2, ≥3	Retrospective	Unclear	Prior-negative Bx	33	65 (61–69[d])	7.1 (5.1–13.6[d])	44 (32–65[d])
Nafie (2014)	SBx	NA	NA	Transrectal	TSB[h]	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Unclear	Bx naive	50	67 (54–84)[b]	8 (4–18)[b]	58 (19–165)[b]

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Table 1 (*Continued*)

Study	Tests						Target condition	Recruitment			Patient characteristics			
	Index tests				Reference standard									
Author (year)	Index tests analysed	MRI scale; threshold	MRI TBx, technique	Route	Technique	Independence	ISUP grade (G)	Study design[a]	Consecutive enrolment	Population	No. of participants	Median age (range/SD)	Median PSA ng/ml (range)	Median prostate volume cm^3 (range)
Nafie (2017)	SBx	NA	NA	Transrectal	TSB[h]	Yes	G = 1, ≥1, ≥2	Prospective	Unclear	Prior-negative Bx	42	65 (50–75)[b]	8.3 (4.4–19)[b]	59 (21–152)[b]
Ploussard (2014)	SBx	NA	NA	Transrectal	TSB[c]	No	G = 1, ≥1, ≥2	Prospective	Yes	Bx naive	2753	64 (8)[b]	12.5 (7.2)[b]	46 (25)[b]
Agreement studies														
Alberts (2017)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	74	73 (72–74[d])	4.2 (3.4–5.8[d])	53 (37–71[d])
										Prior-negative Bx	84			
Boesen (2017)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Unclear	Prior-negative Bx	206	65 (58–68[d])	12.8 (8.9–19.6[d])	NR
Boesen (2018)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	1020	67 (61–71[d])	8 (5.7–13[d])	53 (40–72[d])
Castellucci (2017)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transrectal	NA	Unclear	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	168	61 (8)[f]	8.3 (6.1)[f]	49 (7)[f]
Chang (2017)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Retrospective	Yes	Prior-negative Bx	65	64 (60–68[d])	10.9 (7.2–14.7[d])	48 (34–63[d])
Chen (2015)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transperineal	NA	Yes	G ≥ 2	Prospective	Yes	Bx naive	420	67 (45–91)	9.7 (2.4–35.7)	45 (21–83)
Cool (2016)	MRI pathway vs SBx	Other	Software	Transrectal	NA	Unclear	G = 1, ≥1, ≥2	Prospective	Unclear	Bx naive	50	59 (8)[f]	6.0 (3.5)[f]	38 (18)[f]
										Prior-negative Bx	50	62 (7)[f]	7.9 (3.9)[f]	56 (27)[f]
Costa (2013)	MRI pathway vs SBx	1–5; ≥4	Cognitive	Transrectal	NA	No	G ≥ 2, ≥3	Retrospective	No	Prior-negative Bx	38	64 (48–77)[f]	14.4 (1.8–33.1)[f]	NR
Delong-champs (2013)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Unclear	G ≥2	Prospective	Yes	Bx naive	391	64 (7)[f]	8.5 (3.9)[f]	56 (30)[f]
Filson (2016)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Unclear	G ≥ 2, ≥3	Prospective	Yes	Bx naive	329	64 (59–69[d])	5.8 (4.4–8.1[d])	45(33–62[d])
										Prior-negative Bx	324	66 (59–70[d])	7.6 (5–11.5[d])	58 (40–84[d])
Garcia Bennett (2017)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transperineal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Unclear	Bx naive	60	64 (6.7)[f]	7.2 (6–9.4[d])	48 (35–63[d])
Grönberg (2018)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	387	64 (45–74)[f]	6.3 (4.4[d])	(32–70)[i]
										Prior-negative Bx	145			
Jambor (2015)	MRI pathway vs SBx	1–5; ≥4	Cognitive	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Unclear, unclear	Unclear	Bx naive	53	66 (47–76)	7.4 (4–14)	42 (17–107)
Jambor (2017)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Prospective	Unclear	Mixed	134	65 (6)[f]	7.5 (5.7–9.6[d])	37 (28–49[d])

Table 1 (*Continued*)

Study	Tests						Target condition	Recruitment			Patient characteristics			
	Index tests				Reference standard									
Author (year)	Index tests analysed	MRI scale; threshold	MRI TBx, technique	Route	Technique	Independence	ISUP grade (G)	Study design[a]	Consecutive enrolment	Population	No. of participants	Median age (range/SD)	Median PSA ng/ml (range)	Median prostate volume cm^3 (range)
											27			
Kim (2017)	MRI pathway vs SBx	1–5; ≥4	Software, cognitive	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Retrospective	Unclear	Bx naive	183	64 (7)[f]	10.2 (15.1)[f]	NR
										Prior-negative Bx	154			
Lee (2016)	MRI pathway vs SBx	1–4; ≥2	Cognitive	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Retrospective	Unclear	Bx naive	76	66 (43–83)	6.4 (3.3–9.8)	39 (17–127)
Lee (2017)	MRI pathway vs SBx	1–4; ≥2	Cognitive	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Retrospective	Unclear	Bx naive	123	62 (10)[f]	6.4 (1.8)[f]	40 (18)[f]
Okcelik (2016)	MRI pathway vs SBx	0–1: ≥1	Cognitive	Transrectal	NA	Unclear	G = 1, ≥1, ≥2	Prospective	Unclear	Bx naive	52	62 (43–79)	5 (3–8.9)	45 (17–93)
Panebianco (2018)	MRI pathway vs SBx	1–5; ≥3	Cognitive	Transrectal	NA	Unclear	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	570	64 (51–82)	NR	NR
										Prior-negative Bx	355			
Peltier (2015)	MRI pathway vs SBx	1–4; ≥2	Software	Transrectal	NA	No	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	110	65 (7)[f]	8.4 (6.3)[f]	49 (22)[f]
Pokorny (2014)	MRI pathway vs SBx	1–5; ≥3	In-bore	Transrectal	NA	Unclear	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	223	63 (57–68[d])	5.3 (4.1–6.6[d])	41 (30–59[d])
Rouvière (2019)	MRI pathway vs SBx	1–5; ≥3	Software	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	251	64 (59–68[d])	6.5 (5.6–9.6[d])	50 (38–63[d])
Say (2016)	MRI pathway vs SBx	1–4; ≥2	Software	Transrectal	NA	Unclear	G = 1, ≥1, ≥2, ≥3	Retrospective	Yes	Prior-negative Bx	143	64 (47–82)[f]	11.59 (0.4–96.9)[f]	69 (17–309)[f]
Tonttila (2016)	MRI pathway vs SBx	1–4; ≥2	Cognitive	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	53	63 (60–66[d])	6.1 (4.2–9.9[d])	28 (24–37[d])
Van der Leest (2018)	MRI pathway vs SBx	1–5; ≥3	In-bore	Transrectal	NA	Yes	G = 1, ≥1, ≥2, ≥3	Prospective	Yes	Bx naive	626	65 (59–68[d])	6.4 (4.6–8.2[d])	55 (41–77[d])

Bx = biopsy; ISUP G = International Society of Urological Pathology grade; MRI = magnetic resonance imaging; MRI pathway = magnetic resonance imaging with or without magnetic resonance imaging-targeted biopsy; MRI TBx = magnetic resonance imaging-targeted biopsy; N = number; NA = not applicable; NR = not reported; PSA = prostate-specific antigen; SBx = systematic biopsy; SD = standard deviation; TSB = transperineal saturation biopsy; TTMB = transperineal template mapping biopsy.

[a] Included participants were part of the same study cohort (no randomised populations were included).
[b] Included participants were part of the same study cohort (no randomised populations were included).
[c] Transrectal.
[d] Interquartile range (as opposed to range).
[e] Ginsburg biopsies.
[f] Mean value (as opposed to median value).
[g] Transperineal optimised prostate biopsy.
[h] In-house transperineal saturation biopsy.
[i] Range of interquartile ranges across three centres.

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Table 2 – Diagnostic accuracy and predictive metrics of the index tests verified by template-guided biopsy as the reference standard for different target conditions

Target condition	Index test[a]	No. of participants (studies)	Proportion negative MRI (95% CI)	Accuracy metrics			Prevalence[b] (95% CI)	Assumptive prevalence[c]	Predictive metrics	
				Sensitivity (95% CI)	Specificity (95% CI)	*p* value			NPV[d] (95% CI)	PPV[d] (95% CI)
ISUP G ≥ 2 prostate cancer	MRI	3091 (12)	0.29 (0.22–0.37)	0.91 (0.83–0.95)	0.37 (0.29–0.46)	$p < 0.01$[e]	0.29 (0.22–0.38)	0.30	0.91 (0.86–0.94)	0.38 (0.36–0.40)
	MRI Tbx[f]	1553 (8)	NA	0.80 (0.69–0.87)	0.94 (0.90–0.97)		0.34 (0.24–0.46)		0.92 (0.88–0.94)	0.85 (0.77–0.91)
	MRI pathway	2257 (8)	0.29 (0.24–0.35)	0.72 (0.60–0.82)	0.96 (0.94–0.98)	$p = 0.06$[g]	0.26 (0.18–0.36)		0.89 (0.85–0.92)	0.90 (0.83–0.94)
	SBx	3421 (4)	NA	0.63 (0.19–0.93)	1.00 (0.91–1.00)		0.34 (0.21–0.51)		0.86 (0.65–0.95)	1.00 (0.73–1.00)
ISUP G ≥ 3 prostate cancer	MRI	1438 (7)	0.31 (0.21–0.42)	0.95 (0.87–0.99)	0.35 (0.26–0.46)	ID[e]	0.14 (0.08–0.23)	0.15	0.98 (0.95–0.99)	0.21 (0.19–0.23)
	MRI Tbx[f]	428 (3)	NA	ID	ID		0.21 (0.12–0.35)		ID	ID
	MRI pathway	604 (3)	0.29 (0.26–0.33)	ID	ID	ID[g]	0.16 (0.09–0.27)		ID	ID
	SBx	626 (2)	NA	ID	ID		ID		ID	ID
ISUP G = 1 prostate cancer	MRI	1764 (10)	0.28 (0.20–0.38)	0.70 (0.59–0.80)	0.27 (0.19–0.37)	$p < 0.01$[e]	0.20 (0.17–0.23)	0.20	0.79 (0.74–0.82)	0.20 (0.18–0.21)
	MRI Tbx[f]	497 (5)	NA	0.51 (0.21–0.81)	1.00 (0.77–1.00)		0.22 (0.19–0.26)		0.89 (0.80–0.94)	0.97 (0.21–1.00)
	MRI pathway	681 (5)	0.24 (0.16–0.36)	0.34 (0.19–0.53)	1.00 (0.90–1.00)	$p = 0.52$[g]	0.21 (0.18–0.24)		0.86 (0.82–0.89)	0.95 (0.37–1.00)
	SBx	3421 (4)	NA	0.55 (0.25–0.83)	0.99 (0.81–1.00)		0.20 (0.16–0.25)		0.90 (0.81–0.95)	0.94 (0.37–1.00)

CI = confidence interval; ISUP G = International Society of Urological Pathology grade; ID = inadequate data; MRI = magnetic resonance imaging; MRI pathway = magnetic resonance imaging with or without magnetic resonance imaging-targeted biopsy; MRI TBx = magnetic resonance imaging-targeted biopsy; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; SBx = systematic biopsy.

[a] Data did not allow differentiation between the mix of included participants (biopsy-naive and prior-negative biopsy men).

[b] Prevalence is pooled estimate of all detected cancer by template-guided biopsy.

[c] Assumptive prevalence is an extrapolation from the pooled estimates of all detected cancer by template-guided biopsy per target condition. This assumptive prevalence is necessary for adequate comparison of PPVs and NPVs between index tests.

[d] Based on the Bayes' theorem using the point estimates and 95% confidence intervals of the pooled positive and negative likelihood ratio and the point estimate of the prevalence.

[e] Comparing sensitivity between MRI and the MRI pathway.

[f] MRI-positive men only, instead of MRI-positive + MRI-negative men, implicating a higher risk profile and increased prevalence of clinically significant prostate cancer.

[g] Comparing sensitivity between the MRI pathway and SBx.

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Table 3 – Summary of Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidance for diagnostic test accuracy of individual index tests

Population:	Men suspected of having clinically significant prostate cancer undergoing their first biopsy (biopsy-naive men) or a repeat biopsy (prior-negative biopsy men)
Setting:	University hospitals and specialised care centres
Reference test:	Template-guided biopsy, which comprehensively samples all zones of the prostate
Threshold:	ISUP grade ≥2 prostate cancer

Index test:	MRI	MRI-targeted biopsy	MRI pathway	Systematic biopsy
Threshold:	MRI score ≥3 out of 5	ISUP grade ≥2 prostate cancer	ISUP grade ≥2 prostate cancer	ISUP grade ≥2 prostate cancer
Population:	3091 (12)	1553 (8)	2257 (8)	3421 (4)
Pooled sensitivity:	0.91 (95% CI: 0.83–0.95)	0.80 (95% CI: 0.69–0.87)	0.72 (95% CI: 0.60–0.82)	0.63 (95% CI: 0.19–0.93)
Pooled specificity:	0.37 (95% CI: 0.29–0.46)	0.94 (95% CI: 0.90–0.97)	0.96 (95% CI: 0.94–0.98)	1.00 (95% CI: 0.91–1.00)
Results per 1000 men tested (95% CI): at a baseline prevalence of 30% ISUP grade ≥2 prostate cancer by the reference test				
True positives:	273 (249–285)	240 (207–261)	216 (180–246)	189 (57–279)
False negatives:	27 (15–51)	60 (39–93)	84 (54–120)	111 (21–243)
True negatives:	259 (203–322)	658 (630–679)	672 (658–686)	700 (637–700)
False positives:	441 (378–497)	42 (21–70)	28 (14–42)	0 (0–63)
Certainty of evidence (tp/fn):	●●○○ Low[a,b]	●●○○ Low[a,b]	●●○○ Low[a,b]	●●●○ Moderate[a,b,c]
Certainty of evidence (tn/fp):	●●○○ Low[a,b]	●●○○ Low[a,b]	●●○○ Low[a,b]	●●○○ Low[a,b,c]

CI = confidence interval; fn = false negative—test indicates that clinically significant prostate cancer is not present but patient actually has clinically significant prostate cancer; fp = false positive—test indicates clinically significant prostate cancer but patient actually does not have clinically significant prostate cancer; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; tn = true negative—test indicates that clinically significant prostate cancer is not present and patient actually does not have clinically significant prostate cancer; tp = true positive—indicates clinically significant prostate cancer and patient actually has clinically significant prostate cancer.

[a] A considerable number of studies had a high or unclear risk of bias, mainly in the participant selection and reference standard domains.

[b] Considerable, clinically relevant, heterogeneity was observed across pooled study results.

[c] Important imprecision was noted, which contributed to decision to downgrade for inconsistency.

increased from 1.05 to 1.12 (1.01–1.23) and from 1.44 to 1.49 (1.22–1.82), respectively.

3.3.2.2. Detection ratios for grade 1 prostate cancer. For men in the biopsy-naive and the prior-negative biopsy settings, cancer proportions of grade 1 prostate cancer were 27.2% (23.9–31.1%; 17 studies, 4079 men) and 23.0% (18.0–30.2%; eight studies, 1202 men), respectively; the pooled detection ratio was 0.63 (0.54–0.74) and 0.62 (0.44-0.88), respectively (Table 4).

3.3.2.3. Added values (discordance) in detection of grade 2 or higher prostate cancer. Per 100 biopsy-naive men, the MRI pathway detected approximately 23 men with grade 2 or higher prostate cancer (23.4% [19.4–28.2]; Table 4). In addition to the MRI pathway, systematic biopsy detected four additional men (4.3% [2.6–6.9%]). The total number of detected cases was 27 (27.7% [23.7–32.6%]). Conversely, systematic biopsy detected 21 men (21.4% [17.2–26.5%]) and the MRI-pathway detected six additional men (6.3% [4.8–8.2%]). Further details on mixed population and prior-negative biopsy men are shown in the Cochrane review [13].

3.3.2.4. Added values (discordance) in detection of grade 1 prostate cancer. Per 100 biopsy-naive men, the MRI pathway detected approximately 11 men with grade 1 prostate cancer (11.2% [8.4–14.9%]; Table 4). In addition to the MRI pathway, systematic biopsy detected 10 additional men (9.8% [8.0–11.8%]). The total number of detected cases was 21 (20.9% [18.0–24.7%]). Conversely, systematic biopsy detected 19 men (18.5% [15.6–22.2%]) and the MRI pathway detected two additional men (2.4% [1.4–4.0%]).

3.3.2.5. Added values (discordance) in detection of grade 2 or higher prostate cancer in MRI-positive and MRI-negative men. Stratifying men further into having positive or negative MRI aids in interpreting the added value in each of these categories. The pooled proportions of positive and negative MRI were respectively 67.0% (58.7–74.4%) and 33.0% (25.6–41.3%) in the biopsy-naive setting, and were equivalent in the prior-negative biopsy setting (Table 4).

Per 100 biopsy-naive men with positive MRI, the MRI pathway detected approximately 39 men with grade 2 or higher prostate cancer (39.2% [33.3–45.7%]). In addition to the MRI pathway, systematic biopsy detected five men (4.9% [2.8–8.3%]). The total number of detected cases was 44 (44.2% [38.6–50.4%]). Conversely, systematic biopsy detected 34 men (34.4% [28.3–41.3%]) and the MRI pathway detected 10 additional men (9.8% [7.1–13.2%]).

Per 100 biopsy-naive men with negative MRI, systematic biopsy detected eight additional men with grade 2 or higher prostate cancer (8.1% [5.6–11.6%]) and 18 additional men with grade 1 prostate cancer (18.4% [14.2–23.7%]).

3.4. Heterogeneity analyses and sensitivity analyses

For the test accuracy analyses (index tests vs reference standard [template-guided biopsy]), we observed considerable heterogeneity in all index tests (Cochrane review [13]). For the agreement analyses (MRI pathway vs systematic biopsy), the heterogeneity (total tau-square = 0.03) is illustrated in Figure 5. We found a statistically significant difference in the detection ratio of the MRI pathway versus systematic biopsy between the subgroups of population (prior-negative biopsy vs biopsy

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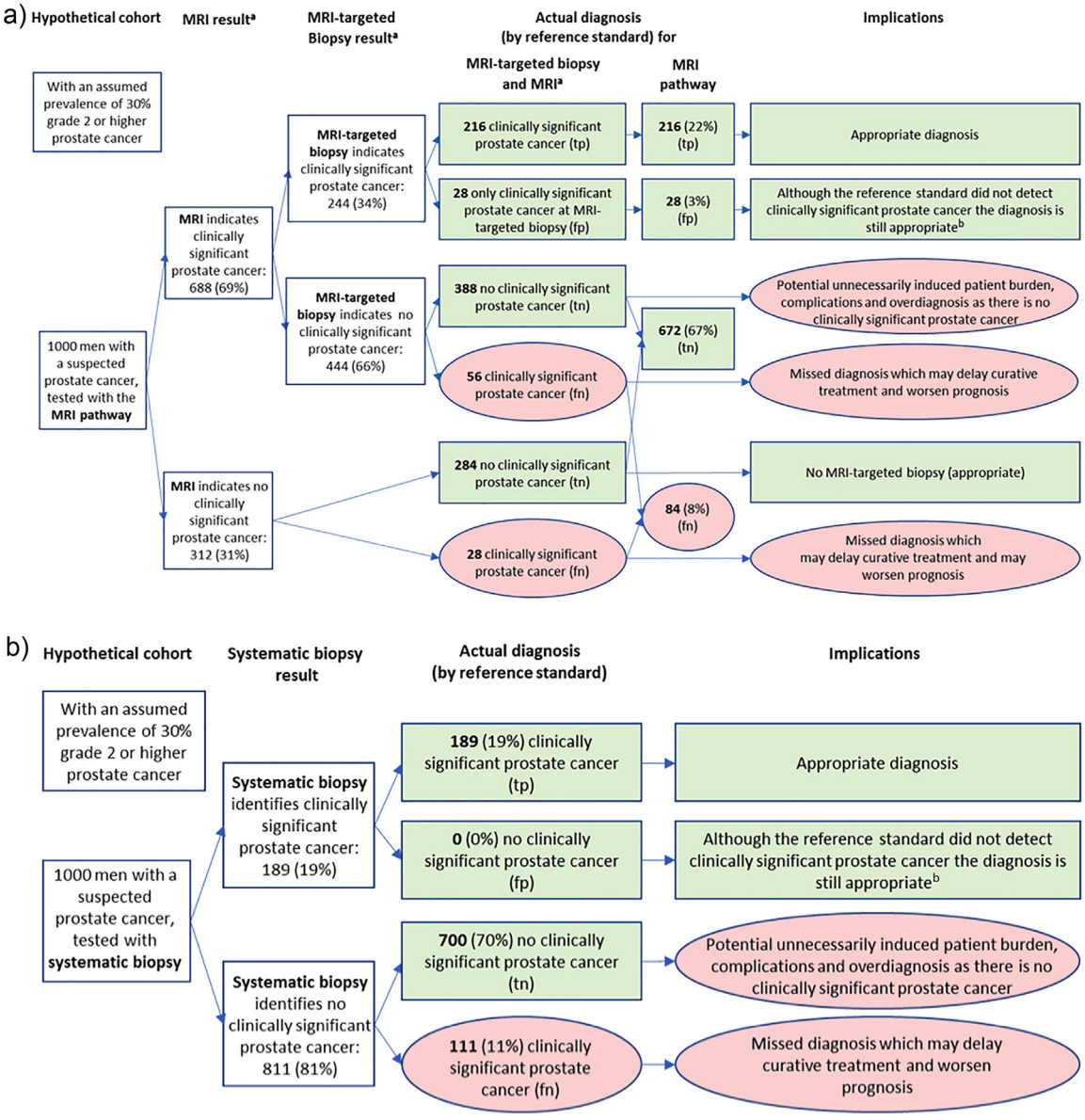


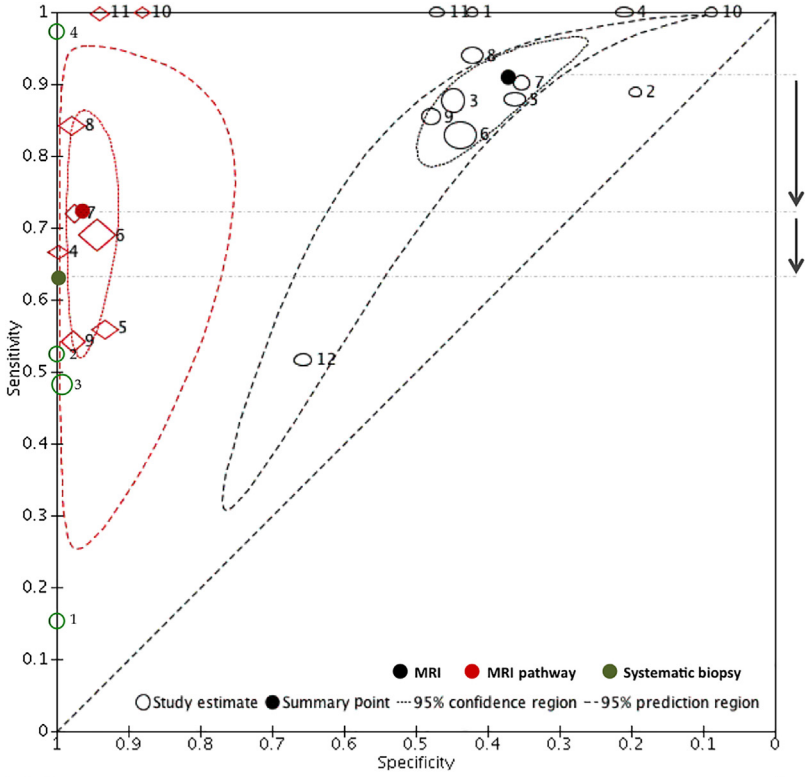
Fig. 3 – Test results and implications of a hypothetical cohort of 1000 men tested for prostate cancer using the (A) MRI pathway and (B) systematic biopsy. fn = false negative—test indicates that clinically significant prostate cancer is not present but patient actually has clinically significant prostate cancer; fp = false positive—test indicates clinically significant prostate cancer but patient actually does not have clinically significant prostate cancer; MRI = magnetic resonance imaging; tn = true negative—test indicates that clinically significant prostate cancer is not present and patient actually does not have clinically significant prostate cancer; tp = true positive—indicates clinically significant prostate cancer and patient actually has clinically significant prostate cancer. [a] The numbers in this figure are based on findings of the MRI pathway; therefore, MRI and MRI-targeted biopsy results differ slightly from the numbers in Table 3. [b] Diagnoses by the MRI pathway and reference standard are based on biopsy histopathology, with equal chance of up- or downgrading following radical prostatectomy.

naive), suggesting that they may be sources of heterogeneity (Cochrane review [13]).

We performed sensitivity analyses for the detection of grade 2 or higher prostate cancer by excluding studies based on certain quality and additional criteria. Excluding studies with a high or an unclear risk of bias or applicability concern in one of the four QUADAS-2 domains did not substantially change the accuracy results of MRI, MRI-targeted biopsy, and the MRI pathway (Cochrane review [13]).

3.5. Discussion

This copublished Cochrane review presents the test accuracy of prostate MRI, MRI-targeted biopsy, MRI pathway (MRI with or without MRI-targeted biopsy), and current standard testing with systematic biopsies in prostate cancer diagnosis, using template-guided biopsy sampling of the whole prostate as the reference standard. This analysis provides evidence to determine their discriminative value in current clinical practice. Both the MRI



Index test:	MRI	MRI pathway	Systematic biopsy
Threshold:	MRI score ≥ 3 out of 5	ISUP grade ≥ 2 prostate cancer	ISUP grade ≥ 2 prostate cancer
Population:	3091 (12)	2257 (8)	3421 (4)
Pooled sensitivity:	0.91 (95% CI: 0.83—0.95)	0.72 (95% CI: 0.60—0.82)	0.63 (95% CI: 0.19—0.93)
Pooled specificity:	0.37 (95% CI: 0.29—0.46)	0.96 (95% CI: 0.94—0.98)	1.00 (95% CI: 0.91—1.00)

Fig. 4 – Comparison of diagnostic test accuracy between MRI, MRI pathway, and systematic biopsy for detecting ISUP grade 2 and higher prostate cancer. Summary ROC plots of MRI, MRI pathway, and systematic biopsy, verified by template-guided biopsy, with references to included studies (see original review for further details [1]). A comparison of MRI with MRI pathway showed a substantial decrease in sensitivity (from 0.91 to 0.72) and an increase in specificity (from 0.37 to 0.96), both of which were statistically significant ($p < 0.01$; Table 3). A comparison of the MRI pathway with systematic biopsy showed a substantial decrease in sensitivity (from 0.72 to 0.63; $p = 0.06$; Table 3), and similar specificities. CI = confidence interval; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; ROC = receiver operating characteristics.

pathway and the systematic biopsy missed considerable proportions of grade 2 or higher prostate cancer, but the MRI pathway missed less than the systematic biopsy.

Furthermore, the agreement analyses for detecting prostate cancer between two index tests (the MRI pathway and the current practice of systematic biopsy) provide additional evidence for biopsy decision making, indicating that the MRI pathway is more favourable than systematic biopsy. The difference between the detection rates of the MRI pathway and systematic biopsy was largest in men with a prior-negative biopsy and insignificant in biopsy-naive men. Evidence further suggested that the MRI pathway beneficially missed more grade 1 prostate cancer than systematic biopsy in both population types. Therefore, the MRI pathway could potentially reduce the amount of overdiagnosis, and harms related to surveillance and overtreatment.

3.5.1. *MRI-directed biopsy management*

The benefits of using MRI (reducing biopsy procedures and the overdiagnosis of grade 1 prostate cancer with improving the detection of grade 2 and higher prostate cancer) are largest if MRI has a direct impact on biopsy decision management and shared decision making. In other words, the MRI before any biopsy and the MRI pathway as the replacement for systematic biopsy, thus omitting systematic biopsy in specified circumstances, might provide the most favourable diagnostic strategy.

Approximately one-third of all men had negative MRI. This is a substantially large population in whom additional systematic biopsies may potentially be avoided. Some expert centres even report up to 50% MRI-negative men, suggesting that an even larger population may benefit when experience in MRI reading may improve [24]. The added value of performing systematic biopsy in MRI-negative men for the detection of grade 2 or higher prostate cancer could be considered as limited with regard to total detection and additional harms. As a prostate biopsy is associated with patient burden, infection, morbidity, overdiagnosis, and related overtreatment, it should be avoided when possible. Omitting systematic biopsy in men with negative MRI might be considered acceptable in some clinical situations. However, benefits and harms are difficult to balance on an individual basis. Therefore, men with negative MRI could

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Table 4 – Agreement analysis of proportion of prostate cancer detected by the MRI pathway and systematic biopsy tests in biopsy-naive men

Population		Target condition (ISUP grade)	Patients (studies)	Proportion prostate cancer detected in % (95% CI)						Detection ratio (95% CI)[b]		Difference between populations, *p* value[c]
Biopsy status	MRI in % (95% CI)[a]			Combined MRI pathway + SBx (total cancer detected)	MRI pathway	SBx	Both MRI pathway and SBx	Only by MRI pathway (added value)	Only by SBx (added value)	MRI pathway versus SBx	*p* value	
Biopsy-naive men	Positive + negative (100 [100–100])	G = 1	4079 (17)	NA	13.5 (10.7–17.2)	22.4 (19.1–26.3)	NA	NA	NA	0.630 (0.535–0.742)	0.000	0.905
		G = 1[d]	4079 (17)	20.9 (18.0–24.7)	11.2 (8.4–14.9)	18.5 (15.6–22.2)	8.8 (6.2–12.3)	2.4 (1.4–4.0)	9.8 (8.0–11.8)	0.611 (0.485–0.769)	0.000	–
		G ≥ 1	4799 (19)	53.2 (48.7–57.9)	41.0 (35.8–46.4)	47.8 (42.8–52.9)	35.6 (30.2–41.2)	5.4 (3.6–8.0)	12.2 (8.7–16.7)	0.845 (0.767–0.930)	0.001	0.121
		G ≥ 2	5219 (20)	27.7 (23.7–32.6)	23.4 (19.3–28.1)	21.4 (17.2–26.5)	17.1 (13.0–22)	6.3 (4.8–8.2)	4.3 (2.6–6.9)	1.050 (0.948–1.162)	0.349	0.002
		G ≥ 3	4306 (16)	15.5 (12.6–19.5)	12.7 (9.9–16.5)	10.8 (8.0–14.8)	8.0 (5.4–11.6)	4.7 (3.5–6.3)	2.8 (1.7–4.8)	1.087 (0.937–1.261)	0.269	0.004
	Positive (67.0 [58.7–74.4])	G = 1	2682 (16)	NA	21.3 (17.0–26.9)	23.7 (19.6–29.1)	NA	NA	NA	0.854 (0.743–0.982)	0.026	0.347
		G = 1[d]	2682 (16)	21.1 (16.7–27.1)	17.0 (12.6–22.9)	17.7 (13.3–23.8)	13.6 (9.3–19.5)	3.4 (2.1–5.3)	4.1 (2.5–6.7)	0.909 (0.770–1.072)	0.257	–
		G ≥ 1	2955 (17)	70.9 (65.0–76.6)	63.7 (56.3–70.6)	63.8 (56.2–70.7)	56.6 (47.7–64.6)	7.1 (4.2–11.9)	7.2 (4.7–10.8)	0.994 (0.915–1.079)	0.881	0.053
		G ≥ 2	2955 (17)	44.2 (38.6–50.4)	39.2 (33.3–45.7)	34.4 (28.3–41.3)	29.5 (23.2–36.5)	9.8 (7.1–13.2)	4.9 (2.8–8.3)	1.119 (1.014–1.234)	0.025	0.005
		G ≥ 3	2899 (15)	24.8 (21.0–29.6)	21.2 (17.4–25.7)	17.5 (13.8–22.3)	13.9 (10.3–18.3)	7.3 (5.4–9.7)	3.7 (2.2–6.1)	1.158 (1.024–1.310)	0.020	0.007
	Negative (33.0 [25.6–41.3])	G = 1	1287 (16)	18.4 (14.2–23.7)	NA	18.4 (14.2–23.7)	NA	NA	18.4 (14.2–23.7)	NA	NA	NA
		G ≥ 1	1343 (17)	25.5 (20.7–30.9)	NA	25.5 (20.7–30.9)	NA	NA	25.5 (20.7–30.9)	NA	NA	NA
		G ≥ 2	1343 (17)	8.1 (5.6–11.6)	NA	8.1 (5.6–11.6)	NA	NA	8.1 (5.6–11.6)	NA	NA	NA
		G ≥ 3	1297 (15)	3.0 (1.6–5.5)	NA	3.0 (1.6–5.5)	NA	NA	3.0 (1.6–5.5)	NA	NA	NA

CI = confidence interval; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; MRI pathway = magnetic resonance imaging with or without magnetic resonance imaging-targeted biopsy; NA = not applicable; SBx = systematic biopsy.

[a] Proportion of participants with a positive or negative magnetic resonance imaging result, based on the studies reporting grade 2 or higher.

[b] Detection ratio is the detection rate of MRI pathway divided by the detection rate of systematic biopsy; the detection rate is the pooled number of positive results of the test divided by the pooled total number of positive results from both tests.

[c] Evaluating the difference in detection ratios between the populations (biopsy-naive men vs prior-negative biopsy) for each target condition.

[d] The tests are considered as "add-on tests", taking into account grade reclassification by each test. Therefore, G = 1e results differ from G = 1 results, where the tests are considered as "replacement tests", not taking into account grade reclassification.

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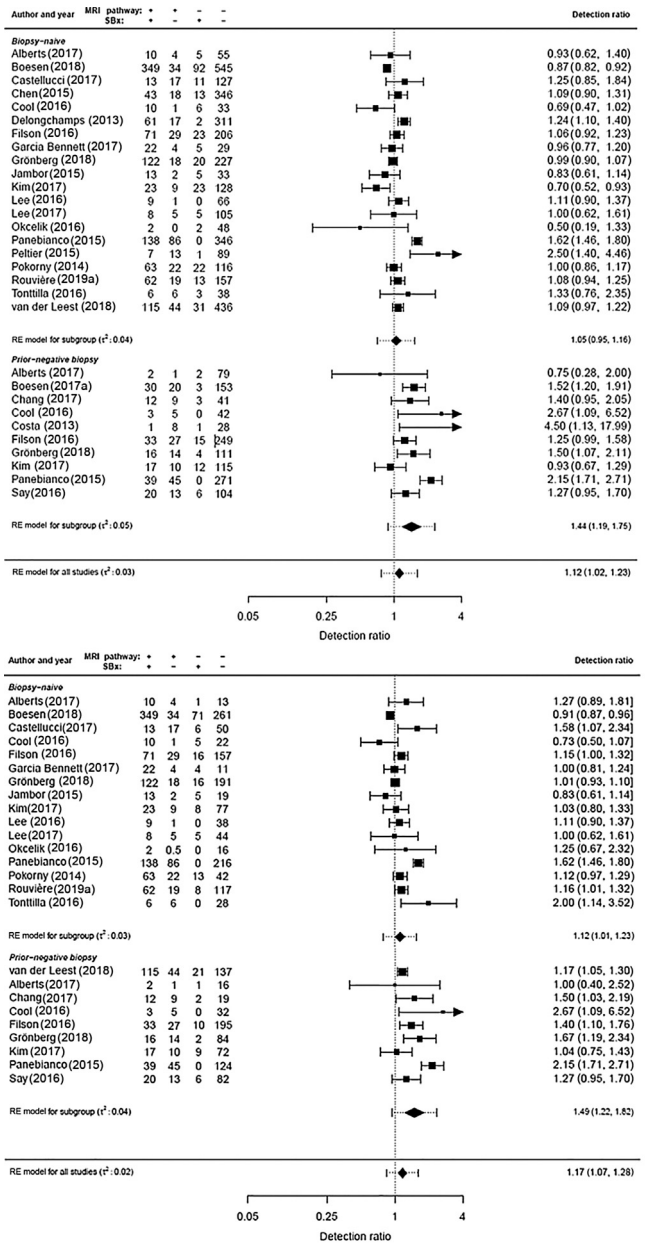

The upper plot is based on all included men; the lower plot is based on MRI-positive men. **MRI pathway:** magnetic resonance imaging with subsequent magnetic resonance imaging-targeted biopsy; **SBx:** systematic biopsy; **+:** positive test result; **-:** negative test result; **detection ratio:** detection rate MRI pathway divided by detection rate SBx; **detection rate:** pooled number of positive results of one test divided by the pooled total number of positive results from both tests; **RE model:** random effects model; τ^2: Tau² (heterogeneity). The continuous lines and brackets indicate study individual 95% confidence intervals; diamonds indicate the pooled summary estimate 95% confidence intervals; the dashed lines indicate the pooled 95% predicition intervals.

Fig. 5 – Forest plots of the agreement analysis (MRI pathway vs systematic biopsy) for detecting grade 2 and higher prostate cancer. The upper plot is based on all included men; the lower plot is based on MRI-positive men. Continuous lines and brackets indicate study individual 95% confidence intervals; diamonds indicate the pooled summary estimate 95% confidence intervals; and dashed lines indicate the pooled 95% prediction intervals. Detection rate = pooled number of positive results of one test divided by the pooled total number of positive results from both tests; detection ratio = detection rate of the MRI pathway divided by detection rate of SBx; MRI magnetic resonance imaging; MRI pathway: MRI with subsequent MRI-targeted biopsy; RE model = random-effect model; SBx = systematic biopsy; τ^2: tau-square (heterogeneity); + = positive result; – = negative result.

be counselled to pursue clinical and biochemical monitoring as a reasonable alternative for systematic biopsy, as also argued by others [25–27].

Men with positive MRI have a clear indication for MRI-targeted biopsy and can opt for additional systematic biopsy. The added value of performing systematic biopsy in MRI-positive men for the detection of grade 2 or higher prostate cancer, however, could be considered as limited with regard to total detection and additional harms. The conditions under which systematic biopsy could be safely avoided in men with positive MRI remain to be defined [26,28,29]. When in this population, the MRI pathway does not detect significant prostate cancer, a monitoring approach could be introduced (instead of systematic biopsy), based on clinical, biochemical, and imaging parameters, and would result in a "safety net". This safety net could easily be adopted in the shared decision making in current diagnostic work-up, as already recommended in international guidelines [30–32].

3.5.2. *Strength and weaknesses*

For the in-depth analysis of quantity and quality of evidence, strengths and weaknesses of included studies, and strengths and weaknesses of the review process, we refer to the original Cochrane review [13].

3.5.3. *Context of other research*

Distinguishing between biopsy-naive men and men with a prior-negative biopsy is paramount in daily practice. The agreement analysis, balancing the results of detecting grade 2 or higher prostate cancer, grade 1 prostate cancer, and reduction of biopsies in MRI-negative men, can be compared with selected high-quality studies (Supplementary Table 1). Recently, two multicentre randomised controlled trials in biopsy-naive men [2,33] investigated the MRI pathway and systematic biopsy. Furthermore, two large high-quality prospective multicentre cohort studies [24,34] investigated the agreement of prostate cancer detection between the MRI pathway and systematic biopsy.

The most remarkable differences are the following. Both randomised controlled trials showed that the MRI pathway detected significantly more grade 2 or higher prostate cancer than systematic biopsy [2,33], in contrast to the results from the agreement analyses in this review [13], including the two cohort studies [24,34]. Hence, while the randomised controlled trials showed superiority of the MRI pathway over systematic biopsy, the agreement studies did not. Despite these inconsistencies, none of the studies showed the MRI pathway to be inferior to systematic biopsy in detecting grade 2 or higher prostate cancer. In addition, in this Cochrane review, the proportion of men with grade 2 or higher prostate cancer detected by the MRI pathway was 23.4% (95% CI: 19.3–28.1%), while this was substantially higher in the two randomised controlled trials (Supplementary Table 1). Regarding the proportions of men with grade 1 prostate cancer, the MRI pathway in this review

detected 14% (95% CI: 11–17%), while this was lower in the two randomised controlled trials. Explanatory reasons might be multiple and are discussed within the context of this review (Cochrane review [13]).

3.5.4. Future research and perspectives

Quality control in the MRI pathway should be further employed to improve MRI acquisition, MRI reading, and MRI-targeted biopsy methods. The role of biparametric MRI as well as the different approaches for targeted biopsy (fusion, cognitive/visual, in bore), the route (transrectal/transperineal), and the clinical validity and utility of artificial intelligence with machine learning tools should be further investigated. Education, training, procedural standardisation, better imaging, and biopsy equipment require a multidisciplinary approach in the management of men with suspected prostate cancer [7,15,35,36]. This diagnostic chain is only as strong as its weakest link [37]. To improve the clinical utility of MRI-driven tests, factors influencing the outcome of the MRI pathway (such as per-lesion instead of a per-patient analysis, number of MRI-targeted biopsy cores, MRI positivity threshold in relation to clinical risk profiles, underlying MRI reading problems, and inaccurate MRI-targeted biopsy) should be further investigated. Risk calculators may aid in balancing harms and benefits by further refining the selection of those men who are at a risk of potentially life-threatening disease. Research should be initiated with recently introduced multivariable risk prediction models, including the MRI suspicion score as an extra input variable, to better identify those who would benefit from MRI and subsequent MRI-targeted biopsy, or an additional systematic biopsy, or both [38–42].

4. Conclusions

Balancing the potential benefits (reduction of biopsies and a decrease of grade 1 prostate cancer overdiagnosis) against the potential disadvantages (missing some grade 2 or higher prostate cancer), in disregard to further economic metrics (availability and costs), we conclude that the MRI pathway may represent a more favourable diagnostic test than systematic biopsy in all men suspected to have clinically significant prostate cancer. Therefore, performing prostate MRI before any biopsy should be structurally incorporated in the diagnostic work-up. Our certainty in our findings was reduced by study limitations. Furthermore, the MRI pathway relies on experience and skills in acquiring and reading MRI images, on targeting biopsy, and on high-end equipment of MRI and biopsy hardware and software, which are not yet widely available. Based on these considerations, further improvement of the prostate cancer diagnostic pathways should be pursued.

Author contributions: Ivo G. Schoots 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.

Study concept and design: Drost, Roobol, Schoots.
Acquisition of data: Drost, Osses.
Analysis and interpretation of data: Drost, Osses, Nieboer, Roobol, Schoots.
Drafting of the manuscript: Drost, Schoots.
Critical revision of the manuscript for important intellectual content: Bangma, Steyerberg, Roobol.
Statistical analysis: Drost, Nieboer.
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Supervision: Schoots.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.06.023.

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