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Moldovan, PC, Van den Broeck, T, Sylvester, R et al. (2017) What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel. European Urology, 72 (2). pp. 250-266. ISSN: 0302-2838

https://doi.org/10.1016/j.eururo.2017.02.026

What is the negative predictive value of multiparametric MRI in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the EAU Prostate Cancer Guidelines Panel

Authors: Paul C. Moldovan, Thomas Van den Broeck, Richard Sylvester, Lorenzo Marconi, Joaquim Bellmunt, Roderick C.N. van den Bergh, Michel Bolla, Erik Briers, Marcus G. Cumberbatch, Nicola Fossati, Tobias Gross, Ann M. Henry, Steven Joniau, Theo H. van der Kwast, Vsevolod B. Matveev, Henk G. van der Poel, Maria De Santis, Ivo G. Schoots, Thomas Wiegel, Cathy Yuan, Phil Cornford, Nicolas Mottet, Thomas B. Lam, Olivier Rouvière.

Corresponding author:
Pr. Olivier Rouvière
Hospices Civils de Lyon, Department of Urinary and Vascular Radiology
Hôpital Édouard-Herriot
Lyon, France
Olivier.rouviere@netcourrier.com

This Systematic Review was performed under the auspices of the:

- European Association of Urology Guidelines Office Board
- European Association of Urology Prostate Cancer Guideline Panel

Word count

Abstract: 432 words

Total text (including abstract): 3,859 words

Abstract

Context: It remains unclear whether patients with suspicion of prostate cancer (PCa) and negative multiparametric magnetic resonance imaging (mpMRI) can safely obviate prostate biopsy.

Objective: To systematically review the literature assessing the negative predictive value (NPV) of mpMRI in patients with suspicion of PCa.

Evidence acquisition: The Embase, Medline and Cochrane databases were searched up to February 2016. Studies reporting pre-biopsy mpMRI results using transrectal or transperineal biopsy as reference standard were included. We further selected for meta-analysis studies with at least 10-core biopsies as reference standard, mpMRI comprising at least T2-weighted and diffusion-weighted imaging, positive mpMRI defined as a PI-RADS/Likert score of ≥3/5 or ≥4/5, results reported at patient level for detection of overall PCa or clinically significant PCa (csPCa) defined as Gleason ≥7 cancer.

Evidence synthesis: 48 studies (9613 patients) were eligible for inclusion. At patient level, median prevalence was 50.4% (IQR, 36.4-57.7%) for overall cancer and 32.9% (IQR, 28.1-37.2%) for csPCa. Median mpMRI NPV was 82.4% (IQR, 69.0-92.4%) for overall cancer and 88.1% (IQR, 85.7-92.3) for csPCa. NPV significantly decreased when cancer prevalence increased, for overall cancer ($r=-0.64$, $p<0.0001$) and csPCa ($r=-0.75$, $p=0.032$). Eight studies fulfilled the inclusion criteria for meta-analysis. Seven reported results for overall PCa. When the overall PCa prevalence increased from 30% to 60%, the combined NPV estimates decreased from 88% (95% confidence interval (95% CI), 77–99%) to 67% (95% CI, 56–79%) for a cut-off score of 3/5. Only one study selected for meta-analysis reported results for Gleason ≥7 cancers, with a positive biopsy rate of 29.3%. The corresponding NPV for a cut-off score of ≥3/5 was 87.9%.

Conclusion: mpMRI NPV varied greatly depending on study design, cancer prevalence, and definitions of positive mpMRI and csPCa. Because cancer prevalence was highly variable among series, risk stratification of patients should be the initial step before considering prebiopsy mpMRI and defining those in whom biopsy may be omited when the mpMRI is negative.

Patient summary: This systematic review examined if multiparametric MRI scan can be used to reliably predict the absence of prostate cancer in patients suspected of

having prostate cancer, thereby avoiding a prostate biopsy. The results suggest that whilst it is a promising tool, it is not accurate enough to replace prostate biopsy in such patients, mainly because its accuracy is variable and influenced by the prostate cancer risk. However, its performance can be enhanced if there were more accurate ways of determining the risk of having prostate cancer. When such tools are available, it should then be possible to use MRI scan to avoid biopsy in patients at low risk of prostate cancer.

1. Introduction

Correlation with radical prostatectomy specimens has demonstrated that multiparametric magnetic resonance imaging (mpMRI) has excellent sensitivity in detecting prostate cancers (PCa) with a Gleason score ≥7 [1-3]. As a result, prostate mpMRI is increasingly used in patients with suspicion of PCa to localize abnormal areas before biopsy. A large body of literature has shown that targeted biopsies of suspicious lesions seen on mpMRI (TBx) improved the detection of clinically significant PCa (csPCa), at least in the repeat biopsy setting [4-6]. As a result, it is now recommended that an mpMRI is performed before repeat biopsy to allow TBx of suspicious lesions in addition to standard biopsies [7].

Some authors have recently suggested that, besides improving csPCa detection, mpMRI could also be used as a triage test so that patients with negative mpMRI findings could obviate biopsy. Such a strategy remains highly controversial [8] and depends upon the negative predictive value (NPV) of mpMRI. Therefore, the European Association of Urology Prostate Cancer Guidelines Panel undertook this systematic review and meta-analysis to assess the NPV of mpMRI in patients with suspicion of PCa, and thus, its potential role in eliminating unnecessary prostate biopsy.

2. Evidence acquisition

2.1. Objective

Our primary aim was to systematically evaluate the performance of negative pre-biopsy prostate mpMRI in predicting a negative biopsy result for overall PCa and csPCa in biopsy-naïve men and in men with previously negative biopsies. A further objective was to explore and define factors that may contribute to relevant thresholds in order to provide guidance for future studies.

2.2. Data acquisition and search strategy

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [9]. The review protocol was published in PROSPERO database (http://www.crd.york.ac.uk/PROSPERO;

registration number CRD42015021929). Databases searched included the Embase and OVID Medline databases, the Cochrane database of systematic reviews and the Cochrane central register for clinical trials, covering 1st January 2000 to 13th February 2016. Systematic or standard prostate biopsies were used as reference standard with positive or negative cases of PCa being determined by histopathological examination. The detailed search strategy is presented in Supplement 1.

2.3. Inclusion and exclusion criteria

Included studies focused on men who were assessed for suspected PCa by mpMRI before undergoing prostate biopsy. Studies enrolling both biopsy-naïve men and men who had undergone previous negative biopsies were included. Pre-biopsy prostate mpMRI was considered the index test and comprised T2-weighted imaging (T2WI) and at least one functional imaging technique (diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCEI) or magnetic resonance spectroscopic imaging (MRSI)). For inclusion, studies had to report on false negatives and true negatives, in order to calculate NPV (i.e. results of systematic/standard prostate biopsies when the mpMRI was negative). When available, false positive and true positive findings were also noted to calculate the positive predictive value (PPV) and the cancer prevalence. There was neither restriction on the biopsy technique (transrectal or transperineal) nor on the number of biopsy cores. Studies using radical prostatectomy specimens as reference standard were excluded, as were studies evaluating men with histologically proven prostate cancer. Studies with less than 50 participants were excluded. No language restrictions were applied.

2.4. Data collection and data extraction

Two reviewers (PM, TVDB) independently screened all abstracts and full-text articles for eligibility. Disagreement was resolved by discussion or reference to an independent third party (LM). All screening was performed using a pre-defined eligibility form.

Using a data extraction form developed *a priori*, the same two reviewers independently extracted data concerning study methodology, patient characteristics, technical characteristics of the MR scanners, mpMRI protocol, mpMRI scoring

system, definition of positive mpMRI, biopsy protocol and definition of csPCa. Any discrepancies concerning data extraction were resolved by consensus, or reference to an independent arbiter (OR or TBL).

2.5. Risk of publication bias

To assess the risk of bias, all included reports were reviewed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies [10].

2.6. Data synthesis and analysis

Outcome data regarding false negative and true negative values of mpMRI before prostate biopsy were recorded as reported by authors. When not available, data were indirectly derived from specificity, sensitivity and prevalence values reported by authors using an online Bayesian statistics calculator (http://www.medcalc.com/bayes.html). Descriptive statistics were used to summarise baseline characteristics and outcomes, including median and interquartile range (IQR) for estimates of NPV across studies. Correlation between mpMRI NPV and positive biopsy rate was done using the Pearson's correlation coefficient.

A meta-analysis was undertaken to calculate pooled NPV and PPV. To ensure appropriate clinical homogeneity of the studies included in the meta-analysis, we selected only the studies enrolling biopsy-naïve patients and/or patients with history of negative biopsy, and fulfilling the following criteria that were defined a priori: (i) reference standard consisting of prostate biopsy with at least 10 samples on all patients; (ii) mpMRI protocol comprising at least T2WI and DWI; (iii) mpMRI results presented as a 5-level score, using a subjective Likert scale or the Prostate Imaging Reporting Data System (PI-RADS) score [11]; (iv) definition of positive mpMRI as a score ≥3/5 or ≥4/5; and (v) results reported on a per patient basis. In addition, only studies defining csPCa as Gleason ≥7 cancers were selected for the meta-analysis assessing the mpMRI NPV for csPCa. A bivariate random effects approach was employed using the Midas package in Stata 12 (StataCorp LP, Texas, USA). Since the NPV decreases and the PPV increases as the prevalence increases, post-test probability estimates of NPV and PPV were reported for given values of the prevalence based on Bayes' theorem.

For other studies not included in the meta-analysis based on the criteria described above, a narrative synthesis of the data was performed. To explore and define clinical heterogeneity, subgroups were analysed at patient level based on the following variables: biopsy-naïve versus previous negative biopsy; patients with positive versus negative DRE; mpMRI perfomed with an endorectal versus without an endorectal coil; transrectal ultrasound (TRUS) versus template transperineal (TTP) biopsy approach; and ≤16 cores versus >16 cores as reference standard. Studies reporting mpMRI NPV for patients with a PSA level ≤10 ng/mL were also reported separately .

3. Evidence synthesis

3.1. Quantity of evidence identified

The study selection process is depicted in the PRISMA flow diagram (Fig. 1). A total of 2,980 abstracts were retrieved. After abstract screening and removal of duplicates, 240 articles were eligible for full text screening, of which 48 studies were eligible for inclusion [12-59].

3.2. Quality of studies

Out of the 48 included studies, 42 were single-centre and 6 were multi-centre studies. Thirty-four studies were prospective, 6 were retrospective whilst the design of the rest was unclear. Risk of bias (RoB) assessment using QUADAS-2 was performed for each of the individual studies (Fig. 2a-2b). Overall, the RoB was highly heterogeneous across studies for all criteria, except for the reference standard domain, in which RoB was low in most studies.

3.3. Characteristics of studies

The 48 studies comprised a total of 9,613 men who underwent prostate mpMRI followed by biopsy. The study and patient baseline characteristics are presented in Table 1. The patient population consisted of biopsy-naive men in 9 studies, men with at least one previous negative biopsy in 16 studies, and both biopsy-naïve men and men with history of previous negative biopsy in 9 studies. In 14 studies, the biopsy history of the patients was unclear.

The magnetic field strength was 1T, 1.5T and 3T in 1, 28 and 15 studies, respectively. Four studies used both 1.5T and 3T MR systems. DWI and DCEI were used in 36 and 35 studies, respectively. Nineteen studies also added MRSI. An endorectal coil was used in 18 studies. The definition of positive mpMRI varied across studies. The PI-RADS v1 score was used in 12 studies, a 5-level subjective (Likert) score was used in 8 studies and one study reported data based on the 2 scoring systems. In-house criteria were used in 13 studies for defining positive mpMRI, and 5 studies used a dichotomous definition. Nine studies did not report on the criteria for positive mpMRI. No study used the PI-RADS v2 score.

Regarding the reference standard, TRUS-guided biopsies were used in 39 studies, TTP biopsies in 6 studies and mixed TRUS-guided and TTP biopsies in 2 studies. In one study, the biopsy approach was unclear. The number of cores per biopsy procedure was ≤16 in 30 studies, >16 in 9 studies and variable among patients in 3 studies. For 6 studies, the number of biopsy cores taken was unclear.

3.4. Negative predictive value of pre-biopsy mpMRI

At patient level, median biopsy positivity rate (i.e. cancer prevalence) was 50.4% (IQR, 36.4-57.7%) for overall cancer and 32.9% (IQR, 28.1-37.2%) for csPCa (Table 2). Median mpMRI NPV was 82.4% (IQR, 69.0-92.4%) for overall cancer and 88.1% (IQR, 85.7-92.3) for csPCa. NPV significantly decreased when cancer prevalence increased, both for overall cancer ($r=-0.64$, $p<0.0001$) and csPCa ($r=-0.75$, $p=0.032$; Fig 3). In addition, NPV was highly dependent on the definition used for csPCa, with differences of up to 21% when several definitions were used in the same dataset [12, 13, 38, 47, 48].

Cancer prevalence tended to be higher and mpMRI NPV lower in the biopsy-naïve group as compared to the repeat biopsy group, in men with positive DRE as compared to men with negative DRE and when an endorectal coil was not used (Table 3). There were no clear differences in prevalence and NPV in the other analysed subgroups (TRUS-guided versus TTP biopsy, biopsy procedures with ≤16 cores versus >16 cores; Table 3). However, comparisons must be interpreted with care, due to the small number of studies in some subgroups. In patients with a PSA level ≤10 ng/mL, median NPV for overall PCa was 86.3% (IQR, 73.3-93.6%) for a median cancer prevalence of 35.4% (IQR, 27.6-42.5%).

3.5. Meta-analysis

3.5.1. NPV and PPV for overall PCa

Eight studies reported NPV at patient level for overall PCa and fulfilled the inclusion criteria for meta-analysis (Table 4) [22, 25, 38, 41, 43, 46, 56, 57].

Seven studies used a score of ≥3/5 for defining a positive mpMRI (Figures 4a-b) [22, 25, 38, 43, 46, 56, 57]. Figure 4c shows the conditional probability plot of 1-NPV and PPV as a function of overall PCa prevalence. Table 5 shows NPV and PPV estimates for given values of PCa prevalence.

Only 3 studies used a score of ≥4/5 for defining a positive mpMRI (Table 4) [41, 46, 57], and a formal meta-analysis could not be performed.

3.5.3. NPV and PPV for Gleason ≥7 cancers

Only one study reporting NPV at patient level for Gleason ≥7 cancers met the selection criteria for inclusion in the meta-analysis. It reported NPV and PPV of 87.9% and 45.1% respectively, for a prevalence of 29.3% (Table 4) [46].

3.6. Discussion

3.6.1. Principal findings

We observed a large variability in reported NPV. Many factors can explain this variability, such as differences in mpMRI protocols, definition of negative mpMRI, or biopsy protocols. However, two major causes of variability must be pointed out. First, the cancer prevalence was highly variable, ranging at patient level from 13% to 74.7% for overall PCa, and from 13.7% and 50.9% for csPCa. This variability was observed both in the biopsy-naïve and repeat biopsy setting. Because NPV depends on prevalence, this had a major impact on reported NPV (Fig 3). Second, the definition of csPCa was highly variable from one series to another, and differences of up to 21% could be observed in NPV when different definitions of csPCa were used in the same dataset [12, 13, 38, 47, 48].

To account for clinical heterogeneity, and to further explore the clinical relevance of the results, we carefully selected studies for inclusion in the meta-analysis based on stringent criteria. Particularly, we included only studies that: (i) had biopsy protocols with at least 10 cores, since it is no longer recommended to obtain

less than 10 cores per biopsy; (ii) used diffusion-weighted imaging, which is the most informative technique, at least for cancers in the peripheral zone [60]; and (iii) reported mpMRI findings using a 5-level score, so that negative findings could be better defined. We accepted studies using a subjective (Likert) scale because experienced readers obtained equivalent [45, 61, 62] or better [63] results with the Likert score than with the PI-RADS v1 score. Because of the large variations of NPV induced by differences in definitions of csPCa, we did not include different definitions in the meta-analysis since this would have introduced unacceptable clinical heterogeneity in the results, possibly resulting in erroneous and biased estimates. We therefore a priori restricted the definition of csPCa to cancers with a Gleason score ≥7, given the low lethal potential of Gleason 6 cancers [64] and the lack of consensus among pathologists on the best method to measure biopsy core invasion length [65, 66].

In this more homogeneous group of studies, the prevalence range was still large (31.3%-63.7%). As a result, we modelled the evolution of NPV (and PPV) as a function of overall PCa prevalence. Unfortunately, we could not duplicate this for csPCa since only one study reporting NPV for Gleason ≥7 cancers met the inclusion criteria for meta-analysis.

3.6.2. Reference standard

We included only studies that reported the results of systematic/standard biopsy in patients with a negative mpMRI, and used the systematic/standard biopsy as a reference standard. It is well known that TRUS-guided biopsy harbours both random and systematic errors, as evidenced by the high rates of positivity of immediate repeat biopsy after a first series of negative biopsies [67, 68], and as confirmed recently by the PROMIS trial [69]. Therefore, using TRUS-guided biopsy as a reference standard may have overestimated the NPV of mpMRI. However, studies using radical prostatectomy specimens as a reference standard have already reported the mpMRI detection rates in relation to PCa Gleason score and volume [1]. In this review, we intended to address the more pragmatic question as to whether a negative mpMRI could predict a negative subsequent biopsy. This is an important question because if the NPV of mpMRI was sufficiently high in comparison with the reference standard of systematic/standard biopsies, then in practice a negative mpMRI result could indeed avoid the need for prostate biopsy. Therefore, studies

reporting only biopsy results when the mpMRI was positive (e.g. obtained through MRI-targeted, guided or fusion biopsies with added systematic biopsies) were not included in this review.

3.6.3. Impact on clinical practice and research

It is now well established that mpMRI is a sensitive tool for detecting aggressive PCa [1-3, 69]. However several reasons preclude its broad use as a triage test before biopsy.

Firstly, the population referred to prostate biopsy is not standardized. The large range of reported prevalence for overall PCa and csPCa suggests substantial heterogeneity in the way patients are selected for biopsy. Because of this heterogeneity, we did not provide a pooled estimate for mpMRI NPV. The role of mpMRI as a triage test before prostate biopsy should be evaluated in the broader context of the selection of patients with suspicion of (aggressive) PCa. In a recent retrospective study of 514 patients, mpMRI NPV for Gleason ≥7 cancers was 91% when the PSA density was ≤0.2 ng/mL/mL, and only 71% when the PSA density was >0.2 ng/mL/mL (p=0.003) [70]. In another series of 288 biopsy-naïve patients, no csPCa (Gleason score ≥7 or maximum cancer core length ≥4 mm) was found in the 44 patients with a PSA density <0.15 ng/mL/mL and a PI-RADS v2 score <3/5 [71]. We believe that such a pre-stratification of the risk of csPCa is an interesting way for rationalizing the use of mpMRI before biopsy. Patients found at very low risk would be spared both mpMRI and biopsy. Patients at low risk - for whom mpMRI would have a NPV high enough to be used as a triage test - could avoid biopsy in case of negative mpMRI. Patients at higher risk would need biopsy even in case of negative mpMRI. Many tools can be used to risk-stratify the population of patients referred to biopsy, ranging from simple parameters such as PSA density to more complicated risk calculators [72, 73]. The impact of these tools on the NPV of pre-biopsy mpMRI needs to be carefully evaluated, both in the biopsy naïve and in the repeat biopsy setting. For the moment, it is impossible to make any recommendations on the best way to risk-stratify patients before referring them for mpMRI.

Secondly, the large variability in the definition of csPCa precludes any definitive conclusion on the ability of mpMRI to rule out aggressive cancer. The issue of the most appropriate definition of csPCa on biopsy is complex, since biopsy results may neither accurately reflect tumour burden nor aggressiveness. Nonetheless, there is

an urgent need to standardize the histological definition(s) of csPCa, to allow meaningful comparisons between studies.

Thirdly, the specificity of mpMRI remains moderate, and there is a substantial proportion of false positives in the lesions scored 3/5 or 4/5 [1, 74, 75], even with the new PI-RADS v2 score [76]. In a series of 62 patients with 116 lesions biopsied under magnetic resonance/ultrasound fusion, the overall cancer detection rates for PI-RADS v2 scores of 3/5 and 4/5 were only 15.8% and 29.8%. [77]. In theory, a triage test used to rule out a disease needs to be highly sensitive for this disease. However, if its specificity is too low, it will be clinically useless since most patients will be positive, whether they have the disease or not. Therefore, if mpMRi is to be used as a triage test in the future, there is a need to improve its specificity. This could be achieved by a continuous refinement of scores [78]. Promising results in characterizing csPCa have also been reported with quantitative analysis [79].

Finally, all published studies were performed in specialized centres. The broad use of mpMRI as a triage test assumes good inter-observer reproducibility. Unfortunately, inter-observer reproducibility of existing scoring systems remains moderate [62, 63, 80] even with the use of the PI-RADS v2 score [80, 81]. Studies evaluating on a large scale the reproducibility of mpMRI findings between expert and non-expert centres are currently lacking.

3.6.3. How this review compares with other reviews

Three systematic reviews (including two meta-analyses) regarding the role of mpMRI in localized prostate cancer have been published recently [4-6]. Crucially, all three reviews focused exclusively on the sensitivity of mpMRI-targeted, guided or fusion biopsies in diagnosing overall PCa and csPCa, using TRUS-guided prostate biopsies as reference standard. The impact of systematic biopsies on the outcome was not addressed in any of the reviews, either within the index test or the reference standard. Our review had a totally different research question and objective, focusing on NPV of mpMRI to see if a negative mpMRI can avoid the need for a prostate biopsy. Because MRI-targeted/guided/fusion biopsies are not relevant if the mpMRI was negative for cancer, it can be argued that the 3 reviews assessed a different index test altogether. As such, we believe the findings of this review are novel and unique, and pave the way for further focused clinical studies.

3.6.4. Strengths and limitations

The current study represents the first systematic review addressing the role of mpMRI as a triage test before biopsy. The review elements were developed in conjunction with a multidisciplinary panel of experts (EAU Prostate Cancer guidelines panel), which included a patient representative, and the review was performed robustly in accordance with recognised standards. However, it is limited by the major heterogeneity of the existing literature in patient population, study design, and definitions of positive mpMRI and csPCa. It highlighted further areas of research that could help in defining the best use of mpMRI in the early detection of aggressive prostate cancer in the future.

4. Conclusion

Although mpMRI can detect aggressive prostate cancer with excellent sensitivity, a definitive conclusion on its role as a triage test before prostate biopsy will be possible only when three main issues are addressed. Firstly, because NPV depends on prevalence, and because overall PCa and csPCa prevalence was highly variable in the published series, it becomes mandatory to define the optimal way to pre-evaluate the risk of csPCa in patients with suspicion of PCa. Depending on the risk category, mpMRI could then be used to obviate biopsies or not. Secondly, there is a need for consensus definitions of csPCa on biopsy findings to allow inter-study comparisons. Thirdly, although efforts have been made to standardize mpMRI technical protocols and interpretation in the past few years [11, 60, 76], there is still a crucial need to improve mpMRI specificity and inter-reader reproducibility.

Legends for figures:

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart.

Figure 2: (A) Assessment of the risk of bias for included studies; (B) risk of bias summary graph.

Figure 3: Negative predictive value of Pre-biopsy multiparametric MRI as a function of cancer prevalence (blue crosses: overall prostate cancer; red crosses: clinically significant prostate cancer).
The blue line is the correlation line for overall prostate cancer; the red dotted line is the correlation line for clinically significant prostate cancer.

Figure 4:
(A-B): Forest plot showing the negative predictive value (NPV; Fig 4A) and positive predictive value (PPV; Fig 4B) of pre-biopsy multiparametic MRI for overall prostate cancer in the seven studies selected for meta-analysis that used a cut-off score of ≥3/5 for defining positive MRI.
Studies have been ranked according to cancer prevalence (left column). Intervals in the right column are 95% confidence intervals (95% CI) of the NPV (Fig 4A) or PPV (Fig 4B). Because NPV and PPV vary with cancer prevalence, combined estimates of NPV and PPV have not been provided.
(C) Conditional probability plot showing the estimation of the combined NPV and PPV in the seven studies, as a function of the prevalence of overall prostate cancer. The x axis (prior probability) indicates the overall prostate cancer prevalence. The y axis (posterior probability) indicates either PPV (dashed line, upper quadrant) or 1-NPV (dotted line, lower quadrant).

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