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Deferring prostate biopsy after magnetic resonance imaging: evidence-graded thresholds for men with suspected prostate cancer – a narrative review

Alaa Menshawy[1*], Rana Elmassry[2]

[1] Faculty of Medicine, Alexandria University, Champollion Street, Azarita, Alexandria 21131, Egypt
[2] Faculty of Medicine, Alexandria University, Alexandria, Egypt

[*] Correspondence: Alaa Menshawy, alaamenshawy664@gmail.com

ABSTRACT

Magnetic resonance imaging (MRI) before biopsy has replaced systematic transrectal ultrasound-guided sampling as the first diagnostic step for men with suspected prostate cancer; the open question is which men can safely forgo biopsy after imaging. This narrative review synthesised randomised trials, paired diagnostic studies, screening trials and meta-analyses identified from 441 unique PubMed records searched to September 2026 (45 sources cited) to derive evidence-graded thresholds for deferring biopsy. A non-suspicious MRI (Prostate Imaging Reporting and Data System [PI-RADS] score 1–2) had a pooled negative predictive value of 90.8% (95% confidence interval [CI] 88.1–93.1) for grade group 2 or higher cancer across 42 studies and 7321 biopsy-naive men: about nine significant cancers are missed per 100 men not biopsied. With a prostate-specific antigen (PSA) density below 0.15 ng/mL/mL as well, subsequent incidence was close to that of the general population (rate ratio 1.4, 95% CI 0.9–2.0). PI-RADS 3 lesions had a pooled positive predictive value of about 13%; density thresholds of 0.10–0.20 ng/mL/mL missed 1–14 significant cancers per 100 men spared, depending on threshold and prevalence. In screening, biopsying only MRI-positive men roughly halved overdiagnosis (relative risk 0.46, 95% CI 0.33–0.64) without a detectable rise in significant cancer, whereas omitting systematic cores in MRI-positive men reduced significant-cancer detection. Transperineal biopsy reduced infection-related admission. Biopsy can be deferred safely only when a negative or equivocal MRI is combined with a low PSA density and a defined plan of repeat PSA testing and imaging.

Keywords: Prostatic Neoplasms · Multiparametric Magnetic Resonance Imaging · Image-Guided Biopsy · Prostate-Specific Antigen · Early Detection of Cancer · Risk Assessment

Key points

- Do not omit biopsy on a non-suspicious magnetic resonance imaging (MRI) scan (Prostate Imaging Reporting and Data System [PI-RADS] 1–2) alone: its pooled negative predictive value for grade group 2 or higher cancer is about 91%, so roughly nine significant cancers are missed per 100 men not biopsied, and the figure worsens as local prevalence rises.
- Calculate prostate-specific antigen (PSA) density from the MRI-measured prostate volume. With a negative MRI and a density below 0.15 ng/mL/mL, later significant-cancer incidence approaches that of the general population; at or above 0.15, biopsy

remains justified whatever the PI-RADS score.
- Treat PI-RADS 3 as a decision point, not a diagnosis: about 13% of these lesions are significant cancer, and a locally chosen density threshold of 0.10–0.20 ng/mL/mL misses 1–14 significant cancers per 100 men spared biopsy.
- When an MRI-visible lesion is biopsied, add perilesional or regional cores to the targeted cores; targeted-only sampling misses significant disease and increases grade misclassification.
- Make every deferral an active plan, not a discharge: repeat PSA with recalculated density at 6–12 months and repeat MRI at about two years, sooner if density rises or symptoms change.

Introduction

For three decades, a raised prostate-specific antigen (PSA) level led directly to a 10–12-core transrectal ultrasound-guided biopsy. That pathway was inaccurate in both directions. Against a template mapping biopsy reference standard in the PROMIS study, transrectal sampling had a sensitivity of only 48% (95% confidence interval [CI] 42–55) for clinically significant cancer, whereas multiparametric magnetic resonance imaging (MRI) reached 93% (95% CI 88–96), at the price of a specificity of 41% versus 96% [1]. The PRECISION trial then showed that using MRI to decide whether and where to biopsy detected more significant cancer (38% versus 26%; adjusted difference 12 percentage points, 95% CI 4–20) and less insignificant cancer (adjusted difference −13 percentage points, 95% CI −19 to −7), while allowing 71 of 252 men (28%) to avoid biopsy altogether [2]. Guidelines followed, and pre-biopsy MRI is now the default in most high-income health systems [3].

The residual problem is narrower and harder. Once MRI is available, the decision that matters is whether a given man can be told, honestly, that he does not need a needle today, and that cannot be read off the Prostate Imaging Reporting and Data System (PI-RADS) score alone. PI-RADS grades the likelihood of significant cancer on MRI from 1 (very unlikely) to 5 (very likely). The decision also depends on the pre-test probability of disease, on prostate volume, on what clinician and patient are prepared to miss, and on whether a safety-net exists to catch the cancers that deferral will leave behind. Published pathways describe what was done; few state what threshold was crossed.

This review asks a specific question: in men with suspected prostate cancer who have had pre-biopsy MRI, which combinations of imaging result and clinical information allow biopsy to be deferred, and at what cost in missed clinically significant cancer? It assembles the randomised, paired-cohort and screening evidence into decision thresholds and quantifies the cost of each in clinically significant cancers missed per 100 men, where the source data permit. Clinically significant cancer is taken throughout as International Society of Urological Pathology (ISUP) grade group 2 or higher unless stated.

Methods

Design and search strategy

This is a narrative review of published evidence. PubMed was searched through the National Center for Biotechnology Information E-utilities interface for records published up to September 2026, using twenty pre-specified topic searches. These covered the named trials and cohorts (PROMIS, PRECISION, MRI-FIRST, the 4M study, the Cochrane diagnostic review, GÖTEBORG-2, ProScreen, STHLM3-MRI, PRIME, PRIMARY and PRIMARY2, and PI-CAI) and the thematic areas of PI-RADS 3 management, PSA density thresholds, MRI-based risk calculators, follow-up after negative MRI, targeted versus systematic sampling, biopsy route, triage with prostate-specific membrane antigen imaging, machine reading of MRI, and the guidelines of the European Association of Urology (EAU), the American Urological Association and Society of Urologic Oncology (AUA/SUO) and the National Comprehensive Cancer Network (NCCN). Four further searches closed gaps on PSA density after a negative MRI, PI-RADS 3 meta-analyses and screening reports published after 2024. No other databases were searched. Guidance from the

National Institute for Health and Care Excellence is not indexed in PubMed in citable form and was not included.

Study selection

Records were selected on study design (randomised trials, paired diagnostic studies, population-based screening trials, systematic reviews and large consecutive cohorts) and on whether the abstract reported an interpretable threshold, detection rate or miss rate. Clinical practice guidelines were included to allow comparison with current recommendations.

Data extraction and synthesis

Numerical estimates were extracted from the titles and abstracts of the retrieved records. No meta-analysis was performed and no statistical software was used; estimates are reported as published, with their 95% CIs where the source reported them. Where a source reported only a point estimate or a p value, it is presented as such and no interval was imputed; outcomes that a source did not report were treated as missing and were not estimated. Where the source data permitted, detection and miss proportions were re-expressed as clinically significant cancers missed per 100 men by direct conversion of the reported proportions.

Grading of recommendations

Each practice recommendation was assigned a certainty of high, moderate or low by the authors, informed by the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach: the design of the supporting studies (randomised and paired within-patient designs rated highest), the number of concordant studies, the consistency of their direction and magnitude, and their directness to the population in question. Formal GRADE evidence profiles were not constructed.

Ethics

Ethics approval and consent were not required because the review used only published data.

Results

Evidence identified

The twenty pre-specified searches yielded 441 unique records, supplemented by four gap-filling searches. Forty-five publications are cited: randomised trials, paired diagnostic studies, population-based screening trials, systematic reviews with meta-analyses, large consecutive cohorts and four clinical guideline documents. Their findings are summarised below by clinical question, and the reported thresholds for deferring biopsy are collated in Table 1.

Table 1. Thresholds for deferring biopsy and their reported cost in missed clinically significant cancer

Strategy (PSA density threshold, ng/mL/mL)	Setting and significant-cancer prevalence	Men spared biopsy or MRI	Significant cancers missed	Ref.
PI-RADS 1–2, no density rule	Pooled, biopsy-naive men	All MRI-negative men	About 9 per 100 (NPV 90.8%)	[18]
PI-RADS 1–2 plus density <0.15	Population-based, Finland	Majority of MRI-negative men	Incidence rate ratio 1.4 (0.9–2.0) versus general population	[21]
PI-RADS 3 plus density <0.10	Referral, 45%	63 per 1000 men	0 in the validation cohort	[25]
PI-RADS 3 plus density <0.15	Multi-institutional, 20%	228 of 349 men with PI-RADS 3	13.6 per 100 men spared	[24]
PI-RADS 3 plus density <0.20	Community, 24%	29% of negative biopsies	1.3 per 100 of all grade group ≥2 cancers	[26]
Pre-MRI density <0.075	Screening, Stockholm	28% of MRI scans	5% of Gleason ≥3+4 cancers	[28]
Pre-MRI density <0.10	Community, 24%	30% of MRI scans	9.6 per 100 of all grade group ≥2 cancers	[26]

Significant cancer is International Society of Urological Pathology grade group 2 or higher unless stated. Density is PSA density (serum PSA divided by prostate volume). Values in parentheses are 95% confidence intervals. MRI, magnetic resonance imaging; NPV, negative predictive value; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; Ref., reference number.

From systematic sampling to an imaging-led pathway

Four studies define the transition, and they do not agree. PRECISION found MRI with targeted cores superior on both detection and overdiagnosis [2]. The Dutch 4M study, using in-bore MRI-guided biopsy (performed inside the scanner) in experienced centres, found identical significant-cancer detection (25% versus 23%) with far less indolent disease (14% versus 25%), and a 49% biopsy-avoidance rate because half the men had a non-suspicious scan. Among those 309 men, immediate transrectal biopsy would have found significant cancer in only 3% (10/309), rising to 4% (13/309) at one year, while overdetecting insignificant cancer in 20% (63/309) [4]. Total cores fell by 89%.

MRI-FIRST reached the opposite conclusion about systematic cores. In 251 biopsy-naive men, systematic and targeted biopsy detected significant cancer at similar rates (29.9% versus 32.3%, p = 0.38), but 5.2% of men would have had significant cancer missed without systematic cores, and 7.6% without targeted cores [5]. The Trio study, in 2103 men with MRI-visible lesions, made the same point at scale: combined biopsy diagnosed 208 more men (9.9%) than either method alone, targeted biopsy alone would have misclassified 8.8% of grade group 3 or higher cancers, and upgrading at prostatectomy was lowest after combined biopsy (3.5%) and highest after systematic biopsy alone (16.8%) [6].

The Cochrane review reconciles these by separating the tests. MRI alone is sensitive but not specific (sensitivity 0.91, specificity 0.37); MRI-targeted biopsy is specific but less sensitive (sensitivity 0.80, specificity 0.94); and the complete pathway, in which MRI-negative men are not biopsied, has a sensitivity of 0.72 and a specificity of 0.96. At 30% prevalence this equates to 216 true positives and 84 false negatives per 1000 men, or 8.4 significant cancers missed per 100 entering the pathway [3]. Systematic biopsy alone performed worse (sensitivity 0.63). All estimates were of low certainty, downgraded for selection bias and inconsistency, and the pathway's advantage was concentrated in previously biopsied men (detection ratio 1.44, 95% CI 1.19–1.75) rather than biopsy-naive men (1.05, 95% CI 0.95–1.16).

One simplification is now well supported. PRIME, a within-patient non-inferiority trial in 490 biopsy-naive men across 22 centres, found biparametric MRI (without intravenous contrast) non-inferior to multiparametric MRI (with contrast) for detecting significant cancer (29.2% versus 29.6%; difference −0.4 percentage points, 95% CI −1.2 to 0.4), with 99% of scans of adequate quality [7]. A meta-analysis of 18 comparative studies found identical pooled negative predictive values (92% each) [8]. Contrast can therefore be omitted where image quality is assured; this is an argument about throughput rather than diagnostic accuracy.

What the screening trials add

Screening cohorts have a lower prevalence of disease than referral clinics, which changes the arithmetic of deferral, and they provide the only randomised evidence on omitting biopsy.

STHLM3-MRI randomised men with PSA ≥3 ng/mL to standard biopsy or to MRI with targeted and systematic cores: significant cancer was detected in 21% versus 18% (difference 3 percentage points, 95% CI −1 to 7; non-inferior), and insignificant cancer in 4% versus 12% [9]. Stockholm3 is a blood-based risk score that combines protein markers, genetic markers and clinical data. A Stockholm3 score of ≥0.15 matched PSA ≥3 ng/mL for sensitivity while requiring 545 rather than 846 MRI examinations, with fewer antibiotic prescriptions (1.8% versus 4.4%) and hospital admissions (1.2% versus 3.4%) [10]. A later randomisation found that a biomarker-plus-systematic-biopsy strategy and a PSA-plus-MRI strategy detected significant cancer equally (2.3% versus 2.5%; relative proportion 0.92, 95% CI 0.73–1.15), but the biomarker route required 43% more biopsies and detected twice as much indolent disease [11]. At two years, a Stockholm3 threshold of ≥11 had a false-negative rate of 10%, against 26% for PSA ≥3 ng/mL, at similar specificity [12].

GÖTEBORG-2 tested the question of interest directly: in men with PSA ≥3 ng/mL undergoing

MRI, is targeted biopsy alone safe? Insignificant cancer was halved (0.6% versus 1.2%; relative risk 0.46, 95% CI 0.33–0.64), while significant cancer showed a relative risk of 0.81 (95% CI 0.60–1.1). Ten men in the reference arm had significant cancer detected only by systematic cores; all were intermediate risk, mainly low volume, and were managed with active surveillance [13]. After four years and roughly 26,000 person-years per arm, the reduction in insignificant cancer deepened at repeat rounds (relative risk 0.25, against 0.49 at the first round), the relative risk of significant cancer was 0.84 (95% CI 0.66–1.07), and advanced or high-risk cancers, the outcome that would signal harm, numbered 15 versus 23 (relative risk 0.65, 95% CI 0.34–1.24) [14]. This is the strongest evidence that not biopsying an MRI-negative screened man does not cost him curability, although the intervals remain compatible with a modest excess. ProScreen, using PSA followed by a four-kallikrein panel and then MRI, reported one additional high-grade cancer per 196 men invited and one additional low-grade cancer per 909 [15]; mortality data are pending.

Two cautions apply. In STHLM3-MRI, omitting systematic cores cost 3.8 missed grade group 2 or higher cancers and 1.1 grade group 3 or higher cancers for each averted grade group 1 diagnosis, and raised upgrading at prostatectomy from 19.2% to 31.5% [16]: a trade-off that looks favourable in aggregate looks unfavourable counted per case. In addition, one third of men in that arm had a PSA test between screening rounds, with significant cancer detected in 0.2% during the interval, mostly in the elevated-risk group [17]. Opportunistic testing therefore quietly supplies part of the safety-net that trial protocols assume.

Negative MRI: how safe is "no biopsy"?

The pooled negative predictive value of PI-RADS 1–2 for grade group 2 or higher cancer in biopsy-naive men is 90.8% (95% CI 88.1–93.1) across 42 studies and 7321 patients, rising to 97.1% for grade group 3 or higher and falling to 86.8% if PI-RADS 3 is also counted as negative [18]. Roughly nine significant cancers per 100 men are therefore left behind when biopsy is omitted on imaging alone. The authors' caution, that institutional data should govern the decision where available, is the important part of that paper.

Longitudinal cohorts reassure but do not settle the matter. Among 4259 men imaged in a Dutch expert centre, 53.6% had PI-RADS ≤2, and in the 320 who underwent repeat MRI at a median of 57 months, significant-cancer diagnosis-free survival was 99.6% at three years [19]. In the FUTURE subgroup, 431 men with a previous negative systematic biopsy and a non-suspicious MRI had 13 significant cancers (3.0%) over a median of 41 months: a low absolute rate, but a standardised incidence ratio of 4.3 (95% CI 2.3–7.4) [20]. A population-based Finnish comparison localised that risk using PSA density, defined as serum PSA divided by prostate volume (ng/mL per mL of prostate). Incidence of significant cancer after a non-suspicious MRI was 1852 versus 552 per 100,000 person-years in the general population (rate ratio 3.4, 95% CI 2.8–4.1), but among men whose PSA density was below 0.15 ng/mL/mL the rate fell to 778 per 100,000 person-years, a ratio of 1.4 (95% CI 0.9–2.0) that was indistinguishable from background [21].

A negative MRI alone therefore identifies a group at roughly three times population risk; a negative MRI with a low PSA density identifies a group at population risk. The density is doing much of the work.

PI-RADS 3 and the density thresholds

PI-RADS 3 lesions make up about 17% of scans and carry a pooled cancer detection rate of 36%, of which significant cancer accounts for 18.5% (95% CI 16.6–20.3; range 3.4–46.5%) [22]. A larger meta-analysis of positive predictive value found 13% for PI-RADS 3, against 40% for PI-RADS 4 and 69% for PI-RADS 5 [23]; biopsying every PI-RADS 3 lesion therefore means about eight negative or indolent results for each significant cancer found.

PSA density converts this into a decision, but the threshold is contested and depends on the prevalence of disease in the population served (Table 1). In 349 men with PI-RADS 3 lesions only, significant cancer was present in 20.0% overall and in 13.6% (31/228) of those with a density below 0.15 ng/mL/mL, a miss rate most clinicians would find uncomfortable in a referral setting

[24]. A stricter threshold performs better: in a cohort with 45% significant-cancer prevalence, no biopsy for PI-RADS 3 with a density below 0.10 ng/mL/mL avoided 63 biopsies per 1000 men without missing a single significant cancer, and outperformed four recalibrated MRI risk models on decision-curve analysis up to a 15% risk threshold [25]. In a community cohort with 24% prevalence the opposite adjustment held: a post-MRI threshold of ≥0.20 rather than ≥0.10 ng/mL/mL left only 1.3% (3/239) of grade group 2 or higher cancers undetected while avoiding 29% of negative biopsies [26]. A clinical risk model accepting a miss rate of 5% or less avoided 34% of targeted biopsy sessions [27].

Density applied before the scan is a different and riskier proposition. In STHLM3-MRI, a pre-MRI cut-off of 0.075 ng/mL/mL reduced MRI use by 28% and Gleason 6 detection by 17% while missing 5% of Gleason ≥3+4 cancers, with no loss of Gleason ≥4+3 detection; every higher threshold lost significant cancer [28]. In MR-PROPER, a pre-MRI threshold of ≥0.10 ng/mL/mL avoided 30% of scans but left 9.6% (23/239) of grade group 2 or higher cancers undetected [26].

Multivariable calculators add discrimination but have proved fragile. Adding PI-RADS and age to the Rotterdam European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator raised the area under the curve for high-grade cancer from 0.76 to 0.84 in biopsy-naive men, yet net benefit was clear only in previously biopsied men, in whom a 10% threshold saved 36% of biopsies while missing high-grade cancer in 4% [29]. Three of four published MRI risk models were poorly calibrated and clinically useless without local recalibration [25]. A simple PI-RADS-plus-density rule, applied locally and audited, is currently more dependable than an imported nomogram.

Targeted alone, or targeted plus systematic cores

The evidence does not support targeted-only biopsy in MRI-positive men outside a screening programme. Beyond MRI-FIRST and the Trio study [5,6], a within-patient paired analysis of 872 men found that 8.0% of significant cancers were detected exclusively by systematic cores and that grade group was higher on systematic cores in 8.4%, with that contribution persisting across all PSA density strata (miss rates 3.4–13.7%) [30]. In screening, omission of systematic cores reduced detection of grade group 2 or higher cancer by 15% and of grade group 3 or higher cancer by 14% [16].

The pragmatic compromise now endorsed by European guidance is targeted plus perilesional or regional sampling rather than full 12-core systematic biopsy. A single-centre non-inferiority trial of 380 biopsy-naive men with a single unilateral lesion found that the two strategies detected grade group 2 or higher cancer identically (58% versus 58%; risk difference 0.53%, 95% CI −9.4 to 11), with fewer complications in the perilesional arm (62% versus 74%, p = 0.023) [31]. With one centre and one lesion pattern, this evidence is supportive rather than definitive.

The safety-net after deferral

Deferring biopsy creates an obligation. Among 694 men with PI-RADS ≥3 and negative targeted and systematic biopsies in ten tertiary centres, cancer detection during follow-up was 26.8% overall and 19.3% for significant disease; those followed by clinical and radiological triggers rather than scheduled re-biopsy had the highest cancer-free survival (96% at two years, 86% at five years) [32]. In a smaller cohort followed for a median of 66 months, the two-year significant-cancer rate was 7.6%, rising to 15.2% at final follow-up. Baseline density above 0.15 ng/mL/mL predicted it (18.2% versus 3.7%, p = 0.036), density below 0.15 ng/mL/mL with PI-RADS 3 gave a two-year rate of 3% (1/34), and rising density and an upgraded repeat MRI were the strongest signals [33].

A defensible safety-net is therefore a repeat PSA at 6–12 months with density recalculated on the MRI-measured volume, and repeat MRI at roughly two years, sooner if density rises or the examination changes. Scheduled re-biopsy without a trigger is not supported.

Biopsy route, molecular imaging and artificial intelligence

When biopsy is needed, the route matters for harm rather than yield. A Bayesian meta-analysis of five randomised trials in 3072 men, almost all MRI-targeted, found that transperineal biopsy reduced infectious complications (pooled odds ratio 0.38, 95% credible interval 0.11–0.90) despite no antibiotic prophylaxis in that arm, with no difference in significant-cancer detection (odds ratio 1.01, 95% credible interval 0.65–1.51) [34]. A larger meta-analysis of ten randomised trials and 4188 biopsies found that transperineal access reduced hospitalisation for infection by 77% (odds ratio 0.23, 95% CI 0.10–0.54) and post-procedural fever (odds ratio 0.68, 95% CI 0.52–0.89) [35]. NORAPP randomised 555 men to cefuroxime or no prophylaxis before transperineal biopsy and observed no sepsis or infection requiring admission in either arm, with a number needed to treat of 137 [36]. Transperineal biopsy under local anaesthesia without antibiotics is the appropriate default; the cost is mild procedural pain.

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) is the most promising second-line triage test. The PRIMARY score gave a sensitivity of 88% and a negative predictive value of 81% for scores 1–2 versus 3–5, against 83% and 72% for PI-RADS 2 versus 3–5 in the same men [37]. PRIMARY2 randomised 660 biopsy-naive men with PI-RADS 2 or 3 scans but high clinical risk to gallium-68 PSMA-11 PET-computed tomography (PET-CT) or systematic transperineal biopsy: significant cancer was found in 12% versus 16% (difference −3.7%, 95% CI −8.9 to 1.5; non-inferior), and 163 of 331 men (49%) in the PET arm avoided biopsy [38]. Combined PSMA PET and MRI, pooled across 20 studies, gave a patient-level sensitivity of 92% and specificity of 64%, with higher specificity than MRI alone [39]. This is a demonstrated effect in one adequately powered trial in a selected population; cost, access and generalisability to other radiopharmaceuticals remain open.

Machine reading is at the same stage. In PI-CAI, an artificial intelligence (AI) system achieved an area under the curve of 0.91 (95% CI 0.87–0.94), against 0.86 (95% CI 0.83–0.89) for 62 radiologists reading the same 400 cases. At the readers' mean PI-RADS ≥3 operating point it detected 6.8% more significant cancers at equal specificity, or produced 50.4% fewer false positives and 20.0% fewer grade group 1 diagnoses at equal sensitivity [40]. Against the historical multidisciplinary standard of care in all 1000 test cases, non-inferiority was not confirmed. A meta-analysis of 29 paired studies found that AI assistance improved reader sensitivity (86.5% versus 82.6%) and specificity (57.8% versus 50.0%), with the largest gains among less experienced readers [41]. AI reduces inter-reader variability where subspecialist radiology is unavailable; it does not replace it.

Discussion

Principal findings

A non-suspicious MRI alone is not sufficient grounds to omit biopsy, but becomes so when combined with a PSA density below 0.15 ng/mL/mL. PI-RADS 3 lesions require a density threshold calibrated to local prevalence. Omitting systematic or regional cores in MRI-positive men trades detection of significant disease for a reduction in overdiagnosis, a trade that is acceptable in some screening settings but not in referral practice. Every deferral must be coupled to scheduled reassessment.

Comparison with guidelines and other studies

These estimates agree with the Cochrane review, whose MRI-directed pathway missed 8.4 significant cancers per 100 men at 30% prevalence [3], and with the pooled negative predictive value of about 91% [18]; this review adds an account of how PSA density and local prevalence modify that figure. Guidelines converge on principle and diverge on detail. The 2026 European multidisciplinary guideline (EAU-EANM-ESTRO-ESUR-ISUP-SIOG) recommends multiparametric MRI to avoid unnecessary biopsies and, when biopsy is undertaken, targeted plus regional cores [42]. The AUA/SUO guideline frames the objective as detection of grade group 2 or higher disease within shared decision-making [43,44], and NCCN guidance addresses MRI use and management after a negative biopsy [45]. None

specifies a density threshold, which the evidence supports: the right threshold depends on local prevalence and on how much missed disease a service will accept.

Implications for practice

The following recommendations translate the evidence into practice; the certainty of each was graded as described in the Methods.

Offer pre-biopsy MRI to all men with a clinical suspicion of prostate cancer who would accept treatment, reported with PI-RADS or an equivalent Likert scheme, using a biparametric protocol where image quality can be assured (high certainty: two randomised trials, a paired confirmatory study, a Cochrane review and a within-patient non-inferiority trial [1–3,5,7,8]).

Do not omit biopsy on a PI-RADS 1–2 result alone. Calculate PSA density from the MRI-measured volume: below 0.15 ng/mL/mL biopsy may be deferred, because subsequent significant-cancer incidence approaches that of the general population; at or above 0.15 ng/mL/mL, biopsy remains indicated (moderate certainty: one population-based cohort with matched comparison, supported by a pooled negative predictive value of 90.8% and concordant cohort data [18,19,21]).

For PI-RADS 3 lesions, set the density threshold according to local prevalence rather than importing one. In referral practice with a significant-cancer prevalence above 40%, use 0.10 ng/mL/mL; in community or screening practice with a prevalence near 20–25%, 0.15–0.20 ng/mL/mL is defensible, missing 1–14 significant cancers per 100 men spared depending on the threshold (low certainty: consistent direction across retrospective cohorts and decision-curve analyses, but no randomised comparison and marked heterogeneity [22–27]).

Do not use PSA density to decide who has an MRI unless the threshold is 0.075 ng/mL/mL or lower; higher pre-MRI thresholds miss around 10% of grade group 2 or higher cancers (moderate certainty: one prespecified screening-trial analysis and one community cohort, concordant [26,28]).

When biopsy is performed for a visible lesion, take targeted cores plus perilesional or regional sampling rather than targeted cores alone (moderate certainty: paired diagnostic studies, a within-patient paired analysis and a screening-trial analysis show that systematic or perilesional cores add 5–16% of significant cancers and reduce grade misclassification; the perilesional substitute rests on a single randomised trial [5,6,16,30,31]).

Use the transperineal route under local anaesthesia without antibiotic prophylaxis in men without specific risk factors for infection (high certainty: two meta-analyses of randomised trials and one dedicated non-inferiority trial [34–36]).

When biopsy is deferred, arrange repeat PSA with recalculated density at 6–12 months and repeat MRI at about two years, brought forward if density rises or symptoms change; do not schedule re-biopsy without a trigger (low certainty: observational follow-up cohorts only [19,20,32,33]).

Consider PSMA PET only for men with PI-RADS 2–3 scans and persistent high clinical risk, and only where funded; it is not a first-line triage test (moderate certainty: one adequately powered randomised non-inferiority trial in a selected population, supported by diagnostic meta-analysis [38,39]).

Use AI-assisted reading to support non-subspecialist radiologists rather than as an autonomous reader (low certainty: one paired confirmatory study in which non-inferiority to routine multidisciplinary practice was not established, plus one meta-analysis of reader studies [40,41]).

Strengths and limitations

The strengths of this review are its focus on randomised, paired within-patient and population-based screening evidence; its re-expression of diagnostic accuracy as clinically significant cancers missed per 100 men, the quantity that clinician and patient must weigh; and an explicit certainty statement for each recommendation. It also has important

limitations. It is a narrative rather than a systematic review: a single database was searched, study selection and data extraction were not performed in duplicate, the numbers of records screened and excluded at each stage were not recorded, and no protocol was registered and no formal risk-of-bias assessment was undertaken, so selective citation cannot be excluded. Numerical estimates were taken from abstracts, which may omit subgroup data and occasionally differ from the full report. The density thresholds for PI-RADS 3 lesions derive largely from retrospective cohorts with heterogeneous reference standards, MRI protocols and reader experience, and certainty grading reflects the authors' judgement rather than formal GRADE profiles. Finally, almost all of the evidence comes from high-income settings and expert centres with subspecialist radiology; its transferability to services with less experienced readers or limited MRI access, including many low- and middle-income countries, is uncertain.

Unanswered questions

Whether deferring biopsy after a negative MRI affects prostate cancer mortality will be answered only by long-term follow-up of the screening trials; ProScreen mortality data, for example, are pending [15]. No randomised trial has compared PSA density thresholds for PI-RADS 3 lesions, and the optimal interval and content of the safety-net after deferral have not been tested prospectively. The cost-effectiveness of PSMA PET as a triage test, its performance with other radiopharmaceuticals, the effect of AI-assisted reading on patient outcomes, and the performance of MRI-led pathways outside expert centres all require prospective evaluation.

Conclusion

MRI-first diagnosis is settled; MRI-only diagnosis is not. A non-suspicious scan alone leaves roughly nine significant cancers per 100 unbiopsied men undetected; a low PSA density brings that close to background; and PI-RADS 3 is a decision point whose threshold depends on how much disease the local population has. Screening trials show that deferring biopsy after a negative MRI halves overdiagnosis without a detectable rise in advanced disease over four years, yet also that dropping systematic cores in MRI-positive men costs more significant cancer than it saves indolent cancer. The safest sentence to say to a man with a negative MRI and a low density is not "you do not have cancer" but "you do not need a biopsy now, and here is when we will look again".

DECLARATIONS

Author contributions

Alaa Menshawy: conceptualisation, methodology, investigation, writing – original draft, writing – review and editing. Rana Elmassry: investigation, validation, writing – review and editing. Both authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Competing interests

None declared. Both authors have completed the ICMJE disclosure form.

Ethical approval

Not applicable. This review used only published data and involved no human participants.

Data availability

No new data were generated or analysed. All data discussed are available in the cited publications; the search topics are listed in the Methods.

Registration

Not applicable; narrative reviews are not eligible for PROSPERO registration.

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