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# Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions

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**Abstract**

***Context:*** The Prostate Imaging-Reporting and Data System (PI-RADS) v2 analysis system for multiparametric magnetic resonance imaging (mpMRI) detection of prostate cancer (PCa) is based on PI-RADS v1, accumulated scientific evidence, and expert consensus opinion.
***Objective:*** To summarize the accuracy, strengths and weaknesses of PI-RADS v2, discuss pathway implications of its use and outline opportunities for improvements and future developments.
***Evidence acquisition:*** For this consensus expert opinion from the PI-RADS steering committee, clinical studies, systematic reviews, and professional guidelines for mpMRI PCa detection were evaluated. We focused on the performance characteristics of PI-RADS v2, comparing data to systems based on clinicoradiologic Likert scales and non–PI-RADS v2 imaging only. Evidence selections were based on high-quality, prospective, histologically verified data, with minimal patient selection and verifications biases.
***Evidence synthesis:*** It has been shown that the test performance of PI-RADS v2 in research and clinical practice retains higher accuracy over systematic transrectal ultrasound (TRUS) biopsies for PCa diagnosis. PI-RADS v2 fails to detect all cancers but does detect the majority of tumors capable of causing patient harm, which should not be missed. Test performance depends on the definition and prevalence of clinically significant disease. Good performance can be attained in practice when the quality of the diagnostic process can be assured, together with joint working of robustly trained radiologists and urologists, conducting biopsy procedures within multidisciplinary teams.
***Conclusions:*** It has been shown that the test performance of PI-RADS v2 in research and clinical practice is improved, retaining higher accuracy over systematic TRUS biopsies for PCa diagnosis.
***Patient summary:*** Multiparametric magnetic resonance imaging (MRI) and MRI-directed biopsies using the Prostate Imaging-Reporting and Data System improves the detection of prostate cancers likely to cause harm, and at the same time decreases the detection of disease that does not lead to harms if left untreated. The keys to success are high-quality imaging, reporting, and biopsies by radiologists and urologists working together in multidisciplinary teams.



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## 1. Introduction

The diagnosis of prostate cancer (PCa) differs from that for other solid organ cancers, where imaging is used to identify patients who require biopsies and the lesions that need to be targeted. Instead, the standard PCa diagnostic pathway offers transrectal ultrasound (TRUS) guided biopsies with multiple needles, with systematic sampling of the entire prostate gland without knowledge of the likely locations of tumors. Patients chosen for this approach include biopsy-naïve men with elevated serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE), those deemed to be at persistent elevated risk of harboring significant cancers despite prior negative TRUS biopsies, and men with low-risk PCa undergoing active surveillance (AS), who need repeated prostate gland sampling for disease monitoring.

The noncancer specific causes of elevated PSA, the semi-randomness and intrinsic sampling errors of the TRUS biopsy procedure, the variable prevalence of PCa among men at risk [1], and the wide genomic diversity and range of prognoses for men with PCa lead to multiple clinical impacts for men with elevated risks. (1) A large proportion of men undergoing TRUS biopsies do not have any cancers detected [2]; these unfruitful biopsies still incur attendant morbidities [3] without giving complete surety on the absence of significant disease capable of causing patient harm. (2) Overdiagnosis of clinically unimportant cancers occurs and contributes unnecessarily to patient anxieties [4], leading to overtreatment and treatment-related harm, with benefits for limited groups of patients [5,6]. (3) Underdiagnosis and undertreatment of clinically important cancers also occur because of tissue sampling and risk stratification errors, contributing to diagnostic and treatment failures, particularly for patients opting for AS.

## 2. Clinical priorities for PCa diagnosis

### 2.1. Minimizing overdiagnosis and detecting clinically significant PCa are joint priorities for biopsy-naïve men

Low 10-yr PCa-specific mortality rates among men with low-risk PCa and the need to avoid overdiagnosis, overtreatment, and treatment-related harm are the driving reasons for the US Preventive Services Task Force (USPSTF) 2017 draft recommendations discouraging the use of PSA screening for older men. On the other hand, there is also an important need to improve the detection of prostate cancers that do require active treatments, to decrease prostate cancer specific death rates. These considerations were emphasized by recent publications, of two large prospective observational studies (ProtecT 2016 and PIVOT 2017).

The ProtecT study showed that active treatment of low-risk disease, had minimal patient survival benefits [6]. The results showed no cancer-specific 10-years survival differences between active therapies (surgery and radiotherapy) and active monitoring but did note that surgery delayed the time-to-metastasis development. These data suggest that TRUS biopsy-based pathologic misclassifications can have long-term clinical impacts on monitored patients with undiagnosed higher grades of disease. The updated PIVOT study results on 731 patients, suggested that the benefits of surgery compared to disease monitoring, occur in selected patients. After a median 12.7 years (range, 12-19.5) of follow-up, there was a non-statistically significant difference in prostate cancer specific mortality rates in favor of surgery (hazard ratio (HR) of 0.63 ($p = 0.06$)). Sub-analyses suggested, that surgery is most likely to achieve mortality reductions in intermediate-risk patients (absolute difference, -14.5%, non-significant) but not for those with low or high-risk disease.

### 2.2. Detecting aggressive PCa locations is the clinical priority in men with a prior negative biopsy and AS patients

The primary motivation for repeating biopsies in patients with prior negative biopsies and persistently elevated or rising PSA is the concern that clinically significant PCa (csPCa) was missed on prior biopsies. Extended saturation biopsies in patients with a prior negative biopsy have shown that systematic 10–12-core TRUS biopsies miss csPCa in anterior and apical locations in a substantial proportion of patients [7]. Uncertainty in accurately assigning risk status also contributes to active management for men with low-risk disease who might be suitable for AS. For example, prostatectomy specimen examinations from low-risk patients have found unfavorable pathologic characteristics in 20-36% [8,9]. Similarly, template mapping biopsies in potential AS candidates or patients undergoing AS demonstrate 30-40% pathologic misclassification rates [10–12]. These pathologic misclassification errors contribute to high AS discontinuation rates of up to 52% by 5 yr, many of which are because of pathologic upgrading or upstaging detected on follow-up [13–15]. Improved risk stratification tools are therefore needed to better direct patient management [8].

## 3. Addressing clinical needs in PCa diagnosis

Multiple universal clinical needs and priorities can be identified for men who are at high risk of harms from PCa. These include (1) determining the causes of elevated PSA, and whether elevated PSA can be ascribed to the presence of csPCa; (2) reducing the number of investigations, including biopsies, needed to determine the cause(s) of elevated PSA, while at the same time minimizing the number of men overdiagnosed with low-risk disease; (3) improving the detection and anatomic localization of csPCa to allow appropriate, directed biopsy for improving risk stratification for diagnosed patients and thereby customizing their clinical care; and (4) minimizing the time taken to arrive at final diagnoses and to start risk-appropriate treatment(s). These priorities and clinical needs should be met at reasonable costs.

Many tools are being developed to meet the clinical needs for more accurate PCa diagnoses. The emerging clinical paradigm is to use advances in both imaging and molecular diagnostics [16–19] to better select patients

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requiring biopsy. The developing idea is that the combined use of PSA metrics (PSA, PSA density [PSAD], PSA velocity), PSA isoform assays such as the prostate health index (PHI) and 4Kscore, and urinary PCa gene methylation tests can act as multivariate risk estimators to identify patients likely to harbor csPCa. However, patient selection methods based on risk calculators cannot localize csPCa within the gland, which may be missed by systematic biopsy. Diagnostic yields of biopsy procedures can be increased by using imaging to refine patient selections [20–23], and thereafter to direct biopsies to suspicious locations, thus reducing the number of men undergoing biopsy and consequently overtreatments of men with insignificant disease [24]. Central to these developments are the emerging roles of multiparametric magnetic resonance imaging (mpMRI) and MR-directed biopsy (MRDB; refers to all biopsy methods using prior mpMRI information) for PCa diagnosis and treatment selection.

## 4. Prostate mpMRI

A large body of research and clinical experience on combined mpMRI-MRDB for PCa diagnosis supports the value of mpMRI for the detection and localization of csPCa [2,25–28]. The mpMRI-MRDB approach increases the diagnostic yield of larger Gleason score (GS) 3 + 3 and higher-grade (GS $\geq$ 3 + 4) csPCa using fewer biopsy cores [24,28–30]. This approach also decreases the detection of insignificant disease [28,31] and improves risk stratification for diagnosed patients [32]. There are challenges in implementing prostate mpMRI-MRDB in clinical practice, including heterogeneity of image quality between centers [33] and consequently variations in the diagnostic performance for PCa detection [34]. Specifically, prostate mpMRI quality depends on MRI equipment capabilities (including equipment vendor, magnet field and gradient strength, coil set used, software and hardware levels, sequence parameter choices), patient factors (medications, body habitus, motion, metal implants, rectal gas), biopsy-related prostate gland hemorrhage, and most importantly the radiologic interpretation of images (learning curve effects, subjectivity of observations, interobserver variations, and reporting styles). To address these challenges, it has become necessary to develop imaging, quality, and reporting standards for prostate mpMRI, and accreditation standards for the future.

## 5. PI-RADS

The Prostate Imaging-Reporting and Data System version 2 (PI-RADS v2) was designed by the joint steering committee of the American College of Radiology (ACR), the European Society of Urogenital Radiology (ESUR) and the AdMeTech Foundation [35]. The aims for PI-RADS v2 were to simplify and standardize the terminology and content of mpMRI prostate reports, to develop assessment categories that summarize levels of suspicion for csPCa, to assist in the selection of patients for biopsies and management, to establish acceptable technical parameters for mpMRI, and to reduce variability in imaging interpretations. It should also be noted that PI-RADS v2 does not directly address the quality standards needed for MR-guided biopsy (MRGB), which is addressed elsewhere [36].

PI-RADS v2 was built on the foundation of PI-RADS v1 [37], but there are important differences between the two systems [38]. For example, PI-RADS v2 does not include spectroscopic imaging, and dynamic contrast enhancement MRI (DCE-MRI) is relegated to a clarification role for peripheral zone (PZ) assessments. Instead, diffusion-weighted imaging (DWI) has been given greater emphasis for evaluation of the PZ and less emphasis in transition zone (TZ) assessments. Likewise, T2-weighted (T2W) features have a greater emphasis for TZ evaluations.

It is important to note that there are a range of malignant and benign pathologies in the prostate gland that have overlapping mpMRI characteristics [39]. Therefore, a low PI-RADS assessment category of 2 does not completely exclude the possibility of csPCa; rather, it simply indicates that it is unlikely. Similarly, assessment category 5 is not proof that a lesion is csPCa, but rather indicates that it is highly likely. The range of likelihood of cancer depends on the study population and the method(s) used for histologic verification, as discussed in more detail below.

There are multiple distinguishing features between the imaging-only PI-RADS v2 system, other non–PI-RADS imaging systems, and clinicoradiologic Likert impressions [40–45], whose performance for disease detection has been reported in the literature [2,26,44,45]. It is important to note that PI-RADS v2 assessment categories are based on combinations of predefined mpMRI features, weighted for the likelihood of malignancy, to be evaluated in a specified order, separately for lesions in the PZ and TZ. Other systems use additional non–PI-RADS imaging criteria (such as number of sequences on which abnormalities are visible and the scaled likelihood of extraprostatic extension [43]) or subjectively incorporate clinical factors such as family history, DRE findings, PSA, and PSAD to arrive at clinicoradiologic impressions of the likelihood of csPCa [36]. However, to promote standardization and reduce observer variability, PI-RADS v2 reduces flexibility in imaging interpretations. Thus, PI-RADS has developed into the universal standard for prostate mpMRI interpretation and reporting. Note that PI-RADS v2 also does not assign specific management algorithms for the PI-RADS assessment categories, acknowledging the essential contribution of clinical features to patient decision-making.

## 6. Prostate mpMRI validation

### 6.1. *Radiologic-pathologic correlations*

Detailed mpMRI-prostatectomy histologic correlation studies have shown improved visibility of larger [46–49], higher-grade lesions [46,48,49] with noncribriform pattern [50], the latter applying mostly to index lesions [46,51,52]. As a guide, GS 3 + 3 lesions with a solid growth pattern need to have a volume of $\geq$0.5 ml (approx. 9–10-mm-diameter sphere) to be detected. Index lesions with a

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primary GS ≥ 3 + 4 pattern with a volume ≥0.2 ml (approx. 7–8-mm-diameter sphere) can also be identifiable in some studies undertaken on modern 3-T scanners using endorectal coils for signal reception [47,51,52]. However, it should be noted that although most index lesions can be detected [46], nonindex lesions are often overlooked, even if they are of high grade, and the size of lesions is often underestimated [53].

The PI-RADS v2 system does not aim to detect all prostate tumors, with poorer sensitivity for lower-volume (<0.5 ml) GS 3 + 3 disease, which is unlikely to cause patient harm (low-risk PCa). This allows mpMRI-MRDB to address the USPSTF concerns of overdiagnosis and overtreatment (https://screeningforprostatecancer.org/ [5,6]) and to reduce the number of men undergoing biopsies while on AS. Indeed, a negative mpMRI (PI-RADS 1 and 2 assessment categories) in the context of selecting patients for AS indicates likely patient suitability [54]. In the same way, a negative mpMRI is an independent predictor for likely downgrading of GS 3 + 4 at TRUS biopsy to GS 3 + 3 at prostatectomy pathology [55].

As expected, larger, higher-grade lesions are more likely to be detected and to have higher PI-RADS assessment categories (PI-RADS categories 4 and 5) [53,56,57]. Detailed radiologic-pathologic correlation studies using the PI-RADs v2 system are not numerous, but do show that smaller, nonindex csPCa foci with a cribriform pattern [50] go undetected or their sizes are underestimated [53], which can have significant implications for PCa detection and gland-sparing therapies. There is an ongoing need to further improve our understanding of the characteristics of detected and undetected cancers by PI-RADS v2 assessment categories, including sensitivity by size, GS, pathologic pattern, and index lesion status, using the methods described by Le et al [46].

### 6.2. PI-RADS v2 test-performance

Multiple patient- and lesion-level analyses have shown that PI-RADS v2 assessment categories are effective for in-situ cancer detection, with increases in the predictive value for each increment in PI-RADS assessment category for all cancers and csPCa. The largest validation study reported on data prospectively collected for biopsy-naïve patients at three high-volume tertiary care centers and used both PI-RADS systems [58]. Patients underwent 18–24-core systematic transperineal biopsies and additional targeted biopsies for positive mpMRI findings (Ginsburg biopsy scheme [59]). Among 807 patients there was a csPCa (GS ≥ 3 + 4) prevalence of 49%. The investigators found that the csPCa prevalence increased with the PI-RADS assessment category: PI-RADS 1–2, 20% (95% confidence interval [CI] 15–25%), PI-RADS 3, 31% (95% CI 25–38%); and PI-RADS 4–5, 71% (95% CI 67–75%).

In a large retrospective analysis of in-bore targeted biopsies among 1057 patients (first biopsy, $n = 184$; prior negative biopsy, $n = 649$; active surveillance, $n = 224$), csPCa (GS ≥ 3 + 4) was found in 17%, 34%, and 67% of patients with PI-RADS 3, 4, and 5 lesions, respectively [27]. Another study among 339 biopsy-naïve patients using TRUS targeting and 12-core systematic biopsy found csPCa (GS ≥ 3 + 4) in 737 targets in 0%, 10%, 12%, 22%, and 72% of cases in the PI-RADS 1, 2, 3, 4, and 5 categories, respectively [25]. In a retrospective study, Greer et al [60] assessed lesion detection using PI-RADS v2 criteria for 163 patients assessed by nine readers; 654 lesions (including 420 PZ lesions) were compared with whole-mount prostatectomy findings for 110 patients and systematic biopsies for 50 patients. The probability of cancer detection incrementally increased with the PI-RADS v2 category (16%, 33%, 71%, and 91% for PI-RADS 2, 3, 4, and 5 lesions, respectively). This study also confirmed the dominant sequence concept incorporated into the PI-RADS v2 system, but only for PZ lesions and not for T2W over DWI in the TZ. Furthermore, Greer et al [60] also documented meaningful contributions by DCE-MRI to diagnostic yields in the PZ for assessment categories 2–4. We encourage further studies evaluating the multireader performance of the PI-RADS v2 criteria with whole-mount histopathology, and evaluations of the dominant sequence concept and the contribution of DCE-MRI to observer performance.

High PI-RADS v2 performance has also been confirmed by systematic reviews and meta-analyses [61,62], including an analysis of 3857 patients that showed that PI-RADS v2 had pooled sensitivity of 89% (95% CI 86–92%) with specificity of 73% (95% CI 60–83%) for PCa detection [61]. Comparative data have also shown that PI-RADS v2 performs better than PI-RADS v1. For example, in a retrospective study comparing PI-RAD v1 to PI-RADS v2 readings in guiding TRUS prostate biopsy in 401 consecutive patients, both PI-RADS versions showed good diagnostic performance, but in the TZ the performance of v2 was better [63]. In a meta-analysis of six head-to-head PI-RADS v1 and v2 comparison studies, PI-RADS v2 had higher pooled sensitivity of 95% (95% CI 85–98%), compared to 88% (95% CI 80–93%) for PI-RADS v1 ($p = 0.04$). However, the pooled specificity was not significantly different (73% [95% CI 47–89%] vs 75% [95% CI 36–94]; $p = 0.90$) [61]. Further studies using PI-RADS v2 and MRDB in various population groups (biopsy-naïve, prior negative TRUS, AS cohorts, Eastern/Western populations [61,62,64]) are needed to develop robust estimates of PCa likelihood corresponding to the PI-RADS assessment categories.

It is important to remember that the combined performance of mpMRI-MRDB is strongly influenced by the respective limitations of both procedures separately and in combination. Heterogeneity of PI-RADS v2 results appears to be related to multiple factors, including the definitions used for csPCa, the prevalence of csPCa in different study populations, mixing of study populations within studies, reference standards used for verification, radiologic expertise and variations in technical performance, and limitations specific to the MRDB procedure used [61,62]. Limitations of MRDB approaches relate to the method used for lesion targeting (in-bore, MR-US fusion, cognitive) and biopsy errors (fusion method, biopsy route, operator expertise, number of cores taken, lesion sampling strategy, lesion histology, and lesion and gland volumes) [30,65–68].

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### 6.3. Supportive validation data from recent non–PI-RADS studies

In an attempt to minimize multiple study biases in literature data, the PROMIS study prospectively benchmarked the diagnostic accuracy of mpMRI before a first prostate biopsy [2]. PROMIS evaluated the accuracy of mpMRI for detecting csPCa in biopsy-naïve patients in comparison to the current standard of TRUS biopsy, using transperineal prostate mapping biopsy (TPMB) for verification. 576 men evaluated in 11 centers underwent three tests: (1) PI-RADS–compliant mpMRI using 1.5-T systems (no endorectal coil) with image interpretation by trained radiologists who did not use the PI-RADS system (instead using the University College London Likert impression system); (2) standard TRUS biopsies; and (3) TPMB with 5-mm sampling of the entire gland. Blinding to the three tests allowed pairwise comparison of mpMRI and TRUS biopsy results with a high level of confidence for assessing relative diagnostic accuracy.

On TPMB, 408 of 576 men (71%) had PCa; 230 (40%) had csPCa (according to a primary definition of GS $\geq$ 4 + 3 and/or any lesion with a maximum cancer core length of $\geq$6 mm). The predictive value increased stepwise with increments in the Likert impression score; for Likert scores of 1, 2, 3, 4, and 5 scores, csPCa was found in 3%, 12%, 21%, 58%, and 81% of cases, respectively. mpMRI was more sensitive (93%; 95% CI 88–96%) than TRUS biopsy (48%; 95% CI 42–55%) but less specific (41%, 95% CI 36–46% vs 96%, 95% CI 94–98%). Since there are differing views on the definition of csPCa on TPMB, the results for other pathologic definitions were also studied. For the most commonly used literature definition of csPCa (GS $\geq$ 3 + 4), TRUS biopsy had sensitivity of 48%, meaning that TRUS misses 52% of csPCas, while mpMRI missed 12% (sensitivity 88%). For clarity, it should be noted that there was no spatial concordance between mpMRI findings and TPMB positivity, which may have affected lesion-based mpMRI sensitivity within PROMIS.

The consistently higher sensitivity and more variable specificity in all mpMRI studies using PI-RADS v1, PI-RADS v2, non–PI-RADS imaging systems, and clinicoradiologic Likert impressions indicate that the "rule out" performance of mpMRI is better than its "rule in" performance for csPCa, meaning that biopsies are required for positive mpMRI scans to confirm the presence of csPCa. The more powerful "rule out" performance (higher sensitivity and negative predictive value [NPV]) has important clinical implications for men with negative scans, as discussed in the section on mpMRI pathway impacts and in the Supplementary material. A degree of caution is needed when applying the results of the better "rule out" performance to clinical practice. It must be remembered that the NPV is inversely related to disease prevalence, which is highly variable, meaning that patients selected for mpMRI assessments are not uniform in the literature [1].

Practice-changing adoption of mpMRI-MRDB therefore requires combined use of clinical parameters and mpMRI findings if we are to take full advantage of the intrinsic excellent sensitivity of mpMRI. It should also be noted that most reports are retrospective evaluations in which suboptimal image data sets are often excluded from analyses. Therefore, more weight should be given to results from prospective analyses. Furthermore, many studies use histologic verification in prostatectomy specimens and thus suffer from selection biases, while other studies use MRDB as its own reference standard, which involves intrinsic verification bias. In addition, studies performed at high-volume expert centers with the advantages of state-of-the-art equipment, optimized protocols, and radiologists highly experienced in subspecialties reduce the generalizability of published results.

## 7. Addressing PI-RADS v2 limitations

PI-RADS v2 has been a major advance towards high-precision PCa diagnosis, but accrued clinical experience has highlighted limitations [69]. Of note, moderate interobserver variability has been identified, even among expert readers [70–73] and particularly for TZ evaluations [73]. This appears to be related in part to the inherent limitations of the accrued mpMRI data and ambiguities in the application of some of the diagnostic criteria. For example, PI-RADS v2 does not fully explain how to handle lesions that appear to arise solely from the central zone [74], and it does not provide separate guidance on image interpretation of anterior-superior tumors substantially involving the anterior fibromuscular stroma. In addition, PI-RADS v2 is unclear regarding the distinction between DWI scores of 3 and 4/5, and for DCE positivity for nonfocal lesions in the PZ; both contributing to greater inter-reader variability. Furthermore, PI-RADS v2 does not sufficiently address how to classify likely nodular benign prostatic hyperplasia, which does not have the classic appearance of encapsulation. These limitations will be addressed by PI-RADS v2.1, together with other minor changes regarding data acquisition parameters and the sector map. While the adoption of these PI-RADS v2.1 amendments will not change the overall test-performance, it is hoped that PI-RADS v2.1 will improve the mpMRI inter-reader variability.

PI-RADS remains a living document and continued evolution is anticipated as further clinical experience and investigative data are accrued. Efforts are already under way to expand and adapt PI-RADS to meet a variety of needs in the evolving paradigms for MRI use in PCa care. This includes clinical recommendations on tissue sampling needs and methods according to mpMRI findings, and the use of mpMRI for selection of patients who are suitable for gland-sparing therapies such as focal ablation and AS. It is anticipated that the next major PI-RADS revision will be a multiyear endeavor requiring additional research data on PI-RADS criteria [43] and clinical usage. A variety of proposals for inclusion have been tabled, but the literature evidence for inclusion is highly variable to date. The PI-RADS committee therefore encourages additional investigations in areas highlighted in Supplementary Table 1; the strength of evidence from investigations will inform future PI-RADS guidance development.

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**Table 1 – Management priorities and proposed MRDB strategies according to mpMRI findings from PI-RADS–compliant protocols**

| Clinical group | Management priority | MRDB strategy | PI-RADS assessment category | | |
|---|---|---|---|---|---|
| | | | PI-RADS 1–2 | PI-RADS 3 | PI-RADS 4–5 |
| Biopsy-naïve | Minimize overdiagnosis and detect csPCa equally | Recommend [e] | TRUS biopsy if high risk [a] | TRUS biopsy ± MRDB | MRDB target + penumbra |
| | | Option | Lower risk clinically, no immediate biopsy; primary care FU | No biopsy if not high risk [a,d]; urologic FU | MRDB target + TRUS |
| Prior negative TRUS/low-volume GS 3 + 3 (AS) | Do not miss csPCa | Recommend | No biopsy for lower risk; urologic FU [b] | TRUS biopsy ± MRDB | MRDB target + TRUS [c] |
| | | Option | SBx or TPMB if high risk [a,b,c] | SBx/TPMB | MRDB target + penumbra<br>MRDB target + SBx/TPMB [f] |
| Negative prior MRDB; no TRUS but at high risk [a] | Do not miss csPCa | Recommend | TRUS/SBx/TPMB according to local rules | TRUS biopsy ± MRDB | MRDB target + penumbra<br>MRDB target + penumbra + TRUS<br>MRDB target + penumbra + SBx |
| | | Option | No biopsy; urologic FU | SBx/TPMB | |

MRDB = magnetic resonance–directed biopsy; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging-Data and Reporting System; AS = active surveillance; csPCa = clinically significant prostate cancer (various definitions); TRUS = transrectal ultrasound systematic 10–12-core biopsy according to international standards; site specific MR-directed biopsy using US/MRI fusion technique or in-bore technique; SBx = saturation biopsy using transrectal or transperineal sampling (eg, Ginsburg approach); TPMB = transperineal mapping biopsy using 5-mm sampling; FU = follow-up.

[a] High risk according to clinical suspicion, family history, prior biopsy result (if applicable), 4K/PHI/PCA3/FH/PSAD risk calculator scores alone or in combination.

[b] National Institute for Health and Care Excellence (NICE) guideline 2014 [86].

[c] European Association of Urology/American Urological Association/Society of Abdominal Radiation 2017 guidelines [87,88].

[d] NHS England guideline, 2018 [99].

[e] Lack of specific clinical guidance.

[f] Depending on size and likely next step in management if csPCa is found.

## 8. Diagnostic pathway impacts

Multiple analyses have shown the ability of mpMRI-MRDB to increase the effectiveness of PCa diagnosis pathways [28,75–81], with the following benefits highlighted: (1) greater precision in determining tumor grade and volume (thus benefiting risk stratification); (2) potential increases in the rate of detection of significant disease; (3) potential reductions in diagnosis of indolent disease (thus reducing overdiagnosis, overtreatment, and patients undergoing biopsies on AS); (4) fewer targeted biopsies per patient, potentially reducing complication rates; and (5) reducing the total number of patients undergoing biopsies without significantly reducing the overall detection rate of csPCa.

These advantages have been demonstrated in prospective and retrospective analyses in all major PCa diagnostic groups. For example, three of four single-institution randomized controlled trials revealed higher diagnostic rates and higher rates of csPCa detection in biopsy-naïve patients [81–84]. The recently published PRECISION trial confirms these findings; the results are generalizable owing to its international multicenter design and pragmatism [28]. Nonrandomized studies also indicate that mpMRI-MRDB limits the over-detection of insignificant disease [2,26,31].

mpMRI can reduce overdiagnosis of indolent disease because of its high NPV [1], and thus can potentially limit the number of patients undergoing biopsy after a negative test. However, as we have already noted, NPV is highly dependent on the csPCa target definition (and its prevalence). The PRECISION study showed that 28% of biopsy-naïve men could avoid biopsy after a negative mpMRI without compromising the detection of csPCa [28]. This confirms the literature projections for avoiding TRUS biopsy, overdiagnosis, and overtreatment [75–81]. The PROMIS trial results suggest that for csPCa prevalence of 53% (GC $\geq$ 3 + 4), 27% of biopsy-naïve patients with negative mpMRI could avoid a biopsy, with an underdiagnosis rate of 24% [2]. The large study by Hansen et al [58] suggests that 29% of patients might avoid biopsy, with an underdiagnosis rate of 20% for GS $\geq$ 3 + 4 prevalence of 49%.

Further prospective studies are comparing targeted mpMRI-MRDB using PI-RADS v2 and systematic 10–12-core TRUS biopsy for biopsy-naïve patients. The multicenter prospective MRI-First (NCT02485379) and 4 M (NTR5555) studies are head-to-head comparisons of mpMRI-MRGB and TRUS biopsy yields in the same patients, examining the impact of biopsy strategy on detection of csPCa and insignificant cancers, the number of men requiring biopsy, and biopsy core number, with minimum follow-up of >1 yr in the 4 M study. The Canadian Urology Research Consortium PRECISE study (NCT02936258) has a similar design and objectives to the PRECISION trial, but men will be followed for 2 yr, compared to shorter follow-up in the PRECISION trial. Other studies, including INNOVATE (NCT02689271) and 4 M (NTR5555), are evaluating the use of blood and urine biomarkers for better selection of patients who would benefit from diagnostic mpMRI-MRDB [85].

Accumulated data have been incorporated into decision tree and decision-curve analyses [86,87] and cost-effectiveness studies [75–77,79,88], and the results have helped

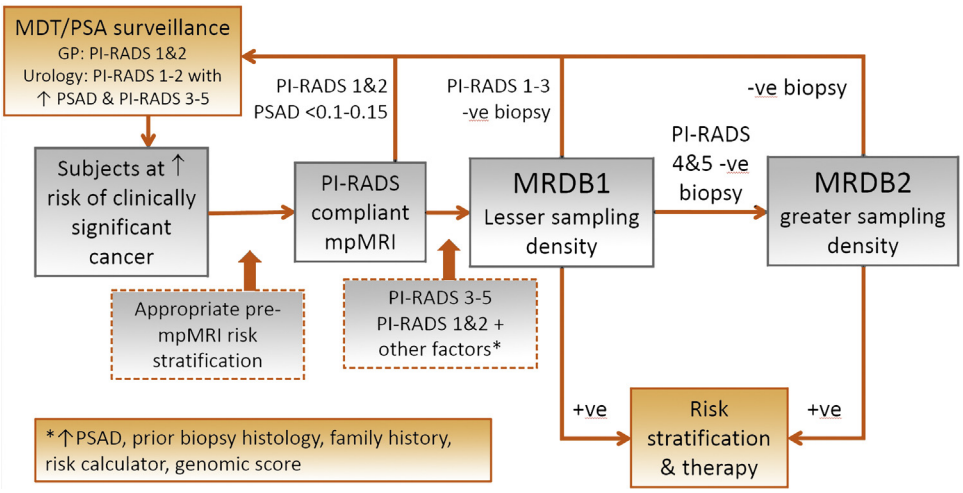


**Fig. 1 – Prostate cancer diagnostic pathway: benefits of incorporating mpMRI, PI-RADS scoring and MRDB sampling. (1) Greater precision in determining tumor grade and volume (improved risk stratification and higher precision in making therapy choices). (2) Potential higher rates of detection of clinically significant disease needing active treatments. (3) Potential reductions in diagnosis of indolent disease, thereby reducing overdiagnosis and overtreatment. (4) Fewer targeted biopsies per patient required to make effective diagnoses and minimization of biopsy-related morbidity. (5) Reduction in the number of patients undergoing biopsy. mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; MRDB = magnetic resonance–directed biopsy; MDT = multidisciplinary team; PSAD = prostate-specific antigen density.**

to promote the uptake of mpMRI in clinical practice. As a result, mpMRI use has been incorporated into multiple national and international clinical care guidelines, mostly in the clinical setting of a prior negative biopsy [89–91] and for patients choosing AS [91]. Pathway benefits of mpMRI inclusion can only accrue if there are mpMRI-directed management impacts. Consensus guidance has emerged on the practicalities of mpMRI-MRDB use in the care of patients with a prior negative biopsy. Detailed recommendations on acceptable actions for negative, indeterminate, and positive mpMRI findings are outlined in Fig. 1, discussed in the Supplementary material, and summarized in Table 1 [91–93]. However, there are few established guidelines on mpMRI-directed management actions for biopsy-naïve patients. Guidance on mpMRI use for biopsy-naïve patients may follow reports from the PRECISION, MRI-First, and 4 M studies, although mpMRI is already being used in this setting in some European countries and Australia [36]. Strategies to mitigate overdiagnosis among biopsy-naïve men might include the following: (1) risk-based preselection of men to undergo mpMRI [94]; (2) most men at lower clinical risk with negative mpMRI should not undergo biopsy and be returned to appropriate clinical care [20]; and (3) at least initially, MRDB should only target visualized abnormalities (no systematic sampling) [28].

These proposed mpMRI-directed actions are contested between radiologists and urologists [95], among urologists, and between different guidelines because of insufficient data on the full range and frequency of pathologies for PI-RADS assessment categories. Clinicians point to the absence of robust data showing that overall csPCa detection rates are not compromised by the use of mpMRI-MRDB alone for biopsy-naïve patients (although this criticism is now tempered by the PRECISION trial data [28]), despite acknowledging the disadvantages of overdiagnosis when additional systematic TRUS biopsies are incorporated [26,31,96]. Discussions will be further clarified by the upcoming data from the MRI-First and 4 M studies. Therefore, decision-making on a patient, clinical center, and health-system basis requires multidisciplinary engagement with active stakeholders and consideration of the central role of mpMRI-MRDB in the diagnostic process.

## 9. Contributing to value-based health care

To demonstrate the heath value of mpMRI-MRDB in PCa detection for greater clinical adoption and to obtain reimbursement, it will be necessary to obtain robust estimates of key performance measures that reflect the effectiveness of incorporating mpMRI-MRDB in diagnostic pathways. Value-based metrics are scarce in the literature, but have been modeled in cost-effectiveness studies [75–81,88]. Multiple real-world (as opposed to model estimates) performance indices are needed to compare the mpMRI-MRDB approach to the current pathway (Supplementary Table 1) in relevant patient groups.

For example, given the potential for reducing overdiagnosis of insignificant cancer, the magnitude of the impact on overtreatment and on AS programs must be accurately assessed in a variety of health care delivery environments (eg, public vs private health systems; underdeveloped vs developed countries; Eastern vs Western populations). It will also be necessary to obtain estimates of the time to diagnosis and to treatment initiation within and between health systems. Given that there is likely to be greater confidence regarding the pathologic state of the prostate

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gland, it is anticipated that there would be changes in the number of patients undergoing gland-sparing procedures, including rates of focal treatments and AS, which also needs to be documented. The impact of mpMRI-MRDB on AS because of better initial selection of patients will affect the need for rebiopsy assessments, and ultimately on dropout rates. Quality-of-life measures related to the avoidance of biopsies and therapy-related side effects and anxiety must also be evaluated [28].

## 10. Need for quality standards

The ability to deliver patient pathway benefits in PCa diagnosis in clinical practice is highly dependent on attaining and maintaining high quality for the entire diagnostic process. Examples of good practice that could assure radiologic quality include attendance at teaching courses on mpMRI-MRDB, reading a minimum number of prescribed cases during supervised training and annualized numbers thereafter, double reading of mpMRI scans in equivocal cases, monitoring to minimize the number of equivocal readings, multidisciplinary team participation with radiologic-pathologic correlations, benchmarking performance via external audits, and monitoring of negative histology for positive mpMRI scans [36,97]. Similar training and performance measures need to be instituted for all operators who perform MRDB procedures to improve interoperator reproducibility.

Borrowing from quality control and assurance successes for other cancers, including ACR accreditation activities (www.acraccreditation.org/dmap-overview), specific guidance needs be developed for multiple aspects, including requesting, performing, and reporting of mpMRI scans [98]. This includes relevant aspects of quality control and assurance for scanners and MRI data acquisition (specifically, PI-RADS compliance). Radiologist training, accreditation, certification, and quality audits (including compliance with structured PI-RADS templates) will be needed. There needs to be agreement on local rules for the use of mpMRI assessments in guiding patient management, including MRDB procedures [36]. As far as possible, international standards should be developed via collaborations among radiologic and urologic professional organizations such as ESUR/EAU and ACR/AUA. It may also be possible to develop country-by-country guidance via collaborations between radiologists, pathologists, urologists, radiographers, and physicists [99].

## 11. Conclusions

It is no longer questioned whether mpMRI can detect and localize csPCa. An abundance of research and clinical practice data has confirmed its clinical utility. In comparison to the current standard-of-care TRUS biopsy, in most studies MRDB finds more clinically significant prostate cancers and fewer low-risk ones. Widespread implementation of PI-RADS v2 has facilitated the standardization of mpMRI acquisition, interpretation, and reporting, and mpMRI use for the diagnosis and management of PCa continues to accelerate. Multiple analyses have shown the potential of mpMRI and MRDB in enhancing the effectiveness of PCa diagnosis pathways. As a result, mpMRI has been incorporated into multiple clinical care guidelines, mostly in the clinical setting of prior negative biopsy. Many potential advantages are also promoted for biopsy-naïve men; however, the latter indication has yet to appear widely in internationally urologic guidelines.

It is acknowledged, that mpMRI and MRDB also miss some csPCa, and that PI-RADS v2 has some important limitations. Thus, while mpMRI is a major advance and is likely to play a central role in the emerging paradigm of high-precision PCa diagnosis, additional work is needed before we know exactly how the PI-RADS system will impact PCa pathways. On the basis of ongoing research and accrued clinical experience, further revisions of PI-RADS are envisaged. It is hoped that PI-RADS v2.1 will improve mpMRI reading performance and decrease inter-reader variability. Looking to the not too distant future, efforts are already under way to expand and adapt PI-RADS to meet a variety of clinical needs in the evolving field of PCa care. The next major revision of PI-RADS is anticipated to be a multiyear endeavor, because it will require additional research data on the clinical use of mpMRI-MRDB, which the combined US-European PI-RADS steering committee encourages.

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*Study concept and design*: All authors.
*Acquisition of data*: All authors.
*Analysis and interpretation of data*: All authors.
*Drafting of the manuscript*: All authors.
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*Other*: None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.05.035.

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