# Multiparametric MRI fusion-guided biopsy for the diagnosis of prostate cancer

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**Purpose of review**
To discuss the timing, benefits, limitations and current controversies of multiparametric magnet resonance imaging (mpMRI) combined with fusion-guided biopsy and consider how additional incorporation of multivariable risk stratification might further improve prostate cancer diagnosis.

**Recent findings**
MpMRI has been proven advantageous over standard practice for biopsy-naïve men and men with previous biopsy in large prospective studies providing level 1b evidence. Upfront multivariable risk stratification followed by or combined with mpMRI further improves diagnostic accuracy. Regarding active surveillance, mpMRI in combination with fusion biopsy can support initial candidate selection and may help to monitor disease progression. mpMRI and fusion biopsy, however, do not spare failure and conflicting data exists to what extend (systematic) biopsies can be omitted.

**Summary**
Integration of mpMRI into the diagnostic pathway for prostate cancer is beneficial; yet more prospective and randomized data is needed to establish reliable procedure standards after mpMRI acquisition.

**Keywords**
multiparametric MRI fusion-guided biopsy, prostate biopsy, prostate cancer, prostate MRI

## INTRODUCTION

The goal of an accurate diagnostic pathway for prostate cancer (PCa) is the detection of significant disease while avoiding the detection of indolent PCa, which otherwise may lead to overtreatment and increased patient morbidity. Standard screening parameters such as prostate-specific antigen (PSA) and digital rectal examination (DRE) as well as the standard diagnostic 12-core transrectal ultrasound (TRUS) biopsy suffer from limited sensitivity and specificity to meet these goals [1,2,3▪▪].

The implementation of multiparametric magnet resonance imaging (mpMRI) combined with fusion biopsy helps to solve this dilemma and increases diagnostic accuracy. Although increasingly being used in the clinical routine and already being recommended by several urologic societies, however, it is still debatable how to best integrate mpMRI and fusion biopsy into the diagnostic pathway for PCa [4–6]. According to the current literature, we herein will discuss the timing, benefits, limitations and current controversies of mpMRI and fusion biopsy and consider how additional incorporation of multivariable risk stratification might further improve PCa diagnosis.

## USING MULTIPARAMETRIC MRI AS AN UPFRONT SCREENING TOOL

Recently, several approaches have been made to evaluate the use of mpMRI as an upfront screening tool. Using template mapping biopsies as reference tests, the prospective, multicentric PROMIS (PROstate MR Imaging Study) represents a landmark for the

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## KEY POINTS

- MpMRI is increasingly used to help diagnose prostate cancer, but further discussion on how to best integrate mpMRI and fusion-guided biopsy into the diagnostic pathway is needed.
- MpMRI significantly outperforms standard 12-core TRUS biopsy for detection of significant prostate cancer, and can thus be used as an upfront screening test.
- Combining mpMRI and clinical parameters into a multivariable risk model further improves diagnostic accuracy.
- There is not yet enough evidence to recommend for or against a systematic biopsy or repeat biopsy in the case of unsuspicious mpMRI or negative prebiopsy. Until a standard procedure is defined, decisions need to be made individually.
- Men under active surveillance, benefit from mpMRI for both, initial risk stratification and follow-up.

use of mpMRI and fusion biopsy in biopsy-naïve men [3▪▪]. With a sensitivity of 93% for the detection of significant prostate cancer (sPCa) and a negative predictive value (NPV) of 89 versus 48 and 74% using 12-core TRUS biopsy, mpMRI is considered a useful triage test for men under suspicion for PCa because of elevated PSA or abnormal DRE [3▪▪]. Triage with mpMRI would spare 27% of men from primary biopsy whereas missing only 7% of sPCa presuming the applied biopsy strategy would yield the same detection rate as a template mapping strategy. Similar results regarding the deficient performance of standard TRUS biopsy were found by Porpiglia *et al.* [7▪], who conducted a trial randomly assigning patients to standard TRUS or mpMRI fusion biopsy and found that the mpMRI-based diagnostic pathway had a significantly better performance than the standard way. These results may soon be confirmed by data from the PRECISION study (NCT02380027), providing level 1b evidence.

To further improve the diagnostic accuracy of mpMRI, attempts have been made to combine clinical parameters and mpMRI for multivariable risk stratification. Adding PSA density helps to increase the NPV of mpMRI. Data from Distler *et al.* [8]and Washino *et al.* [9] support abstaining from biopsy in case of unsuspicious mpMRI and low PSA density (<0.15 ng/ml). For biopsy-naïve men only, Thompson *et al.* [10] reported an increase in the area under the curve (AUC) in receiver-operating characteristics (ROC) analysis from 0.78 to 0.88 by combining PSA, prostate volume and age with prostate imaging reporting and data system (PI-RADS). Aiming to even further optimize noninvasive sPCa-risk prediction to provide guidance in advising for or against a prostate biopsy, Radtke *et al.* [11] developed a risk model based on PSA, prostate volume, DRE, age and PI-RADS with an AUC of 0.83 for biopsy-naïve men. In a similar approach, van Leeuwen *et al.* [12] used PSA, prostate volume, DRE, age, previous biopsy and PI-RADS for their risk model and found an AUC of 0.88 versus 0.80 without taking mpMRI into account. Although the different AUCs of these studies can be explained by including (s)PCa prevalence, mpMRI parameters and slightly different variables, all show a significant net benefit of including mpMRI and thereby demonstrate the high value of mpMRI as an upfront screening tool. All these models, however, are still based upon biopsy indications, which were based on PSA or DRE deviation compared from standard screening threshold values. In a pilot study evaluating three different screening strategies – patients with PSA at least 3 ng/ml with systematic biopsy, patients with PSA at least 3 ng/ml combined with mpMRI and targeted biopsy and patients with PSA at least 1.8 ng/ml – Grenabo Bergdahl *et al.* [13] found a screening strategy using a lowered PSA cut-off of at least 1.8 ng/ml in combination with mpMRI and targeted biopsy to be most accurate in detecting significant cancer and minimising unnecessary biopsies.

One of the major concerns in using mpMRI as an upfront screening tool is the financial impact this might have on healthcare systems. Most recently, Faria *et al.* analyzed data on cost-effectiveness derived from the PROMIS study [3▪▪,14▪]. They demonstrated that a diagnostic pathway using mpMRI first, and then up to two MRI-targeted biopsies detects more sPCa per pound spent than a strategy using 12-core TRUS biopsy first (sensitivity, 0.95 versus 0.91) and is cost-effective [8350 € per quality-adjusted life years (QALY) gained] [14▪]. On the other hand, Alberts *et al.* [15] evaluated a pathway that first determines the risk of having sPCa by the use of the ERSPC risk calculator 4, based on the Fifth European Randomized study of Screening for Prostate Cancer (ERSPC) screening round. They only perform mpMRI and biopsy in patients with a risk at least 20%. This approach would avoid 65% of mpMRIs or standard TRUS biopsies, but at the same time miss 17% of sPCa [15].

## INCORPORATION OF MULTIPARAMETRIC MRI FUSION-GUIDED BIOPSY INTO RISK MODELING FOR PROSTATE CANCER

Compared with radical prostatectomy specimen, mpMRI detects 85–95% of index lesions and

significant PCa (sPCa) [16,17]. Targeted biopsy, mostly used in a fusion biopsy setting, of suspicious mpMRI lesions improve the detection of sPCa by 30% [18].

To identify men with sPCa and concurrently to avoid unnecessary biopsies, multivariable risk-based approaches have been introduced [19–21]. Using risk calculators built on ERSPC data, Roobol *et al.* [21] demonstrated that 33% of standard biopsies can be avoided in men who are at risk of PCa below 12.5%. Recent risk calculators, however, do not include MRI data. Targeted biopsy of mpMRI-suspicious lesions alone is a promising strategy to reduce overdetection of insignificant disease, but MRI-invisible sPCa can be missed by such an approach [18,22–24]. In contrast to the approach proclaimed by Alberts *et al.*, Radtke *et al.* [11] and van Leeuwen *et al.* [12] added prebiopsy mpMRI to clinical parameters and developed risk calculators to determine an individual sPCa risk using a validated biopsy approach combining fusion-guided targeted biopsy and transperineal systematic saturation biopsies as reference on the one hand and transperineal mapping and targeted biopsy combined with 12-core TRUS on the other hand. Van Leeuwen *et al.* [12] demonstrated that a model combining age, PSA, DRE, prostate volume, a previous biopsy result and mpMRI PI-RADS Likert score outperforms the model of clinical parameters alone with a discrimination of 0.90 in the AUC of ROC curve analysis. The internal validation was performed on the cohort of 398 men from St. Vincent's clinic, Sydney, Australia [12]. On external validation in 198 men from Royal North Shore Private Hospital, Sydney, Australia, the discrimination of the full model slightly decreased to an AUC of 0.86 [12]. In addition to the model for biopsy-naïve men, Radtke *et al.* [11] internally validated a risk model combining PSA, prostate volume, DRE, age and mpMRI PI-RADS Likert scoring for men after previous negative biopsy. The model was compared with a validated clinical parameter risk calculator (ERSPC RC 4) and PI-RADS and significantly outperformed both tools alone [11]. In conclusion, risk models including mpMRI PI-RADS and clinical parameters improve the accuracy of the decision to perform a biopsy in a patient with suspicion of sPCa in comparison with models based on clinical parameter or PI-RADS alone for both, men prior to initial and men after previous negative biopsy [11,12]. By comparing risk models including mpMRI and clinical parameters with risk models that are only based on clinical parameters or PI-RADS alone, the accuracy of the decision to perform a biopsy in a patient with the suspicion for sPCa can be improved. In conclusion, risk models that include mpMRI are superior to those risk models not only for men prior to initial biopsy but also for patients after previous negative biopsy.

## AVOIDING MULTIPARAMETRIC MRI FUSION BIOPSY FAILURE

Though undoubtedly advantageous, mpMRI fusion biopsy does not spare failing. Four mechanisms for the potential failure of mpMRI fusion biopsy have been identified: mpMRI reader oversight, mpMRI invisible cancer, inaccurate sampling and intralesion Gleason Score heterogeneity [25]. Muthigi *et al.* found that in 71% of cases wherever systematic biopsy detected sPCa and targeted biopsy did not, the cancerous finding was within the sextant of the target lesion, confirming the result of Cash *et al.* [26] who identified inaccurate sampling as one of the main reasons for fusion biopsy failure. Similarly, Bryk *et al.* [27] identified a combination of targeted biopsy and ipsilateral systematic biopsy as the best strategy to detect sPCa and avoid detection of low-risk PCa, comparing targeted biopsy only, targeted biopsy and ipsilateral systematic biopsy and targeted biopsy and contralateral systematic biopsy in patients with unilateral mpMRI lesion using targeted biopsy and both sided systematic biopsy as reference. Although these findings suggest that an extended sampling of the target area might be useful to overcome inaccurate sampling and intralesion Gleason Score heterogeneity, Porpiglia *et al.* [28] found that two targeted cores placed in the centre of the lesion are sufficient to accurately depict the index lesion, stressing the need for further studies addressing this question. Characterized by a repeatedly found negative predictive value for mpMRI of 63–98% the mpMRI fusion biopsy failure caused by mpMRI invisible cancer can only be solved through additional systematic biopsy [29,30]. Most groups combining targeted biopsy with 12-core systematic biopsy, however, did not find a significant benefit for the detection of sPCa by the combination of both methods over targeted biopsy alone [18,31,32]. Contrary to that, Filson *et al.* [33] found the combined biopsy method to detect significant more sPCa than targeted biopsy or systematic biopsy alone. This supports our own analyses, which demonstrates a significant increase in the detection of sPCa by combining targeted biopsy and systematic biopsy, but using a median of 24 systematic biopsy cores [34]. These controversial results lead to the conclusion that the superiority of sPCa detection in a combined biopsy approach compared with a targeted biopsy-only approach increases with the amount of systematic biopsy. At the same time a raise in systematic biopsy cores, however,

ill-promote the detection of low-risk disease. The debate, whether to omit systematic biopsy or not might, therefore, may never get entirely solved and decisions should be made customized to biopsy indications and patient's needs.

## MULTIPARAMETRIC MRI FUSION-GUIDED BIOPSY IN MEN REQUIRING A REPEAT BIOPSY

Men with prior negative biopsy and ongoing suspicion for PCa represent a patient group with special needs. As a result of prior sampling, overall disease prevalence is reduced compared with a biopsy-naïve population, but those patients presenting with ongoing suspicion for PCa suffer because of limited NPV of 12-core TRUS biopsy. Therefore, the use of mpMRI in the repeat biopsy setting is recommended and benefit has been proven in various studies [4–6]. Most recent studies analyze these patients as a subgroup of a larger cohort, but some works pay special attention to this patient group; equivalent to the PROMIS study, Simmons *et al.* [35▪] evaluated the diagnostic accuracy of mpMRI in men requiring a repeat prostate biopsy (PICTURE study), though only 31% of men had a previous negative biopsy. Whenever using a mpMRI score of at least 3 as a positive test result, mpMRI has a sensitivity of 97%, a specificity of 22%, a NPV of 91% and a positive predictive value of 47% [35▪]. The authors conclude that this would potentially spare 14% of men from repeat biopsy at the cost of missing 9% sPCa [35▪]. Hansen *et al.* [36] demonstrated a significantly improved AUC whenever combining PI-RADS with PSA density (0.82 versus 0.85) suggesting to only abstain from repeat biopsy in case of unsuspicious mpMRI and low PSA density. Again, no clear evidence exists upon the question when to safely omit systematic biopsy. Arsov *et al.* [37], however, analyzed in a prospective randomized trial setting inbore targeted biopsy compared with fusion-guided targeted biopsy and 12-core TRUS systematic biopsy. They demonstrated that additional systematic biopsy had no significant additional benefit on the detection of sPCa. Contrary to that, recent publications comparing targeted biopsy alone approaches with 24-core or 12-core systematic biopsy demonstrate that a considerably amount of sPCa is missed by a targeted biopsy-only approach [33].

## MULTIPARAMETRIC MRI FUSION-GUIDED BIOPSY FOR MEN UNDER ACTIVE SURVEILLANCE

Men with PCa eligible for active surveillance represent another patient group with special needs as the diagnostic goal shifts from avoiding overdiagnosing low-risk disease to a maximally accurate risk classification of potentially insignificant disease. To reach this goal, mpMRI in combination with fusion biopsy can support initial candidate selection and may help to monitor disease progression. Radtke *et al.* [38] demonstrated in a cohort of 149 men that initial mpMRI and fusion biopsy before active surveillance, result in significant lower rates of subsequent active surveillance, qualifications (20 versus 48%) compared with men who were selected for active surveillance, based on 12-core TRUS biopsy. Also, Henderson *et al.* [39] demonstrated in a prospective trial that the apparent diffusion coefficient (ADC) is a useful marker whenever selecting patients for active surveillance, as a low ADC value is associated with a shorter time to adverse histology. Several recent studies evaluated mpMRI and fusion biopsy in the context of detecting disease progression. Most of them consistently show that mpMRI predicts the risk of pathological progression and that in contrast to that patients with stable mpMRI findings have only a low rate of disease progression [40–43]. Also including clinical parameters to the decision-making process seems to be beneficial for active surveillance, as well. Alberts *et al.* [15] found in a cohort of 210 men, no upgrading at baseline, confirmatory or surveillance biopsy in case of unsuspicious mpMRI and PSA density below 0.15 ng/ml suggesting to reduce follow-up biopsy in these cases. Controversy, however, exists regarding whether or not follow-up with fusion biopsy limited to mpMRI-visible targets is sufficient. Meng *et al.* [44] and Frye *et al.* [41] both report that on combined systematic biopsy and targeted biopsy follow-up mpMRI fusion-targeted biopsy detects a significant higher amount of upgrading than systematic biopsy, supporting the idea of omitting systematic biopsy. On the contrary, Tran *et al.* [43], Ma *et al.* [45], and Recabal *et al.* [42] found a relevant proportion of high-grade cancer to be detected by systematic biopsy only, supporting the need for additional systematic biopsy. Although these contradicting results can partly be explained because of different study parameters including differences in median-targeted biopsy and systematic biopsy cores, they also stress the need for further studies addressing the questions of long-term results, serial mpMRI for replacing repeat biopsies and sufficiency of follow-up biopsies limited to mpMRI targets.

## CONCLUSION

Large prospective studies demonstrate the benefits of mpMRI as an upfront screening tool as well as in a repeat biopsy setting [3▪▪,35▪]. In combination with

mpMRI, fusion-guided biopsy helps to detect sPCa more accurately. Upfront multivariable risk stratification followed by or combined with mpMRI further improve PCa diagnosis and risk models can be used to decide whether or not to proceed with the biopsy [10–13,15]. mpMRI and fusion biopsy, however, do not spare failure. The choice for or against concurrent systematic biopsy considerably influences both, the rate of under-detection of sPCa and the rate of over-detection of indolent disease. Evidence up-to-date is inconsistent; therefore, decisions should be made based on individual risk-adapted patient counselling.

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## Conflicts of interest

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The PROMIS, a trial with Level of Evidence Ib, tested whether a mpMRI scan before biopsy could identify men who might safely avoid a biopsy. PROMIS compared the accuracy of both mpMRI and 12-core TRUS-biopsy against a template mapping biopsy as reference test. PROMIS found that a mpMRI before biopsy would allow at least one in four men to safely avoid a biopsy. This was because the chance that men with a negative mpMRI had important prostate cancer was very low. The mpMRI identified more than 90% of patients who had clinically important cancer, compared with TRUS, which only identified 48% of the men who had clinically important cancer.

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