

Clinical-Prostate cancer
Applying the PRECISION approach in biopsy naïve
and previously negative prostate biopsy patients

Nancy N. Wang, M.D., M.P.H.^{a,*}, Nikola C. Teslovich, M.D.^b, Richard E. Fan, Ph.D.^a,
Pejman Ghanouni, M.D., Ph.D.^c, John T. Leppert, M.D., M.S.^{a,d}, James D. Brooks, M.D.^a,
Sarir Ahmadi^a, Geoffrey A. Sonn, M.D.^{a,c}

^a Department of Urology, Stanford University School of Medicine, Stanford, CA

^b Stanford University School of Medicine, Stanford, CA

^c Department of Radiology, Stanford University School of Medicine, Stanford, CA

^d Department of Urology, Veterans Affairs, Palo Alto Health Care System, Palo Alto, CA

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Abstract

Objectives: The PRECISION trial provides level 1 evidence supporting prebiopsy multiparametric magnetic resonance imaging (mpMRI) followed by targeted biopsy only when mpMRI is abnormal [1]. This approach reduced over-detection of low-grade cancer while increasing detection of clinically significant cancer (CSC). Still, important questions remain regarding the reproducibility of these findings outside of a clinical trial and quantifying missed CSC diagnoses using this approach. To address these issues, we retrospectively applied the PRECISION strategy in men who each underwent prebiopsy mpMRI followed by systematic and targeted biopsy.

Methods and Materials: Clinical, imaging, and pathology data were prospectively collected from 358 biopsy naïve men and 202 men with previous negative biopsies. To apply the PRECISION approach, a retrospective analysis was done comparing the cancer yield from 2 diagnostic strategies: (1) mpMRI followed by targeted biopsy alone for men with Prostate Imaging Reporting and Data System ≥ 3 lesions and (2) systematic biopsy alone for all men. Primary outcomes were biopsies avoided and the proportion of CSC cancer (Grade Group 2–5) and non-CSC (Grade Group 1).

Results: In biopsy naïve patients, the mpMRI diagnostic strategy would have avoided 19% of biopsies while detecting 2.5% more CSC ($P=0.480$) and 12% less non-CSC ($P<0.001$). Thirteen percent ($n=9$) of men with normal mpMRI had CSC on systematic biopsy. For previous negative biopsy patients, the mpMRI diagnostic strategy avoided 21% of biopsies, while detecting 1.5% more CSC ($P=0.737$) and 13% less non-CSC ($P<0.001$). Seven percent ($n=3$) of men with normal mpMRI had CSC on systematic biopsy.

Conclusions: Our results provide external validation of the PRECISION finding that mpMRI followed by targeted biopsy of suspicious lesions reduces biopsies and over-diagnosis of low-grade cancer. Unlike PRECISION, we did not find increased diagnosis of CSC. This was true in both biopsy naïve and previously negative biopsy cohorts. We have incorporated this information into shared decision making, which has led some men to choose to avoid biopsy. However, we continue to recommend targeted and systematic biopsy in men with abnormal MRI. © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license.

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Keywords: Prostatic neoplasms; Image-guided biopsy; Magnetic resonance imaging; Needle biopsy

1. Introduction

Prostate multiparametric magnetic resonance imaging (mpMRI) is a powerful tool for detecting clinically significant prostate cancer (CSC), but when and how it is used remains controversial. Kasavivsanathan et al. published the first

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*Corresponding author. Tel.: (650) 793-5585; fax: (650) 498-5346.

E-mail address: nwang4@stanford.edu (N.N. Wang).

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multicenter randomized trial comparing the performance of mpMRI and targeted biopsy against TRUS-guided systematic biopsy in biopsy naïve men. The PRECISION study found that mpMRI followed by targeted biopsy detected 12% more CSC (Grade Group ≥ 2) and 13% less non-CSC (Grade Group 1) compared to standard TRUS-guided biopsies [1]. Additionally, 28% of the 252 men randomized to the mpMRI arm had a normal mpMRI and avoided biopsy altogether. However, it is unknown how many men had undiagnosed CSC as biopsies were not performed in men with normal MRI and systematic sampling was omitted for men with abnormal mpMRI who underwent targeted sampling.

This landmark trial highlights the benefits of mpMRI with targeted biopsy, yet important questions remain. First is whether the results are generalizable. The PRECISION trial was conducted at 25 sites across 11 countries, the majority of which were in Europe where prostate-specific antigen screening has been less prevalent than in the United States and where prostate mpMRI has already been widely integrated into clinical care. It is unclear how the differences in cancer prevalence impacts results. Additionally, radiologists in PRECISION were far more experienced (median 300 prostate MRIs/year) than the average radiologist in the United States. Given the tremendous importance of radiologic expertise in prostate MRI performance characteristics [2–4], it is unknown if the results are reproducible at centers with differing expertise. Additionally, the PRECISION trial enrolled only biopsy-naïve men. However, in practice, mpMRI is frequently used for men with previous negative biopsies with ongoing suspicion of cancer. It is unknown whether the PRECISION findings apply to this clinically relevant population.

A second important question involves missed cancer diagnoses. PRECISION omitted systematic sampling in men randomized to the mpMRI \pm targeted biopsy arm. This precludes quantification of additional CSC that systematic sampling would have detected in this arm [5]. The current practice in the United States and recommendations outlined in the EAU guidelines advise clinicians to include systematic biopsy along with targeted biopsy [6]. The PRECISION trial does not address this practice and it remains unclear how many men will have undiagnosed CSC if systematic biopsy is no longer performed.

Given these questions, our objective was 2-fold: to externally validate the PRECISION findings in a medical center in the United States, and to quantify the number of CSCs missed using the PRECISION approach. We also tested the PRECISION approach in men with previous negative biopsies, as this is a large and clinically relevant group of patients in the United States where $\sim 90\%$ of private-payer insurance does not cover mpMRI for biopsy naïve men [7].

2. Materials and methods

2.1. Patient population

We identified men in the Stanford targeted biopsy database with no prior biopsy ($n = 358$), and those with ≥ 1 prior

negative biopsy and continued concern for cancer ($n = 202$). Clinical, imaging, and pathology data were prospectively collected. All subjects underwent mpMRI, MRI-TRUS fusion targeted biopsy, and systematic biopsy between March 2014 and May 2018 at Stanford. Consent for data collection prior to biopsy was obtained under IRB-approved protocols and the data registry was HIPAA compliant. Data collected under this protocol have been previously published [2]. Data are reported in compliance with START criteria where applicable [8].

2.2. Imaging and histopathology

All mpMRIs were performed using a 3T scanner (MR750, GE Healthcare, Waukesha, WI) with an external 32-channel body array coil. An endorectal coil was never used. The imaging protocol consisted of T2 weighted imaging (T2WI), diffusion weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging sequences. Additional details of the protocol can be found in a prior publication [2]. MpMRI scans were read by attending radiologists during routine care and all visible lesions were assigned a Prostate Imaging Reporting and Data System (PIRADS) score. Version 1 was used until adoption of version 2 in 2015.

2.3. Biopsy protocol

Prostate mpMRI was performed prior to biopsy in all men. Patients with normal mpMRI (PIRADS < 3) underwent systematic biopsies only (median = 14 cores). Patients with visible lesions underwent MR-fusion targeted biopsies followed by systematic biopsies. Systematic core locations were determined by the Artemis robotic biopsy device (Eigen, Grass Valley, CA) independent of the presence or location of any mpMRI lesions. Biopsies were performed by 2 urologic oncologists with extensive experience in targeted biopsy. Tissue samples were reviewed by fellowship trained genitourinary pathologists.

2.4. Study design and statistical analysis

A retrospective analysis was used to compare cancer diagnostic yield for each man in two hypothetical diagnostic scenarios: (1) mpMRI screening with targeted biopsy of PIRADS lesions ≥ 3 and (2) systematic biopsy for all men (Fig. 1). Although all patients in our database underwent systematic biopsy in addition to targeted biopsy of eligible mpMRI lesions, we analyzed the histopathology results according to the scenarios described. In scenario 1, we analyzed only the targeted cores for men with abnormal mpMRIs. In scenario 2, we analyzed only the systematic biopsies. Given the retrospective design of our study, each patient served as his own control. This analysis was repeated in the biopsy naïve and the previously negative biopsy cohorts.

As in PRECISION, the primary outcome was the proportion of men diagnosed with CSC (Grade Group ≥ 2) and

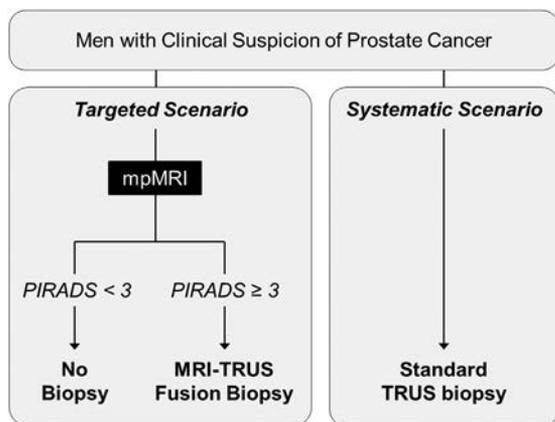


Fig. 1. Schematic of the retrospective analysis. All men were evaluated using targeted and systematic biopsy diagnostic scenarios. Targeted: All underwent mpMRI and only those with eligible lesions (PIRADS ≥ 3) underwent targeted fusion biopsy. Systematic: All men underwent standard TRUS biopsy.

non-CSC (Grade Group 1) in each diagnostic scenario. Secondary outcomes included the proportion of men with normal mpMRI who were diagnosed with CSC on systematic biopsy and the proportion of men found to have CSC using the combination of targeted and systematic biopsy. This reflects the number of diagnoses missed by omitting systematic biopsies in the mpMRI diagnostic scenario.

Clinical information, MRI reads, and biopsy findings were prospectively collected using REDCap electronic data capture tools hosted at the Stanford Center for Clinical Informatics [9]. Data for all biopsy-naïve and previously

negative biopsy subjects who underwent mpMRI and completed systematic biopsy with targeted biopsy of eligible lesions were included in the analysis. While the data analysis was not prespecified at the time of data collection, the analysis mirrored PRECISION to minimize bias inherent to retrospective studies. For statistical analysis, Pearson-variant chi-squared testing for independence was performed to examine the relationship between diagnostic scenarios and the detection rates of CSC and non-CSC. In the study design, as each patient undergoes both scenarios, the between-scenario comparison was considered a matched-pairs analysis. McNemar-variant chi-squared testing was also performed which yielded the same findings of significance as the Pearson-variant testing. JMP v10.0.2 statistical software (SAS Institute Inc., Cary, NC) was used to repeat independent Pearson-variant chi-squared testing in the biopsy-naïve and previously negative biopsy cohorts. Statistical significance was assessed at a 95% confidence level.

3. Results

Table 1 describes characteristics of the study population.

3.1. Biopsy naïve ($n = 358$)

The targeted biopsy scenario detected CSC in 36% ($n = 129$) and non-CSC in 14% ($n = 52$; Fig. 2). The systematic biopsy scenario detected CSC in 34% ($n = 120$) and non-CSC in 27% ($n = 95$). In the MRI-targeted scenario, a

Table 1
Comparison of cancer detection by diagnostic scenario

	Biopsy naïve ($n = 358$)			Previously negative biopsy ($n = 202$)		
Median Age, years (s)	65 (9.1)			65 (7.7)		
<i>Demographic:</i>						
White (%)	224 (62.9%)			120 (59.4%)		
Black (%)	17 (4.7%)			10 (5.0%)		
Hispanic (%)	17 (4.7%)			11 (5.4%)		
Other (%)	42 (11.7%)			26 (12.9%)		
Unknown (%)	58 (16.2%)			35 (17.3%)		
Median PSA, ng/ml (s)	6.3 (7.5)			9.8 (7.6)		
Outcome	Systematic biopsy	Targeted biopsy	% Difference (P value ^d)	Systematic biopsy	Targeted biopsy	% Difference (P value ^d)
<i>Gleason Grade Group</i>						
Benign ^a	143 (39.9%)	177 (49.4%)		102 (50.5%)	127 (62.9%)	
1 ^b	95 (26.5%)	52 (14.5%)	–12.0% ($P < 0.001$)	46 (22.8%)	19 (9.4%)	–13.4% ($P < 0.001$)
2	47 (13.1%)	62 (17.3%)		23 (11.4%)	26 (12.9%)	
3	38 (10.6%)	27 (7.5%)		14 (6.9%)	11 (5.4%)	
4	16 (4.5%)	20 (5.6%)		9 (4.5%)	12 (5.9%)	
5	19 (5.3%)	20 (5.6%)		1 (0.5%)	7 (3.5%)	
Clinically significant cancer ^c	120 (33.5%)	129 (36.0%)	+2.5% ($P = 0.480$)	53 (26.2%)	56 (27.7%)	+1.5% ($P = 0.737$)

^a Patients declared benign by the targeted scenario includes those with normal mpMRI and with PIRADS < 3 ROIs.

^b Gleason Grade Group 1 represents nonclinically significant cancer (non-CSC).

^c Clinically Significant Cancer (CSC) represents Gleason Grade Group ≥ 2 found by histopathology.

^d Determined by Pearson chi-square testing.

	non-Clinically Significant Cancer (Grade Group 1)		Clinically Significant Cancer (Grade Group ≥ 2)		
	Systematic	Targeted	Systematic	Targeted	
Biopsy Naïve	26.5%	-12.0% p<0.001	14.5%	33.5% +2.5% p=0.480	36.0%
Previously Negative Biopsy	22.8%	-13.4% p<0.001	9.4%	26.2% +1.5% p=0.737	27.7%
PRECISION	22%	-13% p<0.001	9%	27% +12% p=0.007	39%

Fig. 2. Cancer detection rates by systematic and targeted scenarios. With comparison to published PRECISION trial data on biopsy naïve cohort. Reported Pvalues calculated by chi-squared testing for independence.

normal MRI (PIRADS < 3) would have spared 19% of men (n = 69) from biopsy. When comparing scenarios, the mpMRI scenario detected 2.5% more CSC (P = 0.48) and 12% less non-CSC (P < 0.001; Fig. 2).

Among the 69 men with a normal MRI, CSC was diagnosed on systematic biopsy in 13% (n = 9) and non-CSC in an additional 25% (n = 17; Fig. 3). Of the 9 patients diagnosed with CSC on systematic biopsy, the breakdown by Gleason Grade (GG) is as follows: 7% (n = 5) GG 2, 4% (n = 3) GG 3, 1% (n = 1) GG 4 (Fig. 3).

However, combining targeted and systematic biopsy yielded the highest detection of CSC at 44% (n = 158). Of these, 18% (n = 29) were diagnosed by systematic biopsy only, 24% (n = 38) by targeted biopsy only, and 58% (n = 91) by both techniques. Omitting systematic biopsy would have missed CSC in 8% (n = 29) of patients. Omitting targeted biopsy would have missed CSC in 11% (n = 38; Supplemental Figure 3).

3.2. Previous negative biopsy (n= 202)

The targeted biopsy scenario detected CSC in 28% (n = 56) and non-CSC in 9% (n = 19; Fig. 2). Systematic biopsy detected CSC in 26% (n = 53) and non-CSC in 23% (n = 46).

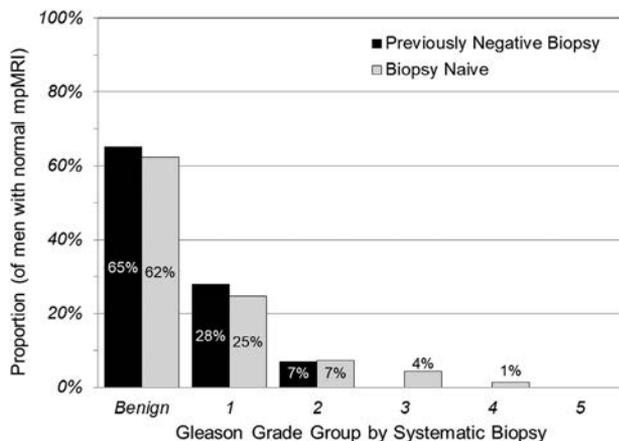


Fig. 3. Systematic biopsy histopathology findings in subjects with normal mpMRI (PIRADS < 3).

In the MRI-targeted scenario, a normal MRI would have spared 21% (n = 43) from biopsy. When comparing scenarios, the MRI scenario identified 1.5% more CSC (P = 0.737) and 13% (n = 27) less non-CSC (P < 0.001).

Among the 43 men with a normal MRI, CSC was diagnosed on systematic biopsy in 7% (n = 3) and non-CSC in an additional 28% (n = 12; Fig. 3). Of the 3 patients with CSC diagnosed on systematic biopsy, all were GG 2.

Again, combining targeted and systematic biopsy yielded the highest rates of CSC detection at 36% (n = 73). Of these 73 patients, 23% (n = 17) were diagnosed by systematic biopsy only, 27% (n = 20) by targeted biopsy only, and 49% (n = 36) by both techniques. Omitting systematic biopsy would have missed CSC in 8% (n = 17) of patients. Omitting targeted biopsy would have missed CSC in 9% (n = 20) (Supplemental Figure 3).

4. Discussion

The PRECISION trial provided level 1 evidence indicating superiority of an MRI-based approach for prostate cancer diagnosis in biopsy naïve men. As this approach is increasingly adopted, it is important to recognize 2 key issues that are unanswered by PRECISION: how generalizable are its findings to routine clinical care, and how many CSC are missed using the MRI-based approach. Our study uniquely targeted these questions and had four important findings.

First, we found no difference in CSC detection between the MRI-targeted biopsy scenario vs. systematic biopsy scenario in biopsy naïve men or in men with previous negative biopsy (Fig. 2). In this respect, the PRECISION result showing increased CSC detection using only targeted biopsy was not generalizable to our institution. Our results, however, were consistent with 2 recent European trials comparing targeted and systematic biopsy. Both the 4M and MRI-FIRST studies showed equivalent detection of CSC in biopsy naïve men [10,11]. Conflicting results have been found in other publications comparing systematic to targeted biopsy in CSC detection [12–16]. These discrepancies might be due to differences in CSC prevalence in the study populations, variability seen in mpMRI performance and interpretation, or the methodology and accuracy of targeted biopsy (software vs. cognitive fusion). Given these differences, validation using US patients is especially important for studies based in Europe.

Second, we found decreased over-diagnosis of low-grade cancer when using the MRI-targeted biopsy approach. These results are nearly identical to those in PRECISION (Fig. 2), and other studies including 4M, MRI-FIRST, and a 2015 meta-analysis by Schoots et al. [17] While PRECISION was restricted to biopsy naïve men, we expand the application of these findings by identifying a similar result in the previously negative biopsy cohort.

Third, in men with a normal MRI, we found CSC on systematic biopsy in 13% of biopsy naïve men and 7% of previously negative biopsy men. The rate of missed CSC diagnosis in men with normal MRI varies considerably in the literature, ranging from 3% to 5% in prospective studies [10,11,18,19], 6% to 16% in retrospective studies [20–22], and up to 26% when compared against a transperineal saturation biopsy [23]. While the majority of significant cancers missed on MRI are GG 2, some higher grade cancers can be missed as well [10]. It is not yet known whether MRI-invisible CSC behaves differently. Houlahan et al. recently reported that MRI visibility was correlated with aggressive molecular markers [24]; however, aggressive cribriform tumors have also been shown to be less visible than other histopathology subtypes [25]. Missing MRI-invisible cases has unknown effects. Because of this uncertainty, both the European Association of Urology and the NCCN currently advise clinicians to perform systematic biopsies along with all targeted biopsies [6,26].

Fourth, we found that detection of CSC was highest when using combined targeted and systematic biopsy in both biopsy naïve and previously negative biopsy patients. Up to 8% of men in both cohorts would have missed a CSC diagnosis if systematic biopsy were omitted. This synergistic finding enforces our recommendation to continue performing targeted and systematic biopsy in men with abnormal MRI.

Our study has several noteworthy limitations. First, our single-site study could also have limited generalizability as Stanford, like the centers in PRECISION, is a tertiary center with a significant referral practice for MRI-targeted biopsy. It is possible that greater differences could be found by comparing PRECISION to community practice. However, we have previously reported on the variability of expertise seen in our radiologic group, which may more accurately reflect clinical practice and thus strengthens the generalizability of our findings [2]. Additionally, the annual case volume of our radiologists (60 cases) is likely more representative of what is seen in community practice compared to the volume read by the radiologists in the PRECISION trial (300 cases) [2].

Second, our database only captures men who had both MRI and biopsy. While we routinely recommend biopsy to men with a normal MRI, some elect to forgo biopsy. This self-selection may contribute to our slightly higher frequency of men with normal MRI who had CSC on systematic biopsy. This study design does however minimize the bias that would result from only biopsying patients with normal MRI who had higher suspicion for cancer. Both biopsy-naïve and previously negative biopsy patients were offered mpMRI which limits the bias of MRI availability and insurance coverage.

Third, all systematic biopsies were performed using the Artemis biopsy device which optimally spaces sampling during systematic biopsy. It is possible that this improves systematic biopsy yield and thereby reduces the difference

in CSC cancer yield between systematic and targeted biopsy.

Despite these limitations, our study provides important complementary information to the landmark PRECISION trial. Our study was motivated by uncertainty as to whether results of PRECISION will be reproducible in our clinical practice given the differences in screening, prostate cancer prevalence, and mpMRI experience between much of Europe and the United States. We believe testing European trials is critical before widely adopting these practices in the United States. In routine clinical care at an academic center where numerous radiologists read mpMRIs, we did not find improved detection of CSC, but we did see reduction in over-detection of low-grade cancer. This was also true in previously negative biopsy patients. Our results suggest that some, but not all the findings in PRECISION, may be generalizable. While we recommend prebiopsy MRI, in light of the non-negligible risk of CSC in the setting of normal MRI, we also recommend close follow-up and consideration of other risk factors such as age and prostate-specific antigen when making biopsy decisions in patients with normal mpMRIs [19]. In the future, it is likely that additional biomarkers will be used in conjunction with MRI to better select which patients can safely avoid biopsy [27–29].

5. Conclusions

To assess generalizability and missed cancers on MRI, we retrospectively replicated the PRECISION trial in a large cohort of men who underwent prebiopsy MRI followed by systematic and targeted biopsy. The PRECISION approach led to fewer biopsies, equivalent detection of CSC, and less over-diagnosis of low-grade cancer. Unlike PRECISION, we did not find more CSC using MRI and targeted biopsy alone. Our results support the role of prebiopsy MRI for targeting purposes, but suggest caution in using MRI to categorically eliminate systematic biopsy.

Conflict of interest

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.urolonc.2019.05.002>.

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