Micro-ultrasound-guided versus multiparametric magnetic resonance imaging-targeted biopsy in the detection of prostate cancer: a systematic review and meta-analysis

A thesis submitted in fulfilment of the requirements for the degree of Master of Science in Medical Research Methodology

By

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Preface

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Abbreviations

CI: confidence interval
DR: detection rate
GG: grade group
mpMRI: multiparametric magnetic resonance imaging
PCa: prostate cancer
PB: prostate biopsy
TRUS: transrectal ultrasound
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Abstract

Background: Prostate cancer (PCa) lacks a reliable diagnostic tool as conventional ultrasound-guided prostate biopsy (PB) has poor sensitivity and high false negative rates. MRI-guided biopsy although more accurate is limited by significant inter-reader variability and learning curve and still misses up to 15% of clinically significant PCa. MRI also adds additional costs, procedural complexity. Micro-ultrasound (US) is a novel imaging modality, aiming to improve the diagnostic accuracy of prostate biopsy (PB) and maintain the convenience of ultrasound-guided PB. Micro-US-guided PB may present comparable detection rates (DRs) with multiparametric magnetic resonance imaging (mpMRI)-targeted biopsy for clinically significant prostate cancer (PCa) diagnosis.

Purpose: We aimed to compare the PCa DR of micro-US-guided PB versus mpMRI-targeted PB.

Methods: We performed a systematic review and meta-analysis of diagnostic accuracy studies comparing micro-US-guided PB with mpMRI-targeted PB as reference standard test (PROSPERO ID: CRD42020198326). Records were identified by searching in PubMed, Scopus, and Cochrane Library databases and sources of grey literature until November 30, 2020.

Results: We included 18 studies in the qualitative and 13 in the quantitative synthesis. In the meta-analysis (quantitative synthesis), 1125 participants received micro-US-guided, followed by mpMRI-targeted and systematic PB. Micro-US and mpMRI-targeted PBs displayed similar DRs across all PCa degrees. The pooled DR for grade group (GG) ≥ 2 PCa was 1.08 (95% CI: 0.94 to 1.23, I² = 0%), for GG ≥ 3 was 1.50 (95% CI: 0.99 to 2.29, I² = 0%) and for clinically insignificant (GG = 1) PCa was 0.94 (95% CI: 0.73 to 1.20, I² = 0%). The overall DR for PCa was 1.00 (95% CI: 0.89 to 1.12, I² = 0%).

Conclusions: Micro-ultrasound-guided PB provides comparable DRs for PCa with mpMRI-guided PB. Therefore, it could be considered as an attractive alternative to mpMRI-targeted PB. Nevertheless, further high-quality studies are warranted to corroborate our findings.

Keywords: micro-ultrasound-guided prostate biopsy, magnetic resonance imaging-targeted prostate biopsy, systematic prostate biopsy, prostate cancer, systematic review and meta-analysis
General part-Background

Prostate cancer incidence and PSA screening

Prostate cancer (PCa) is highly prevalent worldwide with about 1.3 million cases and 360 thousand deaths expected yearly (1) and is currently the most commonly diagnosed malignancy in men. Prostate cancer is a growing global killer with an incidence estimated at 13.5% for 2018, 1,282,500 new cases and a mortality rate of 6.7% with 361,800 deaths.(2). In 2019, registry data have shown that death from prostate cancer has overruled death from colorectal cancer being the second most cause of cancer-related death in men behind lung cancer. For 2020, 33,000 PCa related-deaths are estimated to occur accounting for 10% of all cancer-related deaths. (3)

PCa is known to show a racial predisposition with an increased incidence in men of African descent (4). Despite screening and resultant decrease in the incidence of fatal PCa by more than 50% since the introduction of the Prostate Specific Antigen (PSA) testing, racial disparity in PCa diagnosis has not narrowed. Recent studies have shown that the rates of fatal PCa were up to 3-fold higher in black men compared to white men and increasing to 4.2-fold among younger men even among cities within the same state in the USA. (5,6)

The Prostate Specific Antigen (PSA), identified in 1987 as a serum biomarker for PCa, has revolutionized PCa diagnosis and treatment since. In 1994 the FDA approved serum PSA as a threshold for prostate biopsy for PSA values greater than 4 ng/ml (7). PSA is almost exclusively produced by the epithelial cells of the prostate and its function is to liquefy semen. The normal prostate excretes the vast majority of the PSA produced into the glandular duct with only a small proportion leaking into the circulation. Mechanism by which PSA reaches the serum is unclear but may be associated with disturbance of normal structure and obstruction of acini and ducts(8). PSA is organ-specific for the prostate but not tumour-specific therefore it can be found elevated in conditions or pathologies that affect the prostate, such as BPH, prostatitis, urethral instrumentation, following ejaculation, etc. This is its main limitation as a tumor marker due to the overlap of its values between benign prostate conditions (BPH) and PCa. In order to increase the ability of PSA to detect PCa the use of several calculated parameters related to PSA have been proposed: PSA velocity, PSA density, age-specific PSA.
PSA velocity (PSAV), calculated as the absolute annual increase in serum PSA (ng/mL/year), although useful in prognosis of treated PCa has a limited role as a diagnostic tool mainly because of background noise (total prostate volume, and BPH). (9)

PSA density (PSAD) is calculated by dividing PSA by the prostate volume measured by ultrasonography. The proposed cut-off value to prompt a prostate biopsy was a PSAD > 0.15ng/ml (10). PSA density does not enhance the ability of serum PSA alone to predict the presence of PCa due to possible errors in the ultrasound estimation of prostate volume, different ratio between patients, of the glandular prostate tissue (which produces PSA) to the stroma (which does not produce PSA). Rather than predictor of PCa, PSAD has been found more useful as a tool in the risk stratification of known PCa eligible for active surveillance (11).

Currently total PSA alone with either a fixed (2.5 ng/ml, 3 ng/ml or 4 ng/ml) or age-specific range is the best tool for case-finding in prostate cancer. Free/total PSA may be helpful in deciding on repeat biopsies for PSA values within the range of 4 ng/ml to 10 ng/ml (12).

The rapid uptake of PSA testing led to a dramatic spike in overall prostate cancer diagnoses since the early 1990s (13) paving the way to the so-called “PSA era” in prostate cancer (14). However throughout the 1990s and 2000s, prostate cancer screening was implemented poorly. Older men were over-screened, younger men were under-screened, low-risk disease was over-treated, and high-risk disease was under-treated. Despite all these shortcomings, PCa mortality rates were driven down by more than 50%, but at the cost of too much avoidable treatment and its attendant side effects.

The goal of PSA screening is not to identify all prostate cancers, rather it is the early detection of aggressive prostate cancer while it can be cured. The question of whether or not prostate cancer screening with PSA testing reduces deaths from PCa was answered by two major global trials, the European Randomised Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) studies.

The PLCO study included 76,693 men aged 55-74 and assigned to annual screening for 6 years versus usual care at 10 US centers between 1993-2001. The study was non-informative with respect to the question of screening versus no screening and prostate cancer mortality (15). However the PLCO study was heavily criticized for not being a fair comparison between screening and no screening; instead it was a comparison between
annual screening and ad hoc screening with over 90% of “control” patients having at least one PSA screening (16).

On the contrary, both the European study (ERSPC) and the Göteborg screening study revealed a relative reduction in prostate cancer deaths with PSA screening (17,18).

In the ERSPC study PSA screening reduced disease-specific mortality by 21%, which is equivalent to one death prevented per 781 men invited for screening or one death per 27 prostate cancer detected. An update of the ERSPC study showed that after 20 yrs of follow-up the number of patients needed to screen and diagnose prostate cancer in order to prevent one prostate cancer death decreased to 101 and 13, respectively (19).

Recent analyses however accounting for differences in the two studies suggest that the efficacy of screening in the PLCO setting might be consistent with what was observed in the ERSPC trial (20).

While PSA is considered by many as the best screening biomarker in the history of oncology despite its inherent flaws and limitations, in 2012 the US Preventive Services Task Force issued a recommendation against PSA-based prostate cancer screening (21).

The main drivers for this recommendation was that the goal of screening should be to identify aggressive prostate cancer while radical and curative treatment can be offered and avoid overdiagnosis and subsequent overtreatment.

There are certain subgroups of men (of African descent, those with a family history of PCA or breast cancer) that share a particularly higher risk for harboring prostate cancer and hence will benefit the most from early screening and diagnosis (22). On the other hand screening may also identify low-risk prostate cancers which usually require no treatment and can be safely initially managed with active surveillance (23) Overdiagnosis and subsequent implementation of unnecessary radical treatment, namely radical prostatectomy and radiotherapy, for low risk prostate cancers causes more harm than saves lives. Radiotherapy and surgery result in long-term adverse events, mainly urinary incontinence and worsening of erectile function in at least 200 to 300 of 1000 men treated with these therapies while radiotherapy is also associated with bowel dysfunction (23) The risk of overdiagnosis has been estimated to be as high as 40% in screen-detected prostate cancer and is particularly important given the slow development of the disease itself (24,25).

The recommendation to not perform PSA testing for early PCA detection led to a change in clinical practice with a 10-18% decline in PSA tests and to a 28% decrease in incident diagnoses of prostate cancer in the year after the USPSTF draft recommendation. (26)
Moreover in the coming years after the USPSTF recommendation a rise in the incidence of diagnosis of advanced and de novo metastatic PCa was seen (27) while studies also showed that cutting back on PSA screening was reversing the trends of declining death rates with rising PCA mortality(28).

The 2012 USPSTF recommendation was later modified by the USPSTF in 2018 (29) in light of evidence from randomized clinical trials showing that PSA-based screening in men aged 55 to 69 years may prevent approximately 1.3 PCa deaths over approximately 13 years per 1000 men screened and approximately 3 cases of metastatic prostate cancer per 1000 men screened (18). However PSA screening was discouraged in men over 70, where the potential benefits of PSA screening do not outweigh the harms(29).

Currently the decision for or against PSA-based screening is left to the patient with a life expectancy of more than 10 years, who is well-informed about the benefits and risks of screening in pursuing an early diagnosis of PCa (29,30). Screening smarter is certainly better than no screening or opportunistic screening and establishing a baseline PSA value at the age of 40-45 is important in initiating a risk-adapted follow-up with the purpose of reducing metastatic prostate cancer and mortality (31). Current recommendations suggest that men between 45 and 60 years of age with a PSA<1 ng/ml should have a recheck not earlier that 5 years later. Men within the same age group with PSA levels between 1 and 2 ng/ml should have their PSA rechecked in 6-12 months or receive an early referral to the urologist in cases of family history or cancer anxiety. Lastly, men between 45 and 60 years of age with PSA values above 2ng/ml should be referred to the urologist for reflex testing and risk stratification but not necessarily for prostate biopsy. Men between 60 and 75 years of age with a PSA < 1 ng/ml should be rechecked in 5 years while those with a PSA between 1-3 ng/ml should have their PSA rechecked in 6 to 12 months and receive an early referral to the urologist if there is a positive family history or anxiety about cancer diagnosis. Those with a PSA above 3 ng/ml should be referred to the urologist for additional testing with the question of whether or not a prostate biopsy is required (32).

Prostate cancer risk stratification and other biomarkers

The goal of screening is identification of potentially lethal prostate cancer while at the same time avoiding unnecessary biopsies. Therefore, before a decision for biopsy is made some patients should be further stratified according to prostate cancer risk with the use of risk
calculators and biomarkers in addition to serum PSA values. Risk calculators include the PCPT, ERSPC and Sunnybrook calculators.

Different molecular biomarkers have been proposed to risk-stratify men and identify those with significant prostate cancer. These tools based on algorithms including PSA or other markers and clinical information can identify clinically significant disease with high accuracy and might further decrease the risk of overdiagnosis (33,34). Serum or urine tests useful to consider before deciding for a biopsy include the PCA3, 4K test, Prostate Health Index (PHI), SelectMDx, ExoDx (35–38) The prostate health index (PHI) uses the PSA isoform of pro-PSA to help discriminate between PCa and benign prostatic conditions, improve the specificity of PCa detection and detect more aggressive disease (36,39).

PHI is calculated using the formula Phi = (p2PSA/fPSA) x square root PSA. Therefore in men with a PSA of 2-10 and a negative DRE, the higher the total and p2 and the lower the free PSA in relation to each other, the more likely the man has prostate cancer. P2PSA in combination with free and total PSA increase specificity. Phi may be useful to reduce unnecessary biopsies with minimal loss of sensitivity for PCa detection in men with PSA 2.0-10 and negative DRE (40).

The PCA3 gene is a molecular marker that has shown promise for improving the diagnosis of prostate cancer. PCA3 is a prostate-specific noncoding mRNA that is over-expressed 60-100-fold more in PCa. The over-expression of PCA3 mRNA can be quantified and expressed relative to the PSA gene (41) The PCA3 Score is calculated as [PCA3 mRNA]/[PSA mRNA] x 1000.(42) PCA3 is measured in urine following digital rectal examination. PCA3 has shown an improved specificity for prostate cancer detection over PSA depending on the threshold, however it is less consistent as predictor for high-grade disease. Studies have shown that PCA3 might be more accurate and useful in cases of previous negative biopsy (43). The PCA3 assay provides additional utility to the PSA test suggesting that PCA3 expression is more specific and a useful adjunct to the serum PSA test (44).

Nonetheless, although those tests may provide complimentary information that enhance prediction of high-grade prostate cancer they should not be considered as alternatives to PSA screening and should not be used as reflex tests. Their integration with other tools such as mpMRI might ultimately reduce the number of unnecessary biopsies without increasing the risk of missing a significant disease (45). The best early detection algorithm should integrate risk calculators, imaging and molecular tests in a model with family history and other clinical information.
Transrectal Ultrasound-guided prostate biopsy (accuracy and limitations)

Prostate cancer was, until recently, the only solid organ malignancy where diagnosis was made without targeted imaging with the hope that random sampling will eventually hit the cancer (46). Prostate cancer diagnosis has traditionally been anchored on systematic, 10 to 12-core, transrectal ultrasound (TRUS) -guided prostate biopsy (47,48). It is estimated that more than two million prostate biopsies are performed in Europe and the US every year (49).

A TRUS-guided biopsy procedure samples less than 1% of the entire gland and hence may miss a tumor focus (50). TRUS biopsy has a cancer detection rate of 40-45% at a PSA range of 4-10 ng/ml and a 25% rate of prostate cancer diagnosis after an initial negative biopsy. TRUS-guided biopsy has an alarming false-negative rate of around 25% and concern for occult cancer with persistently elevated PSA leads to a high rate of repeat biopsies.

TRUS-guided prostate biopsy false negative rates is related to technical limitations including limited access to the apical and anterior areas of the prostate, especially in large glands. Apart from issues related to access within the gland, TRUS-guided biopsy will miss small cancer lesions, 79% of lesions between 0.2-0.5 ml are missed resulting in an overall 30-45% rate of false-negative biopsies (51). Extended biopsy schemes have been proposed in order to increase TRUS-guided biopsy cancer detection rate including additional cores to the standard 12-core biopsy from the lateral peripheral zone and transition zone (52). Still the detection rate of TRUS-guided prostate biopsy has not improved much despite the implementation of extended sampling schemes with false negative rates ranging from 16-41%.

Characteristically 43% of the patients enrolled in the PLCO prostate cancer screening trial had a repeat biopsy within 3 years of the initial biopsy due to persistently elevated PSA.(53)

Results from the same study however have shown that within 13 years of follow up only 1.1% of men with an initial negative biopsy died from prostate cancer (54) suggesting that most missed PCAs were probably low risk.

TRUS-guided biopsy is certainly not devoid of complications as it is associated with a 22% risk of hematuria, 36% risk of blood from the rectum, more than 50% risk of prolonged hematospermia, and a 0.5-6% chance of urinary tract infection including a 1-2% risk of sepsis.(49,55,56) A large study of 10,474 biopsies showed a 4.2% rate of febrile UTI and a 0.8% hospitalization rate, with prostate size above 40 ml and diabetes mellitus as risk factors (57). The rate of infectious complications after TRUS-guided prostate biopsies has recently
increased owing to increased resistance to fluoroquinolones prescribed prophylactically. Recent studies have shown a 10-22% rate of bowel colonization of fluoroquinolone-resistant bacterial strains resulting in 4 times increases risk of infection after prostate biopsy (58).

One limitation of TRUS-guided biopsies is that clinically insignificant PCa is often detected while clinically significant PCA is sometimes missed. TRUS is not able to reliably identify target lesions within the gland as prostate cancer foci can be hyperechoic or isoechoic and cannot be discerned from BPH especially at PSA values below 10 ng/ml, where only 30% of prostate cancer are visible on TRUS (59) On the other hand the presence of an hypoechoic area within the prostate is associated with an overall prostate cancer detection rate of 50.7% and rate of clinically significant cancer (Gleason score>7) of 69% (60). Another limitation of TRUS-guided prostate biopsy is that biopsy is not truly “systematic” in the sense that sampling of the prostate is not symmetrical as has been shown in a study comparing free-hand TRUS-biopsy to robotic-assisted biopsy where an average 9mm target error in positioning of the needled was demonstrated (61).

The ideal way to overcome the shortcomings of TRUS-guided prostate biopsy would be to perform standard template transperineal mapping biopsies (TPMB) where the whole gland is sampled at 5mm intervals. The TPMB approach has a 95% sensitivity and a 95% negative predictive value and is considered the reference test for prostate cancer detection. (62) TPMB provides access to the whole prostate and especially the apex and anterior prostate, is related to negligible risk of UTI as the needles are placed through the perineum and not the rectum and has a very low rate of false negative results(49). On the other hand, TPMB is more costly and time consuming, usually requires general anaesthesia since more biopsy cores are taken, has a higher likelihood of overdiagnosis of low risk cancers and a 5-10% risk of retention in large glands. For the above reasons the utilization of TPMB is reserved for cases with previous negative biopsy or suspicious areas located at the anterior prostate theoretically not accessible with standard TRUS-guided biopsy (63).

**mpMRI-guided prostate biopsy (accuracy and limitations)**

Over the last years, multiparametric magnetic resonance imaging (mpMRI)-targeted PB brought upon a revolution in prostate imaging and is currently recommended in
combination with systematic PB in biopsy-naïve men for the diagnosis of localized PCa (64–66).

In mpMRI of the prostate anatomical sequences (T2 Weighted) are combined with functional sequences (Diffusion Weighted Images (DWI) and Dynamic Contrast Enhanced (DCE) sequence) on a 1.5 or 3 Tesla MRI with or without an endorectal coil. The mpMRI findings are scored and interpreted by using the Prostate Imaging-Reporting and Data System (PI-RADS) version 2.1. (67) Each lesion is assigned a PI-RADS Assessment Category using a 5-point scale (PI-RADS 1:very low to PI-RADS 5:very high) based on the likelihood that findings on T2W, DWI and DCE correlate with the presence of a clinically significant cancer at a particular location.

A PIRADS score greater than 3, is considered an indication for prostate biopsy in men with an elevated PSA or abnormal findings on DRE. PIRADS 4 and 5 lesions are associated with a more than 90% chance of harboring prostate cancer and 60-80% of harboring clinically significant prostate cancer (Gleason score≥ 3+4) according to the results of the landmark PROMIS trial. (68) Apart from offering the possibility of targeting suspicious areas, mpMRI is also able to provide information on local staging (size of the lesion, infiltration of the prostatic capsule, pelvic lymph nodes status).

mpMRI-guided prostate biopsy can be performed in three different ways, as in-bore MRI biopsy where the biopsy is done by the radiologist with use of a rectal probe and the patient inside the MRI scanner. There is the MRI/US fusion biopsy where specific software is used to superimpose the MRI images to real-time TRUS images in order to identify and target suspicious areas, MRI/US fusion is less operator dependent but more costly. And then there is the cognitive registration method which does not require any software but relies on the experience of the physician, this approach has a learning curve. Studies have shown that MRI/US fusion biopsy is superior to TRUS-guided biopsy with 30% more significant PCa diagnosis and 17% fewer diagnosis of insignificant PCA (69). A recent meta-analysis however demonstrated that for clinically significant PCa detection there was no significant advantage of any one technique of MRI-guided biopsy (70).

The PROMIS study was the first study to offer evidence for the use of mpMRI as a secondary screening tool for prostate cancer detection among men with elevated PSA. PROMIS recruited 740 men with prostate cancer suspicion due to elevated PSA, family history or abnormality in DRE. All men underwent mpMRI and TPMB along with TRUS-guided prostate biopsy. The study showed that around 25% of men could be spared the biopsy based on negative findings (PI-RADS<3) on mpMRI. A negative mpMRI had a negative prognostic
value of 82% for cancer and 98% for clinically significant cancer compared to 74% NPV of TRUS-guided biopsy. (68)

The diagnostic accuracy of mpMRI is good but not perfect, with a sensitivity of 58-96% and a negative predictive value of 82% for overall cancer and 88% for clinically significant cancer (71–73). mpMRI miss 1 out of 10 clinically significant (Gleason score ≥ 3+4) prostate cancers or extensive volume Gleason score 3+3=6 lesions (72). In another study, 16% of clinically significant prostate cancers were missed on mpMRI (74). For the above reasons the guidelines suggest TRUS-guided biopsies in addition to mpMRI-guided biopsies for biopsy naive men at risk for PCa (46).

The subtype of prostate cancer is also related to mpMRI cancer detection rates. It has been shown that the cribriform growth of Gleason 4 prostate cancer is related to higher likelihood of distant metastases and death after radical prostatectomy (75,76). There is evidence that cribriform pattern growth is less visible on mpMRI and hence may not be targeted, and hence missed, at mpMRI-guided biopsy. Truong et al in their study correlating mpMRI findings to final histopathology showed that all lesion > 2 cm were visible on mpMRI except 23% of cribriform tumors (77).

An issue with PI-RADS v2 is that this 5-point scale has to be translated into a binary clinical decision, to biopsy or to not biopsy. Therefore scoring a lesion as PIRADS 3, or intermediate, and not being able to provide a definitive answer as to whether or not a biopsy is indicated is one of the limitations of the PIRADS system, although studies have shown that the more experienced the radiologist the less PIRADS 3 lesions assigned. In cases of PIRADS 3 lesions PSA density (PSAD) and lesion volume have been shown to be useful in decision-making with studies showing that PIRADS 3 lesions and a PSAD<0.15 should be biopsied (78,79).

As mentioned previously the accuracy of mpMRI in prostate cancer detection is depended on the experience of the radiology team performing and reading the scan. There is considerable interobserver variability in PIRADS score assignment and significant different cancer yield across radiologists (80) often requiring evaluation from experienced radiologists for proper interpretation (81).

In conclusion, mpMRI is certainly useful but its results are not gospel and should be interpreted with caution due to certain limitations. There is evidence that mpMRI can identify >90% of men with clinically significant PCa and can reduce the number of unnecessary biopsies by at least 25%. mpMRI followed by biopsies can significantly reduce over-diagnosis of non-clinically significant PCa. On the other hand it is a relatively expensive technology,
with problematic access for the patients for whom it is indicated. MRI interpretation is complex, subject to variability and gaining expertise requires a significant learning curve. mpMRI-guided biopsy is associated with a 15% missed diagnosis of prostate cancer. mpMRI is not good enough for accurate local tumor staging, extracapsular extension and underestimates the tumor volume (82).

**Micro-Ultrasound-guided prostate biopsy**

High resolution micro-ultrasound (micro-US) is a novel technology developed by Exact Imaging, Toronto, Canada, which offers the potential to image lesions suspicious for PCa and perform real-time targeted biopsies with significantly improved cancer visualization compared to conventional ultrasound. Micro-US incorporates a scoring system (Prostate Risk Identification using Micro-UltraSound-PRIMUS, Grades 1-5) that is similar to the PIRADS-2 system used for MRI. This facilitates assignment of a risk category based on the characteristics of the region of interest. (83)

Micro-ultrasound operates at 29 MHz, compared to traditional ultrasound systems that operate at frequencies of 8-12 MHz. The axial resolution is improved from 200 μm with conventional ultrasound to <70 μm with micro-ultrasound with a similar improvement in lateral resolution due to 90 μm crystal spacing. This resolution is approximately the diameter of a prostatic duct, and allows for the visualization of subtle changes in ductal anatomy associated with cancer. Highly cellular tissues exhibit lower diffusion coefficients therefore micro-US is able to identify changes associated with high grade cancer with the same accuracy as mpMRI (87).

High resolution micro-US offers the benefit of a comparatively simple technology, with imaging and biopsy performed as a single procedure and controlled by the urologist so the learning curve for micro-US imaging appears to be short. In one study, the AUC flattened after 15 cases. The footprint and cost of the device is similar to conventional ultrasound. (88).

High-resolution micro-US is a novel imaging modality, aiming to improve the diagnostic accuracy of PB, while maintaining the convenience of ultrasound technology in prostate biopsies (84). Available data suggest that high-resolution micro-US-guided PB provides greater sensitivity in detecting clinically significant PCa than conventional transrectal US (85) and that it may present comparable detection rates (DRs) with mpMRI-targeted biopsy for clinically significant PCa diagnosis (86).
In this scope, we generated a systematic review and meta-analysis aiming to assess the accuracy of micro-ultrasound-guided prostate biopsy compared with multiparametric MRI-targeted prostate biopsy for the detection of clinically significant and insignificant prostate cancers.
Micro-ultrasound-guided versus multiparametric magnetic resonance imaging-targeted biopsy in the detection of prostate cancer: a systematic review and meta-analysis

Systematic review and Meta-analysis

Materials and Methods

This systematic review and meta-analysis was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and its extension for diagnostic test accuracy studies (PRISMA-DTA) (Appendix 1) (87,88). The aims and methods of our study were prespecified and registered in a protocol at PROSPERO (ID: CRD42020198326).

Search strategy

We systematically searched PubMed, Cochrane Library and Scopus databases from inception up to November 30, 2020 for studies comparing the DR of high-resolution micro-US-guided versus mpMRI-targeted PB for PCa. We also conducted a targeted search of the potentially grey literature, including conference abstracts published in major urology journals, clinical trial registries (ClinicalTrials.gov and EudraCT) and websites providing appropriate information about relevant trials (exactimaging.com). Moreover, we hand-searched the reference lists of all eligible studies and relevant reviews. All searches were performed by two independent reviewers (PS, NP). The detailed search syntax and search string are presented in Data Supplement 2.

Inclusion and exclusion criteria

We included prospective or retrospective diagnostic accuracy studies where each individual underwent consecutively micro-US and mpMRI-targeted PB. On the contrary, we excluded studies comparing high-resolution micro-US or mpMRI-targeted PB versus systematic PB. Additionally, we excluded case reports and single-arm studies. When multiple records with potential overlapping populations were identified, the most recent or the study reported as full-text was only included.
Data extraction and quality assessment

Two authors (PS, NP) screened for eligibility all identified records. Any disagreements were resolved by consensus. Data collection was performed independently in a predefined Microsoft Excel spreadsheet. For each included record, we retrieved information about study and participant characteristics, interventions and PCa classification according to the International Society of Urological Pathology (ISUP) Grade Group (GG). Micro-US-guided PB was considered the index test and mpMRI-targeted PB the comparator test (reference standard). To ensure consistency in reviewing, we conducted a pilot test (89).

We estimated the risk of bias and applicability concerns of each study using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool (90). QUADAS-2 comprises of four domains that include patient selection, index test, reference standard and flow and timing. Each domain is evaluated in terms of risk of bias while the first three domains are also evaluated in terms of applicability concerns. Moreover, signaling questions are included to help assessor to better judge risk of bias. The QUADAS-2 tool is applied in four phases. First of all, each assessor summarizes the review question, tailors the tool and produces a review-specific guidance. Subsequently he constructs a flow diagram for the primary study and judges the risk of bias and applicability concerns of each study. Overall, this tool allows for transparent rating of risk of bias and applicability concerns of diagnostic accuracy studies.

Accordingly, we evaluated the risk of bias across studies (publication bias) via visual assessment of contour-enhanced funnel plot asymmetry and the Egger’s statistical test (p<0.05) (91). In general, the potential sources of funnel plot asymmetry and suspected publication bias comprise: (i) the real publication bias; (ii) the poor methodological quality leading to spuriously inflated effects among included studies; (iii) the true heterogeneity among included studies and; (iv) chance (Egger’s statistical test is applied to rule out chance. It should be stressed that in meta-analyses displaying high heterogeneity, funnel plot asymmetry is not always informative, and the Egger’s statistical test cannot examine small biases across studies. Furthermore, contour-enhanced funnel plot aids the interpretation of the funnel plot. In particular, not only it considers the study estimates but it also indicates conventional milestones in statistical significance levels (i.e <0.01, <0.05, <0.1). For example, if studies are missing in the non-significance areas, then this indicates that the asymmetry may be attributed to publication bias. On the contrary, if the identified missing studies are located in areas of
statistical significance, this may suggest that the cause of the asymmetry may be attributed to factors, irrelevant to publication bias, such as the quality of the included studies.

Grading of evidence, data synthesis and statistical analysis

We determined the overall strength of evidence for the DR of clinically significant, clinically insignificant and any PCa between micro-US and mpMRI-targeted PB using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (92). GRADE helps to evaluate the quality of provided evidence by taking into account a variety of parameters from the included studies. Two reviewers (PS, NP) graded risk of bias, inconsistency, indirectness, imprecision and publication bias among included trials. Any discrepancies were resolved by consensus of with the addition of a third author.

We performed an inverse variance random effects meta-analysis of DRs. In particular, we synthesized DRs with the corresponding 95% confidence intervals (CIs) for the following outcomes: i) detection rate of micro-US versus mpMRI-targeted PB for clinically significant PCa (GG ≥ 2); ii) detection rate of micro-US versus mpMRI-targeted PB for clinically significant PCa (GG ≥ 3); iii) detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically insignificant PCa (GG = 1); iv) detection rate of micro-US versus mpMRI-targeted prostate biopsy for any grade of PCa.

DRs were defined as the number of men with the relevant GG of PCa for each outcome divided by the total number of men who received both micro-US and mpMRI-targeted PB. Furthermore, we performed a subgroup analysis based on the type of study reporting outcomes (full-text article, conference abstract or multicenter registry provided by Exact Imaging) Accordingly, we undertook a sensitivity analysis including only studies at low risk of bias and with low applicability concern. We calculated heterogeneity with the I² (substantial heterogeneity when I² > 50%) and its significance was determined with the p value of the Cochran’s Q test. For all estimations, p-values lower than 0.05 were considered statistically significant. All analyses were performed with the R statistical program (version 3.6.3) using the “meta” and “metafor” packages.
Results

Study results and quality assessment
The literature search yielded 1084 potentially relevant records through databases searching and 19 through sources of grey literature. After removing duplicates, we screened as title or abstract 1060 records. Ultimately, 49 studies were assessed as full-texts, of which 18 studies were included in the qualitative (93–108) and 13 in the quantitative synthesis (93–103). The reasons for exclusion were documented and all identified records were paired cohort studies. Overall eight trials were published as full-texts (93,94,98,100,101,103,104,109), four as conference abstracts (96,99,102,105) and three in one prospective multicenter registry study provided by Exact Imaging, Toronto, Canada (95,110). Regarding the later, all centers reporting data on the DR of micro-US versus mpMRI-targeted PB regularly updated their registries and republished their patient series. The step-by-step selection process of studies is illustrated in Data Supplement 3 and 4.

Applying the QUADAS-2 tool for the included published studies, the overall methodological quality was evaluated as moderate. In particularly, regarding the risk of bias, five trials were considered at low risk, eight at moderate risk and two at high risk of bias. Regarding the applicability concerns, twelve trials presented low and three moderate concerns. The detailed assessment is available in Data Supplement 5.

Study characteristics
A total of 1683 participants from 15 published trials with a mean age of 65.9 ± 8.4 were analyzed. The mean PSA values were 8.7 ± 2.2 ng/dL and the mean prostate volume 46.5 ± 17.4 ml. Overall, 695 patients had previously undergone PB and 177 had an abnormal digital rectal examination. Ultimately, 1391 participants received both micro-US-guided and mpMRI-targeted PB. In most studies, patients underwent first micro-US-guided PB, followed by mpMRI-targeted PB and by 10 or 12-core systematic PB. The histological results of the exact GG after radical prostatectomy were not provided in any study. PBs were performed by a transrectal or a transperineal approach under local or general anesthesia and no complications were reported during all procedures.
Suspicious lesions were identified with the micro-US based on the prostate risk identification using micro-ultrasound (PRI-MUS) protocol (PRI-MUS ≥ 3) (111) and with the mpMRI based on the prostate imaging – reporting and data system volume 2 (PI-RADS v2) protocol (PI-RADS v2 ≥ 3) (67).

Regarding PRI-MUS, lesions with PRI-MUS 1 are considered any lesions presented as small regular ducts or “Swiss cheese” with no other heterogeneity or bright echoes, lesions with PRI-MUS 2 are hyperechoic with or without ductal patches (possible ectatic glands or cysts), lesions with PRI-MUS 3 present mild heterogeneity or bright echoes in hyperechoic tissue, lesions with PRI-MUS 4 have a heterogeneous cauliflower/smudgy/mottled appearance or bright echoes (possible comedonecrosis) and lesions with PRI-MUS 5 present irregular shadowing (originating in prostate, not prostate border) or mixed echo lesions, or irregular prostate and/or peripheral zone border.

In studies reporting the number of cores sampled per target, micro-US-guided PB required fewer specimens than mpMRI-targeted PB. The operators performing micro-US-targeted PB received appropriate training and all mpMRIs were evaluated by a radiologist experienced in mpMRI. Moreover, all mpMRIs were performed within three months before PB, with a strength of 1.5 or 3 Tesla with or without an endorectal coil. Regarding the type of mpMRI-targeted PB, a cognitive approach was preferred in 9 and a fusion targeting system in 6 studies, detecting similar cases of PCa.

Both techniques detected similar cases of PCa. The characteristics of the included study records are depicted in Table 1 and the details of the upcoming relevant trials identified through ClinicalTrials.gov are presented in Data Supplement 6.

**Clinically significant PCa detection rate**

In the analysis of men with GG ≥ 2 PCa, we included a total of 13 cohort studies comprising 1125 participants receiving micro-US-guided, followed by mpMRI-targeted and systematic PB (93–96,98–103,109,110). By adding the results of the three techniques, 437 patients with GG ≥ 2 PCa were identified. The micro-US-guided PB identified 341 and the mpMRI-targeted PB 327 cases (DR: 1.05, 95% CI: 0.93 to 1.19, I² = 0%) (Figure 1). In the subgroup analysis based on the type of study reporting outcomes, no significant differences were observed among full-texts, conference abstracts and the Exact Imaging registry (p = 0.92). This effect was also evident in the sensitivity analysis of the five cohort studies with good methodological quality
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(DR: 1.08, 95% CI: 0.87 to 1.35, $I^2 = 43\%$) (Data Supplement 7.1). Additionally, funnel plot inspection and Egger’s statistical test did not indicate any important publication bias among the trials included in our quantitative synthesis ($p = 0.67$) (Data Supplement 8).

Regarding patients with GG ≥ 3 PCa, a total of five cohort studies with 546 individuals, receiving micro-US-guided, followed by mpMRI-targeted and systematic PB, provided relevant data (93,94,97,102,103). Ultimately, 122 cases of GG ≥ 3 PCa were reported by adding the results of the three techniques. The micro-US-guided PB identified 99, while the mpMRI-targeted PB 79 patients (DR: 1.25, 95% CI: 0.95 to 1.64, $I^2 = 0\%$) (Figure 2). No significant difference was calculated between the four full-texts and the conference abstract ($p = 0.77$).

Clinically insignificant and overall PCa detection rate

A total of nine cohort studies with 893 patients undergoing consecutively micro-US-guided, mpMRI-targeted and systematic PB reported cases of clinically insignificant PCa (GG = 1) (93,94,96,99–103,109). The total number of men with clinically insignificant PCa was 158, of which 95 were identified after micro-US-guided PB and 102 after mpMRI-targeted PB (DR: 0.94, 95% CI: 0.73 to 1.20, $I^2 = 0\%$) (Figure 3). Regarding the type of reported outcomes, no significant difference was estimated between the six full-texts and the three conference abstracts ($p = 0.19$). Similar results were observed in the sensitivity analysis of the 4 cohort studies with good methodological quality (DR: 0.84, 95% CI: 0.62 to 1.17, $I^2 = 0\%$) (data Supplement 7.3).

The same nine cohort studies reported the total cases of PCa diagnosed through micro-US-guided, mpMRI-targeted and systematic PB (93,94,96,99–103,109). From the 503 individuals with positive biopsy, both diagnostic modalities identified 299 cases (DR: 0.99, 95% CI: 0.89 to 1.11, $I^2 = 0\%$) (Figure 4). Similarly, no differences were observed in the subgroup analysis based on the type of study reporting outcomes ($p = 0.28$) and in the sensitivity analysis based on studies with good methodological quality (DR: 0.97, 95% CI: 0.85 to 1.11, $I^2 = 0\%$) (Data Supplement 7.4).
Grading of evidence

Although the importance of our findings was deemed critical, the overall strength of evidence was determined as low for all outcomes between the reviewers. The fact that the operators performing micro-US-guided PB were not familiar with this novel technique may suggest a higher DR of micro-US in PCa diagnosis, while no effect was observed. On the other hand, the observational design of all studies, the unclear or high risk of bias of some trials and the fact that about half of the included records were published as conference abstracts or registries downgraded the quality of evidence. The detailed grading is summarized in Table 2.
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Discussion

This systematic review and meta-analysis provides evidence that micro-ultrasound-guided PB is a promising alternative diagnostic modality to mpMRI-targeted PB and systematic PB. Although the overall strength of the provided evidence was deemed low, the DRs for clinically significant and insignificant PCa were similar between micro-ultrasound-guided and mpMRI-targeted PB. Of interest, micro-ultrasound identified more clinically significant PCa cases requiring fewer cores per lesion. It should be also stressed that our findings were consistent across subgroup and sensitivity analyses.

The “MRI-pathway” in PCa diagnosis results in avoiding unnecessary biopsies, as it identifies more clinically significant PCa and fewer clinically insignificant PCa cases (68,112,113). Still, guidelines recommend that PB-naïve patients should undergo both mpMRI- and systematic TRUS-guided PB (46), as MRI-targeted PB may miss some clinically significant PCa cases (114,115). In particular, it has been demonstrated that 16% to 35% of all lesions harboring clinically significant PCa remain undetected or underestimated by mpMRI (74,116). Moreover, apart from the apparent drawbacks of cost and accessibility compared to TRUS-guided PB (117), MRI-targeted PB presents also limited inter-reader and intraoperator reproducibility even among experienced radiologists (118). Another limitation of mpMRI-guided PB is that the accurate interpretation of prostate mpMRI findings requires a high level of expertise and training (73). Similarly, mpMRI-guided PB, either with cognitive or fusion approach, is usually performed via a TRUS probe and, thus, prone to cross-modality registration errors (119).

Therefore, there is certainly room for more sophisticated ultrasound modalities that overcome the limitations of the mpMRI-guided PB and provide improved imaging and accuracy in PCa detection. Advances in imaging technologies have led to the development of the first 29 MHz micro-ultrasound system (120). The ExactVu™ platform is an accessible, fast, less costly and urologist-friendly imaging modality that provides easier lesion targeting than mpMRI-targeted PB without registration errors (111,121,122). Micro-ultrasound has the potential to become an accessible modality for PB, as it follows the standardized schemes of conventional TRUS and is more sensitive in detecting clinically significant PCa than conventional TRUS (85). Hence, the diagnostic accuracy of micro-ultrasound is possibly limited by large prostate volume and
specific tumor location, such as the transitional zone, while the accuracy of mpMRI is independent to these factors (109).

According to a recent meta-analysis of 769 patients, micro-ultrasound displays a sensitivity, specificity, diagnostic odds ratio and an area under the summary receiver-operating characteristic (ROC) curve of 0.91, 0.49, 10 and 0.82 respectively (123). Of interest, a meta-analysis published only as a conference abstract included 274 men undergoing consecutively micro-ultrasound and mpMRI-targeted PB and demonstrated that micro-ultrasound presents higher sensitivity and negative predictive value, similar positive predictive value and lower specificity than mpMRI-targeted PB (86).

**Strengths and limitations**

To our knowledge, we provided the first qualitative and quantitative synthesis comparing the DRs of micro-ultrasound-guided PB to mpMRI-targeted PB for PCa. Accordingly, we explored the effect of the two biopsy techniques in the diagnosis of clinically significant, clinically insignificant and any PCa grade and validated the robustness of our findings by undertaking subgroup and sensitivity analyses. Of interest, our outcomes displayed minimal within and between-study variation and the strength of available evidence was also assessed, highlighting the need for further studies.

The findings of our study present some limitations, which need to be taken into consideration. All trials were performed in a non-randomized, paired design and only half of them were published as peer-reviewed, full-text articles. In some cases, the studies raised performance bias concerns, as the operators were unblinded to the mpMRI findings before the micro-ultrasound-guided PB. Accordingly, in most trials, data were collected retrospectively. Interestingly, given that broad eligibility criteria were applied across the included studies, our results may vary among different subgroups of patients undergoing PB. In particular, the included studies enrolled men with clinical suspicion of PCa, men on active surveillance protocols, PB-naïve individuals or patients with previous negative PB. Nevertheless, the absence of adequate relevant data did not allow us to conduct further predefined subgroup analyses.
Future perspectives
It should be stressed that, although high-resolution micro-ultrasound may constitute a step forward in the detection and localization of clinically significant PCa, further large-scale studies are necessary to validate the robustness of our findings. Most centers using the micro-ultrasound are expected to update their published patient series and the results of other centers conducting similar trials are anticipated with great interest. Due to the current lack of RCTs comparing micro-ultrasound to mpMRI in PCa diagnosis, high quality randomized trials are needed to evaluate the diagnostic accuracy of both pathways in clinically significant and low risk PCa. Furthermore, blinded studies should provide higher level of evidence regarding the absolute added value of each pathway compared to conventional systematic TRUS-guided PB.

Conclusions
Our findings indicate that micro-ultrasound-guided PB displays similar DRs of clinically significant and insignificant PCa with multiparametric MRI-targeted PB. Due to its high sensitivity and negative predictive value as well as its ability to implement systematic PB with real-time targeting of suspicious lesions, micro-ultrasound may be an attractive diagnostic alternative to multiparametric MRI-targeted biopsy for the detection of PCa. Still, head-to-head RCTs comparing micro-ultrasound-guided to mpMRI-targeted PB are warranted to corroborate our findings and to establish micro-ultrasound in the diagnostic pathway of PCa.

Conflict of interest
None declared.

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References

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<table>
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<tr>
<th>Author</th>
<th>Center, Country</th>
<th>Study duration</th>
<th>Compared techniques</th>
<th>Population</th>
<th>No. of patients</th>
<th>Age (yr)</th>
<th>PSA (ng/dl)</th>
<th>No. with abnormal DRE</th>
<th>Prostate volume (mL)</th>
<th>Patients with both tests</th>
<th>Number of cores per micro-US target</th>
<th>Number of cores per mpMRI target</th>
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<tbody>
<tr>
<td>1) Abouassaly 2020 (93)</td>
<td>Cleveland, USA</td>
<td>1/18 - 8/18</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa</td>
<td>67</td>
<td>65 ± 7.4</td>
<td>5.9 ± 3.41</td>
<td>7</td>
<td>37.5 ± 19.26</td>
<td>19</td>
<td>2.3 ± 0.74</td>
<td>2.9 ± 0.37</td>
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<td>2) Cornud 2020 (104)</td>
<td>Paris, France</td>
<td>2/19 - 7/19</td>
<td>Micro-US vs mpMRI</td>
<td>Suspicion of PCa and at least one mpMRI lesion (PI-RADS ≥ 3)</td>
<td>118</td>
<td>66 ± 13</td>
<td>11 ± 19</td>
<td>16</td>
<td>53 ± 26</td>
<td>118</td>
<td>5 ± 2</td>
<td>5 ± 2</td>
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<tr>
<td>3) Eure 2019 (94)</td>
<td>Virginia Beach, USA</td>
<td>12/16 - 12/16</td>
<td>Micro-US vs mpMRI vs Systematic biopsy vs Conventional transrectal US</td>
<td>Men with PCa in active surveillance protocol</td>
<td>9</td>
<td>65.6 ± 4.44</td>
<td>6 ± 1.06</td>
<td>9</td>
<td>38.8 ± 8.15</td>
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<td>4) Klotz 2020 (95)</td>
<td>Toronto, Canada</td>
<td>NA</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa</td>
<td>77</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>77</td>
<td>NA</td>
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<td>5) Lopez 2019 (96)</td>
<td>Bordeaux, France</td>
<td>NA</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Elevated PSA or abnormal DRE</td>
<td>51</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>51</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>6) Luger 2020 (95)</td>
<td>Linz, Austria</td>
<td>NA</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa</td>
<td>62</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>62</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7) Lughezzani 2019 (109)</td>
<td>Rozzano, Italy</td>
<td>10/17 - 3/18</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa and at least one mpMRI lesion (PI-RADS ≥ 3)</td>
<td>104</td>
<td>64.5 ± 5.33</td>
<td>7.9 ± 3.38</td>
<td>20</td>
<td>61.2 ± 26.75</td>
<td>104</td>
<td>1.1 ± 0.5</td>
<td>1.3 ± 0.33</td>
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<td>8) Martel 2019 (105)</td>
<td>Lausanne, Switzerland</td>
<td>5/18 - 3/19</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Biopsy-naive patients, patients with previous negative biopsy or on active surveillance or patients undergoing PCa stratification</td>
<td>148</td>
<td>66.3 ± 8.15</td>
<td>7.3 ± 4.3</td>
<td>NA</td>
<td>NA</td>
<td>148</td>
<td>NA</td>
<td>NA</td>
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<td>9) Pereira-Arias 2019 (98)</td>
<td>Bilbao, Spain</td>
<td>2/17 -1/18</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Elevated PSA or abnormal DRE</td>
<td>96</td>
<td>67 ± 5.5</td>
<td>7.5 ± 5.6</td>
<td>NA</td>
<td>56 ± 16.33</td>
<td>79</td>
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<td>10) Perez 2019 (99)</td>
<td>Saint-André-les-Vergers, France</td>
<td>NA</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa and available mpMRI</td>
<td>55</td>
<td>NA</td>
<td>15.3 ± 8.95</td>
<td>NA</td>
<td>NA</td>
<td>55</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Start Date - End Date</td>
<td>Study Design</td>
<td>Inclusion Criteria</td>
<td>Number of Patients</td>
<td>Mean PSA ± SD</td>
<td>Mean PI-RADS ± SD</td>
<td>Mean Age ± SD</td>
<td>PSA at Diagnosis ± SD</td>
<td>Mean PI-RADS ± SD</td>
<td>PSA at Diagnosis ± SD</td>
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<tr>
<td>1) Rojas-Claros 2020 (100)</td>
<td>Paris, France</td>
<td>2/17 - 9/18</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa and at least one mpMRI lesion (PI-RADS ≥ 3)</td>
<td>269</td>
<td>67.5 ± 7.4</td>
<td>7.8 ± 3.48</td>
<td>NA</td>
<td>49.5 ± 21.48</td>
<td>47</td>
<td>3 ± 1.48</td>
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<td>12) Shore 2020 (110)</td>
<td>Myrtle Beach, USA</td>
<td>NA</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa</td>
<td>14</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>14</td>
<td>NA</td>
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<tr>
<td>13) Socarrás 2020 (101)</td>
<td>Madrid, Spain</td>
<td>2/18 - 9/19</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Elevated PSA or suspicious DRE or PI-RADS ≥ 3 in mpMRI</td>
<td>194</td>
<td>62 ± 7.4</td>
<td>6.5 ± 3.33</td>
<td>31</td>
<td>58.1 ± 33.26</td>
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<td>2 ± 1.48</td>
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<tr>
<td>15) Wiemer 2020 (103)</td>
<td>Berlin, Germany</td>
<td>2/18 - 12/18</td>
<td>Micro-US vs mpMRI vs Systematic biopsy</td>
<td>Suspicion of PCa</td>
<td>159</td>
<td>69.5 ± 7.4</td>
<td>8.2 ± 4.24</td>
<td>42</td>
<td>54.5 ± 17.04</td>
<td>159</td>
<td>2.3</td>
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</table>

Table 1: Baseline characteristics of included studies. Variables are presented as mean ± SD. DRE: digital rectal examination, mpMRI: multi-parametric magnetic resonance imaging, NA: not available, PCa: prostate cancer, PI-RADS: prostate imaging-reporting and data system, PSA: prostate-specific antigen, US: ultrasound
<table>
<thead>
<tr>
<th>Std: Certainty</th>
<th>Std: Effect</th>
<th>Std: Patients</th>
<th>Std: Risk of bias</th>
<th>Std: Inconsistency</th>
<th>Std: Indirectness</th>
<th>Std: Imprecision</th>
<th>Std: Other considerations</th>
<th>Std: micro-US</th>
<th>Std: mpMRI</th>
<th>Std: Relative (95% CI)</th>
<th>Std: Absolute (95% CI)</th>
<th>Std: Certainty</th>
<th>Std: Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically significant PCa (GG ≥ 2)</td>
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<tr>
<td>13</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>all plausible residual confounding would suggest spurious effect, while no effect was observed</td>
<td>299/909 (31.9%)</td>
<td>271/909 (29.8%)</td>
<td>DR 1.08 (0.94 to 1.23)</td>
<td>24 more per 1,000 (from 18 fewer to 69 more)</td>
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<td>Clinically significant PCa (GG ≥ 3)</td>
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<tr>
<td>4</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>all plausible residual confounding would suggest spurious effect, while no effect was observed</td>
<td>45/226 (19.9%)</td>
<td>30/226 (13.3%)</td>
<td>DR 1.50 (0.99 to 2.29)</td>
<td>66 more per 1,000 (from 1 fewer to 171 more)</td>
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<td>Clinically insignificant PCa (GG = 1)</td>
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<tr>
<td>9</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>all plausible residual confounding would suggest spurious effect, while no effect was observed</td>
<td>97/677 (14.3%)</td>
<td>104/677 (15.4%)</td>
<td>DR 0.94 (0.73 to 1.20)</td>
<td>9 fewer per 1,000 (from 41 fewer to 31 more)</td>
<td></td>
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<tr>
<td>PCa (GG ≥ 1)</td>
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<tr>
<td>9</td>
<td>observational studies</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>all plausible residual confounding would suggest spurious effect, while no effect was observed</td>
<td>299/677 (44.2%)</td>
<td>299/677 (44.2%)</td>
<td>DR 1.00 (0.89 to 1.12)</td>
<td>7 fewer per 1,000 (from 82 fewer to 82 more)</td>
<td></td>
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</table>

Table 2: Grading of evidence. a. Most of the included studies are conference abstracts, registries or studies at unclear or high risk of bias. CI: confidence interval; DR: detection ratio, GG: grade group, PCa: prostate cancer.
Figure 1: Forest plot of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically significant PCa (GG ≥ 2). Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.
Figure 2: Forest plot of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically significant PCa (GG ≥ 3). Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.
Figure 3: Forest plot of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically insignificant PCa (GG = 1). Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.
Figure 4: Forest plot of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for any grade of PCa. Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.
Data Supplement

Data Supplement 1: PRISMA-DTA checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>PRISMA-DTA Checklist Item</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE / ABSTRACT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review (+/- meta-analysis) of diagnostic test accuracy (DTA) studies.</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
<td>Abstract: See PRISMA-DTA for abstracts.</td>
<td>2</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3</td>
</tr>
<tr>
<td>Clinical role of index test</td>
<td>D1</td>
<td>State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for comparative design).</td>
<td>3</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of question(s) being addressed in terms of participants, index test(s), and target condition(s).</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>4</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (participants, setting, index test(s), reference standard(s), target condition(s), and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>4</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>4</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full search strategies for all electronic databases and other sources searched, including any limits used, such that they could be repeated.</td>
<td>Data Supp.</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
<td>4, Data Supp.</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>4,5</td>
</tr>
<tr>
<td>Definitions for data extraction</td>
<td>11</td>
<td>Provide definitions used in data extraction and classifications of target condition(s), index test(s), reference standard(s) and other characteristics (e.g. study design, clinical setting).</td>
<td>4</td>
</tr>
<tr>
<td>Risk of bias and applicability</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostic accuracy measures</td>
<td>13</td>
<td>State the principal diagnostic accuracy measure(s) reported (e.g. sensitivity, specificity) and state the unit of assessment (e.g. per-patient, per-lesion).</td>
<td>4,5</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe methods of handling data, combining results of studies and describing variability between studies. This could include, but is not limited to: a) handling of multiple definitions of target condition, b) handling of multiple thresholds of test positivity, c) handling multiple index test readers, d) handling of indeterminate test results, e) grouping and comparing tests, f) handling of different reference standards</td>
<td>5</td>
</tr>
<tr>
<td>Section/topic</td>
<td>#</td>
<td>PRISMA-DTA Checklist Item</td>
<td>Reported on page #</td>
</tr>
<tr>
<td>------------------</td>
<td>----</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>15</td>
<td>Report the statistical methods used for meta-analyses, if performed.</td>
<td>6</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>6</td>
</tr>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study selection</td>
<td>17</td>
<td>Provide numbers of studies screened, assessed for eligibility, included in the review (and included in meta-analysis, if applicable) with reasons for exclusions at each stage, ideally with a flow diagram.</td>
<td>Data Supp.</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each included study provide citations and present key characteristics including: a) participant characteristics (presentation, prior testing), b) clinical setting, c) study design, d) target condition definition, e) index test, f) reference standard, g) sample size, h) funding sources</td>
<td>7</td>
</tr>
<tr>
<td>Risk of bias and applicability</td>
<td>19</td>
<td>Present evaluation of risk of bias and concerns regarding applicability for each study.</td>
<td>7</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For each analysis in each study (e.g. unique combination of index test, reference standard, and positivity threshold) report 2x2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest or receiver operator characteristic (ROC) plot.</td>
<td>7,8</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.</td>
<td>7,8</td>
</tr>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression; analysis of index test: failure rates, proportion of inconclusive results, adverse events).</td>
<td>8,8, Data Supp.</td>
</tr>
<tr>
<td><strong>DISCUSSION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary of evidence</td>
<td>24</td>
<td>Summarize the main findings including the strength of evidence.</td>
<td>9</td>
</tr>
<tr>
<td>Limitations</td>
<td>25</td>
<td>Discuss limitations from included studies (e.g. risk of bias and concerns regarding applicability) and from the review process (e.g. incomplete retrieval of identified research).</td>
<td>9</td>
</tr>
<tr>
<td>Conclusions</td>
<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g. the intended use and clinical role of the index test).</td>
<td>11</td>
</tr>
<tr>
<td><strong>FUNDING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funding</td>
<td>27</td>
<td>For the systematic review, describe the sources of funding and other support and the role of the funders.</td>
<td>11</td>
</tr>
</tbody>
</table>
**Data Supplement 2: PubMed search syntax and search string**

### Search syntax

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<thead>
<tr>
<th>ID</th>
<th>Search</th>
</tr>
</thead>
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<tr>
<td>#1</td>
<td>biopsy [All fields]</td>
</tr>
<tr>
<td>#2</td>
<td>biopsies [All fields]</td>
</tr>
<tr>
<td>#3</td>
<td>biops* [All fields]</td>
</tr>
<tr>
<td>#4</td>
<td>biopsy [MeSH terms]</td>
</tr>
<tr>
<td>#5</td>
<td>pathology [All fields]</td>
</tr>
<tr>
<td>#6</td>
<td>aspiration [All fields]</td>
</tr>
<tr>
<td>#7</td>
<td>OR #1-6</td>
</tr>
<tr>
<td>#8</td>
<td>prostate [All fields]</td>
</tr>
<tr>
<td>#9</td>
<td>prostate [MeSH terms]</td>
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<td>#10</td>
<td>prostatic [All fields]</td>
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<tr>
<td>#11</td>
<td>prostat* [All fields]</td>
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<tr>
<td>#12</td>
<td>OR #8-11</td>
</tr>
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<td>#13</td>
<td>&quot;micro ultrasound&quot; [All fields]</td>
</tr>
<tr>
<td>#14</td>
<td>&quot;micro US&quot; [All fields]</td>
</tr>
<tr>
<td>#15</td>
<td>mUS [All fields]</td>
</tr>
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<td>#16</td>
<td>29Mhz [All fields]</td>
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<tr>
<td>#17</td>
<td>&quot;29 Mhz&quot; [All fields]</td>
</tr>
<tr>
<td>#18</td>
<td>“29 Megahertz” [All fields]</td>
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<td>EXACTVU [All fields]</td>
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<td>#20</td>
<td>&quot;high resolution&quot;</td>
</tr>
<tr>
<td>#21</td>
<td>OR #13-20</td>
</tr>
<tr>
<td>#22</td>
<td>#7 AND #12 AND #21</td>
</tr>
</tbody>
</table>
Search string

(((((((biopsie[All Fields] OR "biopsy"[MeSH Terms]) OR "biopsy"[All Fields]) OR "biopsied"[All Fields]) OR "biopsies"[All Fields]) OR "biopsy s"[All Fields]) OR "biopsying"[All Fields]) OR "biopsys"[All Fields]) OR "pathology"[MeSH Subheading]) OR "pathology"[All Fields]) OR ((((((biopsie[All Fields] OR "biopsy"[MeSH Terms]) OR "biopsy"[All Fields]) OR "biopsied"[All Fields]) OR "biopsies"[All Fields]) OR "biopsy s"[All Fields]) OR "biopsying"[All Fields]) OR "biopsys"[All Fields]) OR "pathology"[MeSH Subheading]) OR "pathology"[All Fields]) OR "biops*"[All Fields]) OR "biopsy"[MeSH Terms]) OR ((((((((((("aspirant"[All Fields] OR "aspirants"[All Fields]) OR "aspirate"[All Fields]) OR "aspirated"[All Fields]) OR "aspirates"[All Fields]) OR "aspirating"[All Fields]) OR "aspiration"[All Fields]) OR "aspirational"[All Fields]) OR "aspirations, psychological"[MeSH Terms]) OR ("aspirations"[All Fields] AND "psychological aspirations"[All Fields])) OR "aspirations"[All Fields]) OR "aspirative"[All Fields]) OR "aspirator"[All Fields]) OR "aspirators"[All Fields]) OR "aspire"[All Fields]) OR "aspired"[All Fields]) OR "aspires"[All Fields]) OR "aspiring"[All Fields]) OR ("pathology"[MeSH Terms] OR "pathology"[All Fields]) OR "pathologies"[All Fields]) OR ("pathology"[MeSH Subheading])) AND (((((("prostat"[All Fields] OR "prostate"[MeSH Terms]) OR "prostates"[All Fields]) OR "prostatic"[All Fields]) OR "prostatism"[MeSH Terms]) OR ("prostat"[All Fields] OR "prostate"[MeSH Terms]) OR ("prostatitis"[MeSH Terms]) OR "prostatitis"[All Fields]) OR "prostate"[MeSH Terms]) OR ((((("prostat"[All Fields] OR "prostrate"[MeSH Terms]) OR "prostates"[All Fields]) OR ("pathology"[MeSH Terms]) OR "prostatitis"[All Fields]) OR "prostat*"[All Fields]) AND (((("micro ultrasound"[All Fields]) OR "micro US"[All Fields]) OR "mUS"[All Fields]) OR ("29MHz"[All Fields]) OR ("29 Mhz"[All Fields]) OR ("29"[All Fields] AND "megahertz"[All Fields])) OR "EXACTVU"[All Fields]) OR "high resolution"[All Fields])

The search strategy was developed for PubMed and modified accordingly for the other databases.
Data Supplement 3: Flow diagram of study selection process

Records identified through database search (n=1585)
- PubMed: 459
- Central: 266
- Scopus: 860

Additional records identified through Exact imaging website, clinical trial registries and conference abstracts (n=19)

Records after duplicates removed (n=1450)

Records screened (n=1450)

Records excluded from title and abstract (n=1401)

Full-text articles assessed for eligibility (n=49)

Full-text articles excluded (n=31)
- Case report (n=2)
- No mpMRI-targeted biopsy (n=13)
- Overlapping (n=16)

Studies included in qualitative synthesis (n=18)

Studies included in quantitative synthesis (n=13)

Studies excluded from meta-analysis (n=5)
- No micro-US and mpMRI outcomes reported (n=1)
- Upcoming clinical trials (n=3)
- Outcomes only on a per-lesion basis (n=1)

Data Supplement 3: Step-by-step selection process of the included studies.
Data Supplement 4: References of all excluded studies with reasons for exclusion.

Case report


No mpMRI-targeted biopsy

13. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the


Overlapping study records

15. Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR, et al. Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer


94. Eure G, Fanney D, Lin J, Wodlinger B, Ghai S. Comparison of conventional


Data Supplement 5: Risk of bias and applicability concern in included studies based on QUADAS-2

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection</th>
<th>Index test</th>
<th>Reference standard</th>
<th>Flow and timing</th>
<th>Applicability concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Abouassaly 2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2 Cornud 2020</td>
<td></td>
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<tr>
<td>3 Eure 2019</td>
<td></td>
<td></td>
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<tr>
<td>4 Klotz 2020</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5 Lopez 2019</td>
<td></td>
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<tr>
<td>6 Lugier 2020</td>
<td></td>
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<td></td>
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<tr>
<td>7 Lughezzani 2020</td>
<td></td>
<td></td>
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<tr>
<td>8 Marrel 2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 Pereira-Arias 2019</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>10 Perez 2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Rojas-Claras 2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Shore 2020</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 Socarras 2020</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Staerman 2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 Wiemer 2020</td>
<td></td>
<td></td>
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</table>

Low
Unclear
High
### Data Supplement 6: Upcoming relevant studies registered at ClinicalTrials.gov

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Status</th>
<th>Center, Country</th>
<th>Study type</th>
<th>Title</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Population</th>
<th>Estimated Competition</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04299620</td>
<td>Not yet recruiting</td>
<td>Los Angeles, USA</td>
<td>Interventional</td>
<td>Micro-US for the detection and localization of PCa tumors in patients undergoing radical prostatectomy</td>
<td>60</td>
<td>Determine if micro-US can be used to identify PCa foci with equivalent (non-inferior) performance relative to mpMRI</td>
<td>Patients undergoing prostatectomy with biopsy-proven PCa (GG ≥ 1) with maximum posterior-to-anterior prostate dimension ≤ 6 cm and mpMRI within the past 12 months</td>
<td>9/2019</td>
</tr>
<tr>
<td>NCT03762616</td>
<td>Completed</td>
<td>San Antonio, USA</td>
<td>Paired design</td>
<td>Urology San Antonio MRI/micro-US comparison</td>
<td>120</td>
<td>Detection rate of csPCa between micro-US–guided biopsy and mpMRI-targeted biopsy</td>
<td>Men (40-75 years old) with available mpMRI report (according to the PI-RADS v2 standard), presenting for prostate biopsy due to clinical suspicion of PCa</td>
<td>12/2020</td>
</tr>
<tr>
<td>NCT03938376</td>
<td>Ongoing</td>
<td>Toronto, Canada</td>
<td>Paired design</td>
<td>Comparison of micro-US targeted biopsy to mpMRI of prostate for detection of csPCa</td>
<td>100</td>
<td>Comparison of micro-US to mpMRI in detection of csPCa in biopsy naïve patients</td>
<td>Men with elevated PSA or abnormal DRE</td>
<td>9/2023</td>
</tr>
</tbody>
</table>

**Data Supplement 6: Upcoming relevant studies. csPCa: clinically significant prostate cancer, DRE: digital rectal examination, GG: grade group, mpMRI: multi-parametric magnetic resonance imaging, MRI: magnetic resonance imaging, PCa: prostate cancer, PI-RADS: prostate imaging–reporting and data system, PSA: prostate-specific antigen, US: ultrasound.**
Data Supplement 7: Sensitivity analysis including studies at low risk of bias and with low applicability concern.

### Data Supplement 7.1: Sensitivity analysis of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically significant PCa (GG ≥ 2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with both tests</th>
<th>Type of MRI-TB</th>
<th>MRI strength (Tesla)</th>
<th>Patients with clinically significant PCa</th>
<th>Detection rate (IV, random), 95% CI</th>
<th>DR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eure 2019</td>
<td>9</td>
<td>Cognitive</td>
<td>3</td>
<td>3</td>
<td>1.00 [0.27; 3.69]</td>
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<td>2.6%</td>
</tr>
<tr>
<td>Lughezzani 2020</td>
<td>320</td>
<td>Biobot robotic targeting system</td>
<td>1.5 or 3</td>
<td>116</td>
<td>0.92 [0.72; 1.19]</td>
<td></td>
<td></td>
<td>29.8%</td>
</tr>
<tr>
<td>Pereira-Arias 2019</td>
<td>79</td>
<td>Cognitive</td>
<td>1.5 or 3</td>
<td>41</td>
<td>1.43 [0.99; 2.07]</td>
<td></td>
<td></td>
<td>20.6%</td>
</tr>
<tr>
<td>Socamras 2020</td>
<td>194</td>
<td>BiopSee targeting system</td>
<td>1.5 or 3</td>
<td>81</td>
<td>0.85 [0.61; 1.19]</td>
<td></td>
<td></td>
<td>22.9%</td>
</tr>
<tr>
<td>Wiemer 2020</td>
<td>159</td>
<td>FusionVu targeting system</td>
<td>3</td>
<td>78</td>
<td>1.31 [0.95; 1.80]</td>
<td></td>
<td></td>
<td>24.1%</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> $I^2 = 43%$, $p = 0.14$</td>
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<td></td>
<td></td>
<td>106</td>
<td>1.08 [0.87; 1.35]</td>
<td></td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Detection rate of clinically significant PCa (GG ≥ 2)

Data Supplement 7.2: Sensitivity analysis of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically significant PCa (GG ≥ 3).

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with both tests</th>
<th>Type of MRI-TB</th>
<th>MRI strength (Tesla)</th>
<th>Patients with clinically significant PCa</th>
<th>Detection rate (IV, random), 95% CI</th>
<th>DR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eure 2019</td>
<td>9</td>
<td>Cognitive</td>
<td>3</td>
<td>2</td>
<td>1.00 [0.18; 5.63]</td>
<td></td>
<td></td>
<td>2.6%</td>
</tr>
<tr>
<td>Lughezzani 2020</td>
<td>320</td>
<td>Biobot robotic targeting system</td>
<td>1.5 or 3</td>
<td>62</td>
<td>1.10 [0.77; 1.57]</td>
<td></td>
<td></td>
<td>62.0%</td>
</tr>
<tr>
<td>Wiemer 2020</td>
<td>159</td>
<td>FusionVu targeting system</td>
<td>3</td>
<td>52</td>
<td>1.65 [1.03; 2.64]</td>
<td></td>
<td></td>
<td>35.4%</td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong> $I^2 = 0%$, $p = 0.39$</td>
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<td></td>
<td></td>
<td>116</td>
<td>1.27 [0.96; 1.68]</td>
<td></td>
<td></td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Detection rate of clinically significant PCa (GG ≥ 3)
### Data Supplement 7.3: Sensitivity analysis of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for clinically insignificant PCa (GG = 1).

Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with both tests</th>
<th>Type of MRI-TB</th>
<th>MRI strength (Tesla)</th>
<th>Patients with clinically insignificant PCa</th>
<th>Detection rate (IV, random), 95% CI</th>
<th>DR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eure 2019</td>
<td>9</td>
<td>Cognitive</td>
<td>3</td>
<td>4 4 4</td>
<td>1.00 [0.36; 2.81]</td>
<td>9.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lughezzani 2020</td>
<td>320</td>
<td>Biojet robotic targeting system</td>
<td>1.5 or 3</td>
<td>40 13 19</td>
<td>0.68 [0.34; 1.36]</td>
<td>22.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socarrás 2020</td>
<td>194</td>
<td>BiopSee targeting system</td>
<td>1.5 or 3</td>
<td>27 13 12</td>
<td>1.08 [0.51; 2.31]</td>
<td>18.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiener 2020</td>
<td>159</td>
<td>FusionVu targeting system</td>
<td>3</td>
<td>35 27 33</td>
<td>0.82 [0.52; 1.29]</td>
<td>49.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $p = 0.83$</td>
<td>682</td>
<td></td>
<td></td>
<td>106 57 68</td>
<td>0.84 [0.61; 1.17]</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Detection rate of clinically insignificant PCa (GG = 1)

### Data Supplement 7.4: Sensitivity analysis of the detection rate of micro-US versus mpMRI-targeted prostate biopsy for any grade of PCa.

Studies were grouped by the type of reported outcomes. CI: confidence interval, DR: detection rate, GG: grade group, IV: inverse variance, MRI-TB: magnetic resonance imaging-targeted biopsy, mpMRI: multi-parametric magnetic resonance imaging, PCa: prostate cancer, US: ultrasound.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients with both tests</th>
<th>Type of MRI-TB</th>
<th>MRI strength (Tesla)</th>
<th>Patients with prostate cancer</th>
<th>Detection rate (IV, random), 95% CI</th>
<th>DR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eure 2019</td>
<td>9</td>
<td>Cognitive</td>
<td>3</td>
<td>7 7 7</td>
<td>1.00 [0.61; 1.64]</td>
<td>7.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lughezzani 2020</td>
<td>320</td>
<td>Biojet robotic targeting system</td>
<td>1.5 or 3</td>
<td>156 97 110</td>
<td>0.88 [0.70; 1.10]</td>
<td>34.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Socarrás 2020</td>
<td>194</td>
<td>BiopSee targeting system</td>
<td>1.5 or 3</td>
<td>108 60 67</td>
<td>0.90 [0.67; 1.19]</td>
<td>21.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiener 2020</td>
<td>159</td>
<td>FusionVu targeting system</td>
<td>3</td>
<td>113 96 78</td>
<td>1.10 [0.89; 1.37]</td>
<td>37.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $p = 0.48$</td>
<td>682</td>
<td></td>
<td></td>
<td>384 250 262</td>
<td>0.97 [0.85; 1.11]</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Detection rate of PCa (GG ≥ 1)
Data Supplement 8: Publication bias assessment with funnel plot and Egger’s test.

Egger's test: p = 0.67

Data Supplement 8: Publication bias assessment with inspection of funnel plot asymmetry and Egger’s statistical test.