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Guideline 27-2 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

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An assessment conducted in January 2023 deferred the review of Guideline 27-2 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document. (PEBC Assessment & Review Protocol)

Guideline 27-2 Version 2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/281

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Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2. See Appendix 1 for a list of definitions and abbreviations.

Strength of Recommendations for This Guideline

Strength	Definition	Verb wording
Recommendation to use the diagnostic tool	The guideline Working Group* believes the benefits of the diagnostic tool in the target patients clearly outweigh the harms for nearly all patients and the group is confident to support the recommended action.	Be recommended to go for …; Should be done
Weak recommendation to use the diagnostic tool	The guideline Working Group* believes the benefits and harms of the diagnostic tool in the target patients are closely balanced or are more uncertain but still adequate to support the recommended action.	Be suggested to go for …; May/can be done; Consider doing …
No recommendation for the diagnostic tool	The guideline Working Group* is uncertain whether the benefits and harms of the diagnostic tool in the target patients are balanced and does not recommend a specific action.	There is no recommendation for or against …
Weak recommendation NOT to use the diagnostic tool	The guideline Working Group* believes the benefits and harms of the diagnostic tool in the target patients are closely balanced or are more uncertain but still adequate to support the recommended action.	Be suggested against …; May/cannot be done; Do not consider doing …
Recommendation NOT to use the diagnostic tool	The guideline Working Group* believes the harms of the diagnostic tool in the target patients clearly outweigh the benefits for nearly all patients and the group is confident to support the recommended action.	Be recommended to against …; Should not be done
	The factors considered in the above judgments include desirable and undesirable effects of the diagnostic tool, the certainty of evidence, patient preference, health equity, acceptability, feasibility, and generalizability in Ontario.	

*The guideline Working Group includes two radiologists, one radiation oncologist, two urologists and one guideline methodologist.

GUIDELINE OBJECTIVES

To make recommendations with respect to:

1. a) The use of multiparametric magnetic resonance imaging (MPMRI) in patients with an elevated risk of clinically significant prostate cancer (CSPCa) who are biopsy naïve,
   b) The use of MPMRI-targeted biopsy plus transrectal ultrasound systematic biopsy (TRUS-SB) or MPMRI-TB alone for biopsy-naïve patients who have undergone MPMRI;

2. a) The use of MPMRI in patients with an elevated risk of CSPCa who have had a prior negative TRUS-SB for any prostate cancer,
   b) The use of MPMRI-TB plus TRUS-SB or MPMRI-TB alone for patients who have had a prior negative TRUS-SB defined as no prostate cancer on biopsy of any grade group;

3. The minimum acceptable standards in the acquisition, interpretation and reporting of MPMRI and the minimal acceptable standards for performance of MPMRI-TB.

TARGET POPULATION

Patients with an elevated risk of CSPCa (defined as International Society of Urologic Pathology [ISUP] Grade Group [GG] ≥2), as estimated by available clinical information and tools such as risk calculators and nomograms, of who are A) biopsy naïve or B) have had a prior negative TRUS-SB defined as no prostate cancer on biopsy of any grade group.

INTENDED USERS

Radiologists, oncologists, urologists, and other clinicians who provide care for patients defined by the target population.

RECOMMENDATIONS

Recommendation 1 (Recommendation to use the diagnostic tool)

For biopsy-naïve patients at elevated risk of CSPCa:
• MPMRI is recommended prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer.
  • If the MPMRI is positive, MPMRI-TB and TRUS-SB should be performed together to maximize detection of CSPCa.
  • If the MPMRI is negative, consider forgoing any biopsy after discussion of the risks and benefits with the patient as part of shared decision making and ongoing follow-up.

Qualifying Statements for Recommendation 1
• Between 8% and 24% of patients with CSPCa may be missed by a negative MPMRI. For this reason, patients should be made aware of the risks and benefits of biopsy avoidance when MPMRI is negative. • MPMRI should only be performed if there is availability of high-quality MPMRI interpretation and operators with experience performing targeted biopsies (see Recommendation 3). • Due to the limited availability, MPMRI is recommended only for patients where there is intent of curative management should the biopsy be positive for CSPCa.

Recommendation 2 (Recommendation to use the diagnostic tool)
In patients who had a prior negative TRUS-SB and demonstrate a high risk of having CSPCa in whom curative management is being considered: • MPMRI should be performed,

- If the MPMRI is positive, targeted biopsy should be performed. Concomitant TRUS-SB can be considered depending on the patients risk profile and time since prior TRUS-SB biopsy,
- If the MPMRI is negative, consider forgoing a TRUS-SB only after discussion of the risks and benefits with the patient as part of shared decision making and ongoing follow-up.

Qualifying Statements for Recommendation 2

- Prior negative TRUS-SB is defined as no cancer of any grade group on prior biopsy.
- MPMRI should only be performed if there is availability of high-quality MPMRI interpretation and operators with experience performing targeted biopsies (see Recommendation 3).
- Due to the limited availability, MPMRI is recommended only for patients where there is intent of curative treatment in the case of a positive biopsy.

Recommendation 3 (Recommendation to use the diagnostic tool)

- MPMRI should be performed and interpreted in compliance with the current Prostate Imaging Reporting and Data System (PI-RADS) Guidelines (v2.1 as of Summer 2020; see https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/PI-RADS).
- MPMRI-TB is recommended for MRI lesions with a PI-RADS score of 4 or 5.
- MPMRI-TB or follow-up is recommended for MRI lesions with a PI-RADS score of 3 depending on the patient's risk profile.
- Biopsy avoidance should be considered when maximum PI-RADS score is 1 or 2 (see Recommendation 1 and 2).
- A structured MPMRI reporting template as recommended by the PI-RADS committee should be used (see https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/PI-RADS).
- When a targeted biopsy is being performed a minimum of two cores should be taken per target with recommendation of four cores for the index lesion. If multiple lesions are described on MPMRI, the biopsy operator may distribute the number of biopsies to keep a reasonable overall core count during the biopsy session.
- MPMRI interpretation and MPMRI-TB should be performed by experienced operators.
- A provincial quality assurance program should be developed. Until this is in place, practitioners should have some form of local quality assurance in place.

Qualifying Statements for Recommendation 3

- Cognitive fusion, TRUS-MRI software-based fusion, and in-bore MPMRI guided biopsy are all acceptable methods of MPMRI-TB. TRUS-MRI fusion and in-bore MRI biopsy may improve target yield in selected patients.
- The use of bi-parametric MRI (BPMRI), meaning omitting the dynamic contrast-enhanced MRI (DCEMRI) may be considered in centres with experienced readers that can demonstrate performance similar to MPMRI.

Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations with respect to:

- a) The use of MPMRI in patients with an elevated risk of CSPCa who are biopsy naïve,
  b) The use of MPMRI-TB plus TRUS-SB or MPMRI-TB alone for biopsy-naïve patients who have undergone MPMRI;

- a) The use of MPMRI in patients with an elevated risk of CSPCa who have had a prior negative TRUS-SB defined as no prostate cancer on biopsy of any grade group,
  b) The use of MPMRI-TB plus TRUS-SB or MPMRI-TB alone for patients who have had a prior negative TRUS-SB defined as no prostate cancer on biopsy of any grade group;

- The minimum acceptable standards in the acquisition, interpretation and reporting of MPMRI and the minimal acceptable standards for performance of MPMRI-TB.

TARGET POPULATIONS

Patients with an elevated risk of CSPCa (defined as ISUP GG ≥2), as estimated by available clinical information and tools such as risk calculators and nomograms, of who are A) biopsy naïve or B) have had a prior negative TRUS-SB defined as no prostate cancer on biopsy of any grade group.

INTENDED USERS

Radiologists, oncologists, urologists, and other clinicians who provide care for patients defined by the target population.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1 (Recommendation to use the diagnostic tool)

For biopsy-naïve patients at elevated risk of CSPCa:
• MPMRI is recommended prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer.
  • <u>If the MPMRI is positive,</u> MPMRI-TB and TRUS-SB should be performed together to maximize detection of CSPCa.
  • <u>If the MPMRI is negative,</u> consider forgoing any biopsy after discussion of the risks and benefits with the patient as part of shared decision making and ongoing follow-up.

Qualifying Statements for Recommendation 1
• Between 8% and 24% of patients with CSPCa may be missed by a negative MPMRI. For this reason, patients should be made aware of the risks and benefits of biopsy avoidance when MPMRI is negative. • MPMRI should only be performed if there is availability of high-quality MPMRI interpretation and operators with experience performing targeted biopsies (see Recommendation 3). • Due to the limited availability, MPMRI is recommended only for patients where there is intent of curative management should the biopsy be positive for CSPCa.

Key Evidence for Recommendation 1

Twenty-three trials (all full-text publications) compared MPMRI with a reference standard (n=5, all cohort studies) or with TRUS-SB (n=18 – 2 randomized controlled trials [RCTs] and 16 cohort studies) for biopsy-naïve men. The certainty of the aggregate study evidence for each comparison showed 14 of the 21 cohort studies to be at either low [1-3] or moderate [4-14] risk of bias based on a GRADE approach [15]. One [16] of the RCTs was assessed to be at low risks of bias and the other was assessed at being at unclear risk [17] (see Appendix 5).

- In the five studies [3-5,18,19] where template transperineal mapping biopsy (TTMB) was the reference standard, MPMRI ranges were sensitivity 87–96%, specificity 29-45%, positive predictive values (PPVs) 46%-65%, and negative predictive values (NPVs) 76-92% (Table 4-2). Of these five studies, PROMIS [3] was a prospective multicentre trial (MCT). In this study, it was estimated unnecessary biopsies could be reduced by up to 27%. MPMRI was more sensitive (88% vs. 48% [95% confidence interval (CI), 43 to 54]; p<0.0001), but less specific (45% vs. 99% [95% CI, 97 to 100]; p<0.0001) than TRUS-SB in this study [3].
- Two RCTs [16,17] compared CSPCa detection rates of MPMRI-TB versus TRUS-SB. Estimates for CSPCa when combining the two RCTs showed increased detection favouring MPMRI by 18% (95% CI, 5% to 32%, p=0.009; Figure 1.1). Estimates for the two RCTs combined for clinically insignificant prostate cancer (CISPCa) showed decreased detection favouring MPMRI by 9% (95% CI,-17% to 1%, p=0.03; Figure 1.2).
- In total, 16 cohort studies [1,2,6-14,20-24] and the two RCTs mentioned above presented detection rates comparing MPMRI-TB to TRUS-SB. Estimates for CSPCa showed increased detection favouring MPMRI-TB by 3% (95% CI, 0% to 7%, p=0.03; Figure 1.1). For CISPCa, the estimate showed decreased detection favouring MPMRI by 8% (95% CI,-11% to 5%, p<0.00001; Figure 1.2).
- Of the above cohort studies examining MPMRI-TB versus TRUS-SB, two [1,2] were prospective MCTs. A paired diagnostic study (MRI-FIRST) [1] enrolled 251 patients. Patients received both TRUS-SB and MPMRI-TB. There were no significant differences in the detection of CSPCa in MPMRI-TB versus TRUS-SB (32% vs. 30%, p=0.225). However, MPMRI-TB detected significantly less CISPCa than TRUS-SB (6% vs. 20%, p<0.0001). Five percent of CSPCa was detected by TRUS-SB that was missed by MPMRI-TB and 8% was detected by MPRI-TB and missed by TRUS-SB. Thus, detection of CSPCa was improved by combining TRUS-SB and MPMRI-TB [1]. Another prospective MCT enrolled 646 men to receive MPMRI followed by TRUS-SB and in-bore MPRI-TB [2]. This study showed similar CSPCa detection rates (25% vs. 23%, p=0.392); however, CISPCa was detected in significantly fewer patients by MPMRI-TB than in TRUS-SB (14% vs. 25%, p<0.0001). MPMRI-TB enabled biopsy avoidance in 49% of patients while missing only 35 cases with CSPCa. Meanwhile, TRUS-SB would have over-detected CISPCa in 20% of patients [2].
- Overall estimates for the studies [1,2,7-11,13,14,22-25] comparing MPMRI-TB plus TRUS-SB to targeted biopsy alone showed 6% increased CSPCa detection when combining the systematic and targeted biopsy (95% CI, 4% to 8%, p<0.00001; Figure 2.1) and 8% increased detection of CISPCa (95% CI, 6% to 10%, p<0.00001; Figure 2.2).

Justification for Recommendation 1

- The issue of how targeted biopsy alone should be interpreted in overall whole gland Gleason scoring has not been resolved in the care community. Targeted biopsy plus systematic biopsy is believed to be necessary if MPMRI is positive in biopsy-naïve patients as multifocality and positive biopsy in other regions not seen by MPMRI is important in clinical decision making and treatment planning given the use of focal dose escalation therapies. In addition, the risk of severe complications such as hospital admission for

urosepsis does not increase when changing from targeted biopsy to targeted biopsy plus systematic biospy, although the risk of less severe complications does increase.
- Multiple MCTs have shown a decrease in CISPCa detection rate without reduction in CSPCa detection rate when using MPMRI-TB, compared with TRUS-SB.
- The principal value of MPMRI in biopsy-naïve patients is biopsy avoidance with up to a 49% reduction in biopsies [2] if MPMRI-negative patients are not biopsied.
- Although MPMRI may miss between 8% to 24% [3,19] of CSPCa in individual patients, these MPMRI-negative patients can be surveilled clinically, while avoiding the disadvantages of TRUS-SB, such as over-diagnosis of CISPCa and complications including urosepsis, urinary retention, hematuria and rectal bleeding. The patients that gain the most in the biopsy-naïve group are the MPMRI-negative patients. The primary goal is safe avoidance of CISPCa detection (over-detection) in this cohort. If no biopsy is performed, it is essential that the patient and urologist commit to ongoing follow-up given the risk of under-detection of CSPCa by MPMRI.
- MPMRI-TB combined with TRUS-SB in MRI-positive patients still allows for overall reduction in TRUS-SB in those patients who are MPMRI negative with only a slight increase in CISPCa detection (8%) while increasing CSPCa detection by 5%.

Recommendation 2 (Recommendation to use the diagnostic tool)

In patients who had a prior negative TRUS-SB and demonstrate a high risk of having CSPCa in whom curative management is being considered:
- MPMRI should be performed,
- If the MPMRI is positive, targeted biopsy should be performed. Concomitant TRUS-SB can be considered depending on the patients risk profile and time since prior TRUS-SB biopsy,
- If the MPMRI is negative, consider forgoing a TRUS-SB only after discussion of the risks and benefits with the patient as part of shared decision making and ongoing follow-up.

Qualifying Statements for Recommendation 2

- Prior negative TRUS-SB is defined as no cancer of any grade group on prior biopsy
- MPMRI should only be performed if there is availability of high-quality MPMRI interpretation and operators with experience performing targeted biopsies (see Recommendation 3).
- Due to the limited availability, MPMRI is recommended only for patients where there is intent of curative treatment in the case of a positive biopsy.

Key Evidence for Recommendation 2

Twenty-two trials (all full-text publications) compared MPMRI with a reference standard (n=7) or with TRUS-SB (n=15) for previously negative men. The certainty of the aggregate study evidence for each comparison showed 15 of the 22 studies to be at either low [26-29], moderate [5,6,8,11,12,30], or unclear [18,31-34] risk of bias based on a GRADE approach [15] (see Appendix 5).
- Seven studies reported on the diagnostic accuracy of MPMRI for previously negative patients [4,5,26,31-34] with sensitivities of 78%-100%, specificities of 30%-100%, PPVs of 36%-100%, and NPVs of 69%-100% (Table 4-5).
- The overall improvement in CSPCa detection rate for the 15 studies comparing MPMRI-TB alone to TRUS-SB was 5% (95% CI, 3% to 7%, p<0.0001; Figure 4.1) with a reduction of CISPCa detection of 7% (95% CI, 4% to 9%, p<0.00001; Figure 4.2).
- The overall improvement in CSPCa detection for the five cohort studies comparing MPMRI-TB plus TRUS-SB to MPRMRI-TB alone was 5% (95% CI, 2% to 8%, p=0.0005; Figure 5.1).

- The overall improvement across studies in CSPCa detection for MPMRI-TB plus TRUS-SB compared with TRUS-SB alone was 11% (95% CI, 8% to 14%, p<0.00001; Figure 6.1).

Justification for Recommendation 2

- All the eligible studies show MPMRI-TB detected a higher number of CSPCa when compared with TRUS-SB.

Recommendation 3 (Recommendation to use the diagnostic tool)

- MPMRI should be performed and interpreted in compliance with the current PI-RADS Guidelines (v2.1 as of Summer 2020; see https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/PI-RADS).
- MPMRI-TB is recommended for MRI lesions with a PI-RADS score of 4 or 5.
- MPMRI-TB or follow-up is recommended for MRI lesions with a PI-RADS score of 3 depending on the patient's risk profile.
- Biopsy avoidance should be considered when maximum PI-RADS score is 1 or 2 (see Recommendation 1 and 2).
- A structured MPMRI reporting template as recommended by the PI-RADS committee should be used (see https://www.acr.org/Clinical-Resources/Reporting-and-Data-Systems/PI-RADS).
- When a targeted biopsy is being performed a minimum of two cores should be taken per target with recommendation of four cores for the index lesion. If multiple lesions are described on MPMRI, the biopsy operator may distribute the number of biopsies to keep a reasonable overall core count during the biopsy session.
- MPMRI interpretation and MPMRI-TB should be performed by experienced operators.
- A provincial quality assurance program should be developed. Until this is in place, practitioners should have some form of local quality assurance in place.

Qualifying Statements for Recommendation 3

- Cognitive fusion, TRUS-MRI software-based fusion, and in-bore MPMRI-guided biopsy are all acceptable methods of MPMRI-TB. TRUS-MRI fusion and in-bore MRI biopsy may improve target yield in selected patients.
- The use of BPMRI, meaning omitting the DCEMRI may be considered in centres with experienced readers that can demonstrate performance similar to MPMRI.

Key Evidence for Recommendation 3

- **This recommendation is based on expert opinion and review of the PI-RADS committee guidelines as well as the Standard Operating Procedure of the American Urological Association (AUA)** https://www.auanet.org/guidelines/mri-of-the-prostate-sop.
- Four cores per lesion have been performed in recent MCTs evaluating MPMRI but if one combines systematic biopsy and four cores/lesion in a patient with multiple MPMRI lesions the core count will be unreasonable. Prior single-centre studies have shown small incremental and diminishing increases in target biopsy yield as core count increases [35-37]. For this reason, the operator is given discretion in the choice of number of cores per target for non-index lesions or when multiple lesions are present.
- MPMRI diagnostic performance varies by reader experience as does MPMRI-TB performance [38].

Justification for Recommendation 3

- All of the published studies demonstrating the performance of MPMRI involved diagnostic radiologists and biopsy operators with training and experience in performing MPMRI and MPMRI-TB. They all used defined five-point scoring schemes and, more recently, have used the PI-RADS v2 scoring scheme. To ensure similar performance in clinical practice,

radiologists interpreting MPMRI and practitioners performing MPMRI-TB should have experience and demonstrate consistent performance levels.

IMPLEMENTATION CONSIDERATIONS

Before MPMRI is used in clinical practice, physicians should be familiar with current PI-RADS prostate MRI protocol and reporting standards [39]. The patient care pathway in Ontario and the incorporation of MPMRI will need ongoing evaluation for impact on patient care and outcomes.

The value of MPMRI cannot be realized without attention to quality assurance. Studies have demonstrated only moderate agreement in PI-RADS scoring among readers [40,41] and a wide confidence interval for the PPV of PI-RADS score ≥3 (35% [95% CI, 27% to 43%]) [42]. There is currently no quality assurance program in place for MPMRI in Ontario. Quality standards or development of a quality assurance program should be in place before wide-scale adoption of these recommendations occurs outside of centres with established expertise. Since prostate MPMRI and MPMRI-TB involve new technologies, skills, and education, knowledge transfer to practitioners across the province should also be considered as part of implementation. Defining a quality assurance program is beyond the scope of this document. In developing a local or provincial quality assurance program metrics to consider collecting include: target yield (defined as the number of CSPCa detected per lesion biopsied) stratified by PI-RADS score and the number of false negative MPMRI (i.e., instances where MPMRI is reported as negative and a CSPCa is diagnosed at TRUS-SB or prostatectomy). Changes may be required in biopsy collection and reporting where all targeted biopsy specimens are labeled and placed in a separate vial that is labelled with target number and location.

Although cost-effectiveness and resource allocation issues are beyond the scope of this Program in Evidence-Based Care (PEBC) guideline, the Working Group (see Appendix 2) was sensitive to the fact that there are limited MRI resources in Ontario. Further study into the resource implications of the implementation of these guidelines is required especially in the biopsy-naïve population addressed in Recommendation 1. The lack of ready access to computer-aided fusion biopsy systems may require the use of cognitive fusion biopsy in many centres which will require additional operator training. Cost savings from biopsy deferral in selected men choosing to forego TRUS-SB with negative MPMRI through shared decision making could be considerable. Further cost savings may be realized through judicious use of BPMRI (see below).

RISK ASSESSMENT AND PATIENT PERFERENCE

Patient preference and risk tolerance are important considerations. Clinicians together with patients should decide whether follow-up without biopsy after negative MPMRI, or in the case of positive MRI, MPMRI-TB or MPMRI-TB combined with TRUS-SB should be performed. Patients should be informed of the possibility of false-negative and false-positive results with MPMRI and the potential complications of prostate biopsy. A safety net with regular follow-up in those patients with negative MRI and an elevated risk profile should be part of the care plan.

MRI PROTOCOLS and BPMRI

MRI protocols should conform to the minimum technical requirements described in PI-RADS v2.1. Meticulous attention to technical parameters of prostate MPMPI is required as adherence to PI-RADS technical specifications varies [43-45]. A 2019 quality assurance project in Eastern Ontario demonstrated that consultation with experienced centres could improve adherence to PI-RADS technical specifications [45] .

The use of BPMRI, meaning omitting the DCEMRI, from MPMRI remains a controversial subject. This is being considered as an alternative to MPMRI principally due to resource issues. By omitting DCEMRI, considerable savings in contrast agent cost and MRI time can be achieved.

This is highly relevant in the context of the expected increase in volume of prostate MRI with major implication on provincial MRI capacity, once MPMRI becomes the anticipated standard of care in biopsy-naïve patients. There are both single-centre studies and meta-analysis data showing noninferiority of BPMRI [46-49] to MPMRI; however, concern remains regarding the retrospective nature of these studies and the potential increase in indeterminate (PIRADS-3) interpretations using only BPMRI. Prospective MCT or trials comparing impact on decision making and outcomes between BPMRI and MPMRI are lacking. For this reason, MPMRI is still recommended as the standard of care; however, given anticipated resource pressures BPMRI can be performed at the discretion of the radiologist in centres that have demonstrated local BPMRI performance similar to MPMRI

For BPMRI, technical considerations are primarily related to the quality of diffusion weighted imaging. DCEMRI helps make up for deficiencies in poor quality diffusion weighted imaging that can occur, for example, in obese patients, in the presence of rectal gas, and in patients with hip prosthesis. If a radiologist or MRI technologist notes these issues with a BPMRI, MPMRI or call back for MPMRI should be considered.

It is expected that additional compelling evidence on the trade-offs in diagnostic performance between MPMRI and BPMRI, its relationship to cost, safety, decision making, and outcomes will alter practice in the future. As the cost implications of implementing MPMRI in Ontario for biopsy-naïve patients may be prohibitive, the Working Group members recognized that BPMRI may ease the financial burdens of performing MRI in this population and is a viable alternative to MPMRI in this population if carefully monitored.

GUIDELINE LIMITATIONS

The Working Group for this guideline did not include patient representatives. However, input from patient representatives was received during the project planning stage of the study and following recommendation development. A systematic review for this information was not performed. Working Group members used their prior clinical experiences involving men with increased risk for prostate cancer, along with patient representative comments, to guide the relevant values and preferences.

Further evidence will be required to define the role of MPMRI more precisely in the decision to perform prostate biopsy in biopsy-naïve men. Given the adoption of MPMRI in many health care systems, this guideline relies on expert opinion in several areas where evidence is lacking.

Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The PEBC is an initiative of the Ontario provincial cancer system, (OH [CCO]). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

The current PEBC (2015) guideline entitled "Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer" is outdated and no longer in keeping with the way in which this health state is currently being managed in other jurisdictions for biopsy-naïve men. There is contemporary, high-quality evidence addressing the utility of MRI in this setting.

GUIDELINE DEVELOPERS

This guideline was developed by the MPMRI in the Diagnosis of Clinically Significant Prostate Cancer GDG (Appendix 2), which was convened at the request of the Cancer Imaging Program (CIP) - in collaboration with Disease Pathway Map (DPM) and the Genitourinary Cancer disease site group (DSG).

The project was led by a small Working Group of the MPMRI in the Diagnosis of Clinically Significant Prostate Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in diagnostic imaging (MH, NS), radiation oncology (AL), urology (JC, NP), and health research methodology (JB). Other members of the MPMRI in the Diagnosis of Clinically Significant Prostate Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [50,51]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft

recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [52] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Articles were eligible for inclusion in the systematic review if they met the study selection criteria. The following sources were searched for guidelines with the search term(s) prostate cancer, prostate carcinoma, clinically significant, clinically insignificant, magnetic resonance (see Appendix 3 for detailed literature search): National Guideline Clearinghouse, National Health and Medical Research Council, New Zealand Guidelines Group, American Society of Clinical Oncology (ASCO), National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), MEDLINE (2013 through September 1, 2020), EMBASE (2013 through September 1, 2020), the Cochrane Central Register of Controlled Trials (OVID CCTR: September 2020), and the Database of Abstracts of Reviews of Effects (OVID DARE: 3rd quarter 2020). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO: 2013 to 2020), the American Society of Therapeutic Radiology and Oncology (2013 to 2020), the American Urological Association (AUA: 2013-2020), the Canadian Urological Association (CAU: 2013-2020), American College of Radiology (ACR: 2013-2020), European Society of Urogenital Radiotherapy (ESUR: 2013 to 2020) and the European Society for Radiotherapy and Oncology (ESTRO: 2013 to 2020) were searched for relevant abstracts.

Assessment of Guideline(s)

There were no guidelines identified through the searches that met the inclusion criteria. A recent NICE guideline was excluded because it did not include the comparisons of interest. https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/prostate-cancer.

PATIENT- AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Two patients participated as Consultation Group members for the MPMRI in the Diagnosis of Clinically Significant Prostate Cancer Working Group. They reviewed copies of the project plan/draft recommendations and provided feedback on their comprehensibility, appropriateness and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

Implementation of guidelines developed by the PEBC may be undertaken by Cancer CIP- in collaboration with DPM and the DSG.

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Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

Section 4: Systematic Review

INTRODUCTION

Prostate cancer is the most common cancer among Canadian men, excluding non-melanoma skin cancers, and is the third leading cause of death in Canadian male cancer patients [53]. It is estimated that on average, 11 Canadian men will die from prostate cancer every day in 2019 [53]. Given these statistics, early and accurate diagnosis for CSPCa in patients with an elevated risk is essential to determine optimal diagnostic and treatment options, thereby improving quality of life and/or survival outcomes.

There is variability in the definition for CSPCa; however, there is growing consensus that CSPCa is defined as any Gleason score (GS) ≥3+4 (International Society of Urologic Pathologists GG ≥2). The current standard for diagnosing CSPCa is TRUS-SB of 10 to 12 cores [54]. This is typically done after an assessment of clinical risk based on multiple parameters including the serum prostate specific antigen (PSA). Because TRUS-SB systematically samples areas from the prostate and not a specific imaged target, this approach has been shown to lead to over-detection of CISPCa [55] and can miss CSPCa [56]. Saturation biopsy techniques such as TTMB are more sensitive than TRUS-SB in detecting CSPCa [57]; however, this is too resource intensive and invasive a technique to be applied as a diagnostic tool in the early evaluation pathway of prostate cancer.

Over the past several years, there has been growing utilization of MPMRI as a non-invasive tool to help diagnose and localize CSPCa. When an MPMRI is performed, different tissue properties can be highlighted by manipulating the way the image is obtained. T2-weighted imaging, diffusion weighted imaging, and DCEMRI are performed and imaging features from these data sets are combined to determine the location of a cancer as part of the MPMRI examination. MPMRI followed by targeted biopsy (MPMRI-TB) means biopsy is performed directly at cancer-suspicious foci detected with MPMRI.

This is an update of a previous PEBC document https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/summary/pebc27-2s_1.pdf. In the previous 2015 guideline, we recommended "MPMRI followed by targeted biopsy (biopsy directed at cancer-suspicious foci detected with MPMRI) should not be considered the standard of care in biopsy naïve patients with an elevated risk of CSPCa" and "MPMRI followed by targeted biopsy may be considered to help in detecting more CSPCa patients compared with repeated TRUS-guided systematic biopsy in patients who had a prior negative TRUS-guided systematic biopsy and demonstrate a growing risk of having CSPCa". Recently, there have been several RCTs and MCTs regarding MPMRI in reducing CISPCa detection rates particularly in biopsy-naïve men without loss of sensitivity for CSPCa. There is a growing acceptance of MPMRI utilization internationally [6,7,16,17,25,27,58]. Thus, there is a need for reconsidering the previous recommendations with respect to the use of MPMRI in the diagnosis of CSPCa in men who have had a previously negative TRUS-SB. In addition, there is a lack of specific guidance in Ontario on performing and interpreting MPRMI or performing targeted biopsy. Thus, the Working Group (the guideline authors, including two radiologists, one radiation oncologist, two urologists, and one methodologist) of the MRI in Prostate Cancer GDG in association with the PEBC of OH (CCO) conducted a systematic review to summarize the relevant studies from the medical literature to develop a clinical guideline for Ontario. Based on the objectives of the guideline, the Working Group derived the research questions outlined below. The scope of these

recommendations does not include the use of MRI in active surveillance. The systematic review has been registered at the international prospective register of systematic reviews (www.crd.york.ac.uk/prospero) as CRD42020142786.

RESEARCH QUESTIONS

Q1a. For biopsy-naïve patients at elevated risk (according to PSA levels and/or nomograms), how accurately does MPMRI or MPMRI followed by targeted biopsy diagnose CSPCa (GG ≥2), compared with the reference standard?

Q1b. For biopsy-naïve patients at elevated risk, does MPMRI followed by targeted biopsy increase the detection rate of CSPCa (GG ≥2) and reduce the detection rate of CISPCa positively change patient management, or improve patient outcomes (including side effects and survival outcomes), compared with TRUS-SB (of at least eight cores)?

Q1c. For biopsy-naïve patients at elevated risk, does MPMRI followed by targeted and systematic biopsies improve the detection rate of CSPCa and reduce the detection rate of CISPCa, positively change patient management, or improve patient outcomes (including side effects and survival outcomes), compared with TRUS-SB alone (of at least eight cores) or targeted biopsy alone?

Q2a. For patients with prior negative TRUS-guided biopsy at elevated risk, how accurately does MPMRI or MPMRI followed by targeted biopsy diagnose CSPCa, compared with the reference standard?

Q2b. For patients with prior negative TRUS-SB at elevated risk, does MPMRI followed by targeted biopsy increase the detection rate of CSPCa and reduce the detection rate of CISPCa, positively change patient management, or improve patient outcomes (including survival outcomes and adverse events), compared with TRUS-SB (of at least eight cores)?

Q2c. For patients with prior negative TRUS-SB at elevated risk, does MPMRI followed by targeted and systematic biopsies improve the detection rate of CSPCa and reduce the detection rate of CISPCa, positively change patient management, or improve patient outcomes (including side effects and survival outcomes), compared with TRUS-SB alone (of at least eight cores) or targeted biopsy alone?

Q3a. What are the minimum acceptable standards to perform and report MPMRI for patients with an elevated risk of CSPCa who have been decided to undergo MPMRI examination?

Q3b. What are the minimum acceptable standards for performance of image-guided targeted biopsy for patients with an elevated risk of CSPCa who have been decided to undergo MPMRI targeted biopsy?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Systematic Reviews

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing systematic reviews published since 2016. Relevant articles were identified by searches of MEDLINE (2016 – September 2020 week 36), EMBASE (2016 – 2020 week 36), and the Cochrane Library (2020). The reference lists of eligible trials were searched for relevant articles. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 3.

Systematic reviews were included if they included eligible primary studies as listed below (Study Selection Criteria and Process). If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per research question was selected by one of the authors (JB) based on its age, quality, and the best match with our study selection criteria stated below.

Search for Primary Literature

Since no recent systematic reviews were found, the primary literature was searched using MEDLINE (May 2013 through September 1, 2020), EMBASE (May 2013 through September 1, 2020), the Cochrane Central Register of Controlled Trials (OVID CCTR: September 2020), and the Database of Abstracts of Reviews of Effects (OVID DARE: 3rd quarter 2020). In addition, the proceedings of the meetings of the ASCO (2013 to 2020), the American Society of Therapeutic Radiology and Oncology (2013 to 2020), the American Urological Association (AUA: 2013 -2020), the Canadian Urological Association (CAU: 2016-2020), American College of Radiology (ACR: 2013-2019), European Society of Urogenital Radiotherapy (ESUR: 2013 to 2020) and the European Society for Radiotherapy and Oncology (ESTRO: 2013 to 2020 were searched for relevant abstracts. The literature search of the electronic databases combined disease-specific terms (prostate cancer, prostate carcinoma, etc.) and treatment-specific terms (magnetic resonance, etc.) for all study designs (Appendix 3).

Study Selection Criteria and Process

Articles were eligible for inclusion in the systematic review if they met the following criteria:

- They were full text, or abstracts that were RCTs, or observational comparative studies ≥100 patients,
- They included men with an elevated risk of CSPCa (according to PSA levels and/or nomograms) who have had a prior negative TRUS-SB or were biopsy-naive,
- They used a reference standard (Q1a and Q2a) that is post-operational pathological report, TTMB/saturation biopsy (≥20 cores) for MPMRI-positive patients or MPMRI followed by targeted biopsy-positive patients, or clinical follow-up for negative results,
- For questions 1a, 2a, they report on outcomes that include accuracy of diagnosis for CSPCa (i.e., sensitivity, specificity, predictive value, etc.),
- For questions 1b, 1c, 2b, 2c, they compare increasing detection rate for CSPCa and reduction detection rates of CISPCa in patient who undergo and do not undergo MPMRI,
- They report a CSPCa definition that includes a threshold of GS ≥3+4 (GG ≥2).

Studies were excluded if they:

- Were studies or abstracts published in a language other than English,
- Were published in the form of letters, editorials, commentaries, or non-systematic review or non-meta-analysis,
- Included patients with diagnosis of prostate cancer at baseline,
- Included reference standard that was MPMRI followed by targeted biopsy or MPMRI plus TRUS-SB.

Data Extraction, Assessment of Risk of Bias, Study Quality and Certainty of the Evidence

All relevant papers identified by the literature search were assessed against the above selection criteria independently by one of the authors (JB) (see Appendix 2 for a list of authors of this report). Uncertainty regarding eligibility was resolved by consensus of all the authors.

The QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) [59] was used to assess study quality in four key domains: patient selection, index test(s), reference standard, and flow and timing. The signalling questions in each domain are rated in terms of risk of bias (low, high, unclear) and concerns regarding applicability (low, high, unclear), with associated signalling questions to help with bias and applicability judgments.

The RCTs were assessed using Cochrane's Risk of Bias tool [60] using the following six domains of bias: random sequence generation, allocation concealment, blinding participants, personnel and outcome assessment, incomplete outcome data, selective reporting, and other concerns. Each domain was judged as being at low, high, or an unclear risk of bias.

The risk of bias for cohort studies was assessed using a modified ROBINS-I tool [61] using the following seven domains of bias: confounding, selection of participants, measures of intervention and outcomes, departure from intervention, incomplete outcome data, selective reporting, and other concerns. The judgment of each domain includes three categories: a low, high, or unclear risk of bias.

Synthesizing the Evidence

If there is no clinical heterogeneity for patient characteristics, MPMRI techniques, etc., for detection rates from two or more studies, meta-analyses were planned assuming a two-sided significance level of $\alpha = 0.05$ and to be performed with the software RevMan 5.3.1 [62]. To keep consistent, all the outcomes in the Tables were calculated by using the same software (RevMan 5.3.1). Outcomes that include accuracy of diagnosis for CSPCa are reported (i.e., sensitivity, specificity, PPV and NPV) in Table format. Results from the previous version of this report are presented (Appendix 7). Subgroup analysis by MPMRI-TB techniques (software, cognitive, in-bore, etc.) used were assessed (Appendix 8).

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed by using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [15].

RESULTS

Literature Search Results

No systematic reviews or guidelines met the inclusion criteria.

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram summarizing this information is provided in Appendix 4.

Articles were retrieved from the MEDLINE (n=2999) and EMBASE (n=6000) databases, and additional records were identified through other sources (Cochrane, conference abstracts, hand-searching of reference lists of included studies n=215). After duplicates were removed from the combined search results, 3754 articles were assessed by title and abstract for possible inclusion in the evidence summary. Of these, 3555 articles were rejected at the title level and the remaining 199 were assessed at the level of full text.

Thirty six studies from 39 publications [1-14,16-34,58,63-67] were included to answer questions 1 and 2, with the most recent publication used where multiple reports existed. Given that there were very few studies fulfilling the inclusion criteria for Q3a and Q3b, recommendations for these questions were based on expert opinion.

Study Characteristics

Table 4-1 shows the characteristics of the studies. Of the 36 studies, 14 had populations that were biopsy naïve (Q1) [1-4,7,9,10,13,14,16,17,19,25,64], 11 had populations that had at least one previously negative systematic biopsy (Q2) [26-28,30-34,58,65,66], and the remaining 11 examined both biopsy-naïve and repeat biopsy populations (and reported on them separately) [5,6,8,11,12,18,20-24]. Seven of the studies were RCTs [6,7,16,17,25,27,58] and the remaining were cohort studies (9 retrospective, 20 prospective). The non-randomized intervention arms of four of the RCTs were of interest for questions Q1 and Q2 [6,7,25,27] and were treated as cohort studies for portions of these questions. Although one of the studies was considered an RCT [6], the only population of interest for questions 1 and 2 was from a side-study of non-randomized patients and thus is only considered a cohort study in this report.

Fifteen studies were included in the original version of this report https://www.cancercareontario.ca/sites/ccocancercare/files/guidelines/summary/pebc27-2s_1.pdf. One was an RCT [68], five were prospective studies [69-73], six were retrospective studies [54,56,74-77], and three articles [78-80] did not report their study designs. Data extracted from these studies are added to the analysis in Appendix 7.

Table 4-1. Study and patient characteristics by type of population

Author, year (n)	Design (description by author)	Age ±SD[a] (years) (range)	PSA±SD[a] (ng/mL) (range)	Prior biopsy number (range) / cores (range)	PI-RAD Version
Mixed Population (Biopsy Naïve & Prior Negative reported separately)					
Alberts, 2018 [6] (n=158 [BN 74, PN 84]) 7 centres, no TTMB	Side-cohort study of non-randomized patients from an RCT	Med. 73.1 (IQR 72.3-74.0)	Med. 4.3 (IQR 3.4-5.7)	Med. 1 (0-2) / NR	2
Borkowetz, 2017 [8] (n=578 [BN 133, PN 445]) Single centre, no TTMB	Prospective study	Med. 66 (Min 46; Max;86)	Med. 8.17 (Min 1; Max12)	NR/NR	1 & 2
Filson, 2016 [11] (n=652 [BN 328, PN 324]) Single centre, no TTMB	Prospective cohort	Med. 64.4 (IQR 58.5-69.4); Med. 65.7 (IQR 59.3-70.2)	Med. 5.8 (IQR 4.4-8.1); Med. 7.6 (IQR 5-11.5)	NR/NR	2
Hansen, 2016 [18] (n=402 [BN 107, PN 295]) Single centre, *TTMB*	Retrospective outcome study.	Med. 65 (IQR 59-69)	Med. 7.8 (IQR 0-12)	NR/NR	1
Mannaerts, 2019 [12] (n=255 [BN 294, PN 159) *2 centres*, no TTMB	Prospective study	Med. 65 (IQR 61-69)	Med. 8.1 (IQR 5.9-12.0)	NR/NR	2
Mariotti, 2016 [20] (BN=246, PN=143) *2 centres*, no TTMB	Retrospective analysis of prospectively generated data.	Centre 1: mean 62.8±8.0 Centre 2: mean 62.7±9.2	Centre 1: mean 8.0±5.6 Centre 2: mean 6.4±6.2	NR/NR	NR
Meng, 2015 [21] (n=464 [BN 292, PN172]) Single centre, no TTMB	Retrospective analysis of prospectively acquired cohort	Mean 65.2 (8.0)	Mean 6.7 (0.3)	NR/NR	NR
Mortezavi, 2018 [5] (n= 249 [BN163, PN 86]) Single centre, *TTMB*	Retrospective analysis	Med. 64 (IQR 58-69)	Med. 6.7 (IQR 4.4-9.6) [24]	NR/NR	NR
Preisser, 2019 [22] (n=219 [BN141, PN78]**)** 1 centre, no TTMB	Retrospective analysis	Med. 67 (IQR 60-73)	Med. 8.4 (IQR 5.5-11.8)	55 = 1 prior biopsy, 23 ≥ 2 biopsy, / Med per session 4 (3-6)	1
Westoff, 2019 [23] (n=517 [BN 307, PN 210]) 1 centre, no TTMB	Retrospective analysis	Med 66.9 (IQR 61-73.1)	Med. 7.6 (5.6-11.9)	NR/ Med. 2 (IQR 2-3)	2
Zalesky, 2019 [24] (n=385 [BN 211, PN 174]) single centre , no TTMB	Retrospective study	BN: Mean 61.37 (8.09) PN: 64.40 (6.14)	BN: Mean 6.67 (6.24) PN: 10.88 (7.80)	NR / NR	1
Biopsy Naïve					
Ahmed, 2017 [3] (n=576) PROMIS study	Prospective multi-centre, paired-cohort	Mean 63.4 ± 7.6	Mean 7.1 ± 2.9 (Range: 0.5-15)	NA	1.

Table 4-1. Study and patient characteristics by type of population

Author, year (n)	Design (description by author)	Age ±SD[a] (years) (range)	PSA±SD[a] (ng/mL) (range)	Prior biopsy number (range) / cores (range)	PI-RAD Version
(see also Brown, 2018) *11 centres*, *TTMB*					
Baco, 2016 [7] (n=175, G1 86, G2 89]) Single centre, no TTMB	RCT	Mean 65 (59-69)	7.3 (5.5-9.9)	0	2
Borkowetz, 2018 [9] (n=214) *2 centres*, no TTMB	Multicentre, prospective trial	Med. 63 (Min 40; Max75)	Med. 6.22 (Min 1; Max49)	NA	1&2
Castellucci, 2017 [10] (n=168) Single centre, no TTMB	Prospective single centre cohort study	Mean 61.4 (± 7.6)	Mean 8.3 (± 6.1)	NA	1
Hansen, 2018 [4] (n=807 [centre 1 163, centre 2 402, centre 3 242]) *3 centres*, *TTMB*	Prospective cohort	Setting Centre 1: Median 64 (IQR 57-69) Setting Centre 2: Median 65 (IQR 60-70) Setting Centre 3: Median 65 (IQR 60-70)	NR	NA	1
Kasivisvanathan, 2018 [16] (n=500 [G1 252, G2 248]) PRECISION study *25 centres*, no TTMB	RCT	MRI Targeted Biopsy Group: Mean 64.4 ± 7.5 Standard Biopsy Group: Mean 64.5 ± 8.0	MRI Targeted Biopsy Group: Med. 6.75 IQR (5.16-9.35) Standard Biopsy Group: Med. 6.50 IQR (5.14-8.65)	NA	2
Peltier, 2015 [64] (n=110) Single centre, no TTMB	Prospective study	Mean 65.1 ± 7.1; Med. 65.8 (Range: 48.0-79.2;IQR 59.5-70.7)	Mean 8.4 ± 6.3; Med. 6.9 (Range; 0.7-40.0;IQR 4.6-9.6)	NA	1
Porpiglia, 2017 [17] (n=212 [Arm A 107, Arm B 105]) Single centre, no TTMB	RCT	Arm A: Med. 64 (IQR 58-70) Arm B: Med. 66 (IQR 60-70)	Arm A: Med. 5.9 (IQR 4.8-7.5) Arm B: Med. 6.7 (IQR 5.5-8.5)	NA	1
Rouviere, 2019 [1] (n=251) MRI-first *16 centres*, no TTMB	Prospective multicentre study	Med. 64 (IQR 59-68)	Med. 6.5 (IQR 5.6-9.6)	NA	2
Sarkar, 2019 [13] (n=100) 1 centre, no TTMB	Prospective comparative effectiveness study	Mean 68 (46-83)	Med. 7.6 (NR)	NA	2
Thompson, 2016 [19] (n=344) *2 centres*, TTMB	Prospective cohort	Med. 62.9 (IQR 55.9-67.1)	Med. 5.2 (IQR 3.7-7.1)	NA	1
Tonttila, 2016 [25] (n=130 [MPMRI 65, Control 65]) Single centre, no TTMB	RCT	Med. 63 (IQR 60-66); Med. 62 (IQR 56-67)	Med. 6.1 (IQR 4.2-9.9); Med. 6.2 (IQR 4.0-10.7)	NA	NR

Table 4-1. Study and patient characteristics by type of population

Author, year (n)	Design (description by author)	Age ±SD[a] (years) (range)	PSA±SD[a] (ng/mL) (range)	Prior biopsy number (range) / cores (range)	PI-RAD Version
Van Der Leest, 2019 [2] (n=626) *7 centres*, no TTMB	Prospective, multicentre, powered, comparative effectiveness study	Med. 65 (IQR 59-68)	Med. 6.4 (IQR 4.6-8.2)	NA	2
Zhang, 2017 [14] (n=224) Single centre, no TTMB	Prospective study	Med. 69 (40-85)	Med. 10.05 (3.61-78.39)	NA	1
Prior Negative					
Arsov, 2015 [27] (n=210 [G1 104, G2 106]) Single centre, no TTMB	RCT	Mean.65.3 ± 7.6 /, 66.7 ± 6.8 Med. 66 (60-71)/ 68 (63-71)	Mean 12.6 ± 7.7 / 14.5 ± 16.7 Med. 10.0 (IQR 7.8-14.9)/ 10.8 (IQR 7.4-15.5)	NA	1
Boesen, 2018 [28] (n=289) Single centre, no TTMB	Prospective study	Med. 64 (IQR 59-67)	Med. 12.0 (IQR 8.3-19)	Med. 2 (1-6) / NR	1
Hansen, 2017 [31] (n=487 [centre 1 287, centre 2 200] 2 centres*, TTMB*	Prospective cohort study	Median 66 (IQR 60-71)	Median 9.7 (IQR 7.1-13.9)	NR/NR	1&2
Lian, 2017 [30] (n=101) *2 centres*, no TTMB	Prospective study	Mean 68.9 ± 8.1	Mean 10.8 ± 6.1	Mean 1.5 ± 0.7/NR	1
Pepe, 2015 [32] (n=100) Single centre, *TTMB*	Prospective study	Med. 64 (IQR 49-72)	Med. 8.6 (Range: 4.2-10)	1/18	1
Pepe, 2017 [34] (n=150) Single centre, *TTMB*	Prospective study	Med. 62 (IQR 47-78)	Med. 9.2 (Range: 4.5-31)	NR/NR	1
Pepe, 2018 [33] (n=1,032) Single centre, *TTMB*	Prospective study	Med. 63 (Range: 47-78)	Med. 8.6 (3.5-46)	NR/NR	1&2
Say, 2016 [65] (n=143) Single centre, no *TTMB*	Retrospective study	Med. 64.1 (47-82)	Med.DA 11.6 (range 0.4-96.9)	1.8 (Range 1-5)/NR	1
Sidana, 2018 [66] (n=779) Single centre, no TTMB	Retrospective review of prospectively maintained database /PN	Med. 63.1 (IQR 58.5-68.0)	Med. 8.5 (5.9-13.1)	2 (IQR 1-16) /NR	2
Simmons, 2018 [26] (see also Simmons 2017) (n=249) PICTURE study Single centre, *TTMB*	Single centre, prospective cohort	Mean 62 ± 7 (Range: 42-83)	Med. 6.8 (4.8-9.8)	Mean 1.41 ± 0.69 (IQR 1-2)/NR	NR
Wegelin, 2019 [58] (n=234) (see also **Exterkate, 2020 [29]**152 underwent both TB and SB)	RCT	Mean 64.7 (SD 6.6),	mean PSA 10.4 ng/ml (SD 7.3)	Med. 1 (IQR 1–2)	2

Table 4-1. Study and patient characteristics by type of population

Author, year (n)	Design (description by author)	Age ±SD[a] (years) (range)	PSA±SD[a] (ng/mL) (range)	Prior biopsy number (range) / cores (range)	PI-RAD Version
MRI vs. MRI *3 centres*, no TTMB FUTURE trial					

BN = biopsy naïve; DA = diagnostic accuracy; G1 = group 1; G2 = group 2; IQR = interquartile range; Med = median; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NA = not applicable; NR = not reported; PI-RAD = Prostate Imaging – Reporting and Data System; PN = previously negative; PSA = prostate-specific antigen; RCT = randomized controlled trial; SB = systematic biopsy; SD = standard deviation; TB = targeted biopsy; TTMB = template transperineal mapping biopsy

Biopsy-naïve patients (Question 1)

Q1a MPMRI (±TB) vs. Reference Standard

Risk of bias assessment for individual studies

Five trials assessed the diagnostic accuracy of MPMRI (±TB) against a reference standard (TTMB). Appendix 5a shows the risk of bias and applicability using the QUADAS-2 tool [59]. All five studies were assessed as being at low risk of bias on the domains of patient selection and index testing. Two studies [4,5] were assessed as being at moderate risk of bias on the reference standard, two were assessed at unclear risk [18,19] and one was assessed as low on this domain [3]. One study [19] was assessed as unclear on the domain of flow and time; the remaining were assessed as low on this domain. All studies were assessed at being at low risk for the applicability concerns regarding patient selection, index testing, and the reference standard. One [3] of the five studies was assessed overall at low risk of bias on the QUADAS-2 tool, two were assessed overall at being at moderate risk of bias [4,5], and two [18,19] was assessed overall at being at unclear risk of bias (see Appendix 5).

For the most part, the diagnostic accuracy outcomes (sensitivity, specificity, etc.) across the five articles assessing the diagnostic accuracy of MPMRI (±TB) for biopsy-naïve patients were comparable, with all showing relatively high sensitivity and low specificity (see Table 4-2) indicating a high false-positive rate. The aggregate study evidence certainty for the comparisons was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

Outcomes (*MPMRI [±TB] vs. Reference Standard)*

Five cohort studies addressed Q1a. Table 4-2 shows the diagnostic accuracy of MPMRI (±TB), compared to a reference standard for CSPCa. All five cohort studies [3-5,18,19] reported diagnostic accuracy outcomes for MPMRI (±TB) in biopsy-naïve patients. Three studies compared MPMRI alone to a reference standard [4,18,19] and two compared the reference standard to MPMRI followed by software fusion-guided targeted biopsy [3,5]. Reported mean/median age for the five studies ranged from of 63 [3,19] to 65 [18] years and PSA ranged from 5.2 [19] to 7.8 ng/mL [18] (Table 4-1).

MPMRI alone

In the 2016 Hansen et al. study [18] the prevalence of CSPCa among 107 patients was 39%. The sensitivity and specificity of MPMRI alone to detect CSPCa was 93% (95% CI, 85 to 101) and 29% (95% CI, 18 to 40), respectively, indicating that 7% of true CSPCa patients were missed and 71% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 46% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 14% (NPV=86%) of patients were true CSPCa patients (see Table 4-2). In the 2018 Hansen et al. study [4] the prevalence of CSPCa among 807 patients was 49%. The sensitivity and specificity of MPMRI alone to detect CSPCa was 88% (95% CI, 85 to 91) and 45% (95% CI, 41 to 50), respectively, indicating that 12% of true CSPCa patients were missed and 55% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 60% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 20% (NPV=80%) were true CSPCa patients. In Thompson et al. [19], the prevalence of CSPCa among 344 patients was 42%. The sensitivity and specificity of MPMRI alone to detect CSPCa was 96% (95% CI, not reported) and 36% (95% CI, not reported), respectively, indicating that 4% of true CSPCa patients were missed and 64% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 52% (PPV) of patients had

CSPCa; among the MPMRI-negative patients, 8% (NPV=92%) were true CSPCa patients (see Table 4-2).

MPMRI-TB

In the Ahmed et al. study [3] the prevalence of CSPCa among 576 patients was 53%. Using MPMRI plus software fusion targeted biopsy, the sensitivity and specificity of MPMRI to detect CSPCa was 88% (95% CI, 84 to 91) and 45% (95% CI, 39 to 51), respectively, indicating that 12% of true CSPCa patients were missed and 55% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 65% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 24% (NPV=76%) were true CSPCa patients. In the 2018 Mortezavi et al. study [5] the prevalence of CSPCa among patients was 26%. The sensitivity and specificity of MPMRI and TRUS fusion (software)-guided targeted biospy to detect CSPCa was 87% (95% CI, 80 to 95) and 45% (95% CI, 35 to 56), respectively, indicating that 13% of true CSPCa patients were missed and 55% of patients without CSPCa were falsely diagnosed. For MPMRI alone, among the MPMRI-positive patients, 59% (PPV) had CSPCa; among the MPMRI-negative patients, 20% (NPV=80%) were true CSPCa patients (see Table 4-2).

Table 4-2. (Q1a) Cohort studies examining diagnostic accuracy of MPMRI (±TB) in biopsy-naive patients (compared with reference standard) by different definitions of clinically significant cancer

Study (Prevalence of CSPCa)	Index test	Positive MRI	Reference standard	CSPCa definition	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MPMRI Alone								
Hansen, 2016 n=107 (39%)	T2WI+ DWI+ DCE	PI-RAD v1 ≥3 of 5	24-core systematic biopsy according to the Ginsburg TRUS-SB protocol	GS 7 to 10	92.9% (85,101)	29.2% (18,40)	45.9% (35,56)	86.4% (72,101)
Hansen, 2018 n=807 (49%)	T2WI+ DWI+ DCE	PI-RAD v1 ≥3 of 5	18-24 core systematic TP biopsy according to the Ginsberg TRUS-SB protocol	GS 7 to 10	87.8% (85,91)	45.3% (41,50)	60.2% (56,64)	79.7% (75,85)
Thompson, 2016 n=344 (42%)	T1WI+ T2WI+ DCE	PI-RAD v1 ≥3 of 5	Median of 30 cores with relative periurethral zone sparing and adjusted for volume	GS 7 to 10	96% (NR,NR)	36% (NR,NR)	52% (NR,NR)	92% (NR,NR)
MPMTI-TB								
Ahmed, 2017 n=576 (53%)	T1WI+T2WI+ DWI+DCE + MRI-directed (software)TR US biopsy	PI-RAD v1 ≥3 of 5	TPMB	Any GS 7 (≥3+4)	88% (84-91)	45% (39-51)	65% (60-69)	76% (69-82)
Mortezavi, 2018 n=163 (26%)	T2WI+ DWI+ DCE MPMRI/TRUS (software) fusion guided	PI-RAD (NR) ≥3 of 5	TPMB	GS ≥7	87% (80,95)	45.3% (35,56)	58.8% (50,68)	79.6% (68,91)

*using the 2014 International Society of Urologic Pathology (ISUP) criteria
CSPCa = clinically significant prostate cancer; DCE = dynamic contrast enhanced-magnetic resonance imaging; DWI = diffusion weighted imaging; GS = Gleason Score; MPMRI = multiparametric magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TP = transperineal; TPMB = template prostate mapping biopsy; TR = transrectal; TRUS-SB = transrectal ultrasound systematic biopsy; T1WI = T_1-weighted imaging; T2WI = T_2-weighted imaging;

Q1b MPMRI-TB vs. TRUS-SB

Risk of bias assessment for individual studies

Eighteen studies (2 RCTs and 16 cohort studies) compared MPMRI-TB with TRUS-SB. Appendix 5b shows the risk of bias assessment using the Cochrane Risk of Bias Tool [60] for two RCTs included for these comparisons. Both were assessed at low risk of bias on random sequence generation and whether participant group allocation was concealed. Blinding of participants and direct personnel was not possible in these types of studies and would not likely influence diagnostic outcomes; thus, blinding of participants was not assessed. It was unclear in one of the RCTs [17] whether outcome assessor blinding was implemented and whether outcome data reporting was complete. The other RCT [16] was rated at low risk of bias on these two domains. Both RCTs were rated at low risk of bias in the area of selective reporting. Overall, one RCT [16] was assessed at being at low risk of bias and one [17] was assessed as being at unclear risk of bias using the Cochrane Risk of Bias tool for RCTs (see Appendix 5).

Appendix 5c shows the risk of bias outcomes for 16 cohort/intervention studies comparing MPMR-TB with TRUS-SB using the ROBINS-I tool [61]. All studies were rated at low risk of bias for confounding. Five studies were assessed at high risk of bias for selection of participants, due to their retrospective nature or to non-consecutive patient selection [20-24]; two [8,13] were assessed as moderate on this domain and the remaining studies were rated as low. Three studies [1,2,6] were assessed at low risk of bias on measurement of intervention and it was unclear in one of the studies [13]. The remaining studies were assessed as being at moderate risk of bias on measurement of intervention mainly due to different versions of PI-RAD being used during the study period or lack of clarity regarding measurement. Eight studies [1,2,6,7,14,22-24] were assessed as being at low risk of bias for departure from intervention and the remaining were assessed as moderate on this domain due to clarity of how intervention was implemented during the study period. Two studies [6,12] were assessed as being at moderate risk of bias due to missing data and the remainder was assessed as being at low risk of bias on this domain. All studies measuring detection rates were assessed as being at moderate risk of bias on measurement of outcome either because it was unclear whether the outcome assessor was blinded to the index test when measuring the reference standard or because no reference standard was used to assess the accuracy of both the MPMRI and TRUS-SB detection. Two of the studies were rated at moderate risk of bias on the domain of selection of reported results [8,22]. The remaining studies were rated low on this domain. Overall, five of the cohort studies were assessed at high risk of bias [20-24] and two were assessed at low risk [1,2]. The remaining cohort studies were assessed overall at being at moderate risk of bias on the ROBINS risk of bias tool.

For CSPCa, confidence intervals were narrow, mainly falling in the same direction of effect favouring MPMRI-TB for the above studies comparing MPMRI-TB to TRUS-SB. Study heterogeneity were relatively high (I^2=63%, p=0.00001), with indication of subgroup differences between the RCTs and cohort studies (I^2=81.2%, p=0.02) (see Figure 1.1). There was no indication of subgroup differences among the types of MPMRI-TB (software, cognitive, in-bore, etc.) used (I^2=17.9%, p=0.30 – see Appendix 8 for subgroup analysis by type of MPMRI-TB).

For CISPCa, confidence intervals were narrow mainly falling in the same direction of effect favouring MPMRI-TB. Study heterogeneity was high (I^2=71%, p<0.00001), with no significant subgroup differences between RCTs and cohort studies (I^2=0%, p=0.77 see Figure 1.2) and no significant differences among MPMRI-TB types (I^2=17.1%, p=0.30 – see Appendix 8).

The aggregate study evidence certainty for the comparisons was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication

bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

Outcomes (*MPMRI-TB vs. TRUS-SB)*

Tables 4-3 and Figures 1.1 and 1.2 show the estimates for CSPCa and CISPCa for the 18 (16 cohort and 2 RCT) studies assessing biopsy-naive patients, Estimates for CSPCa show an overall effect of 0.03 (0.00 to 0.07, p=0.05) (see Figure 1.1). For CISPCa, the overall effect was -0.08 (95% CI, -0.11 to -0.05, p<0.00001) (see Figure 1.2).

RCTs

Table 4-3 and Figures 1.1 and 1.2 show the detection rates of CSPCa and CISPCa for the two RCTs comparing MPMRI-TB to TRUS-SB alone for biopsy-naïve patients [16,17]. In a multicentre, non-inferiority trial, Kasivisvanathan et al. [16] randomized 500 biopsy-naïve men to either MPMRI [MPMRI+TRUS fusion] (mean age 64.4 years, median PSA 6.8 ng/mL) or TRUS-SB alone (mean age 64.5 years, median PSA 6.5 ng/mL). CSPCa was defined as GS ≥3+4. Likewise, Porpiglia et al. [17] randomized 212 men to either MPMRI (±TB) [(MPMRI(+), TRUS fusion] (median age 64 years, median PSA 5.9 ng/mL) or TRUS-SB (median age 66 years, median PSA 6.7 ng/mL). The study defined CSPCa as GS ≥7 or maximum cancer core length ≥5 mm. CSPCa was detected in 38% of men receiving MPMRI (±TB) and in 26% in the TRUS-SB group in the Kasivisvanathan study (p=0.005), and 44% (MPMRI [±TB]) and 18% (TRUS-SB) in the Porpiglia study (p<0.001). The overall risk difference (RD) for CSPCa detection when combining the two studies was 0.18 (95% CI, 0.05 to 0.32, p=0.009) (see Figure 1.1 – as RCT subgroup analysis). CISPCa was detected in 9% of men receiving MPMRI (±TB) and in 22% of those receiving TRUS-SB in the Kasivisvanathan study (p<0.0001), and 7% (MPMRI [±TB]) and 11% (TRUS-SB) in the Porpiglia study (p=NR). The overall RD for CISPCa detection when combining the two studies was -0.09 (95% CI,-0.17 to -0.01, p=0.03) (see Figure 1.2).

Cohort Studies

Table 4-3 and Figures 1.1 and 1.2 show the detection rates from the 16 cohort studies of MPMRI-TB versus TRUS-SB in biopsy-naïve men. Two were intervention arms from RCTs [6,7], nine were prospective cohort studies [1,2,8-14], and five were retrospective cohort studies [20-24]. Ten studies used software fusion-guided targeted biopsy [6-9,11,12,20-23], three used cognitive fusion [10,14,24], one used in-bore [2], one used either cognitive or software [1], and one [13] did not report the MRI technique used (see Table 4-1 for study characteristics and Appendix 8 for subgroup analysis by MPMRI-TB type).

Figure 1.1 shows the individual and overall RDs for CSPCa, with an overall RD for the cohort studies combined of 0.02 (95% CI, -0.01 to 0.0=5, p=0.23). Figure 1.2 shows the individual and overall RDs for CISPCa, with an overall RD for the cohort studies combined of -0.08 (95% CI, -0.11 to -0.05, p<0.00001).

Among the 16 cohort studies noted above, two [1,2] were prospective MCTs. A prospective 16-centre, paired diagnostic study (MRI-FIRST) enrolled 251 patients referred for prostate MPMRI. Patients received both TRUS-SB and either cognitive (6 centres) or MRI-TRUS fusion (10 centres) targeted biopsy (for MPMRI-positive patients only). There were no significant differences in detection of CSPCa (TB 32% vs. TRUS-SB 30%; RD 0.02 [95% CI,-0.06 to 0.10]; p=0.38). However, targeted biopsy detected significantly less CISPCa than TRUS-SB (TB 6% vs. TRUS-SB 20%; RD -0.14 [95% CI, -0.20 to -0.08]; p<0.00001). Five percent of CSPCa was detected by TRUS-SB that was missed by MPMRI (±TB) and 8% was detected by targeted biopsy and missed by TRUS-SB. The authors concluded that "detection was improved by combining both techniques and both techniques showed substantial added value [1]". A prospective four-

centre, powered, comparative effectiveness study enrolled 646 men to receive MPMRI followed by TRUS-SB and in-bore targeted biopsy (for MPMRI-positive patients only). MPMRI-*TB* detected CSPCa in 26% of patients and TRUS-SB detected 23% (RD 0.02 [95% CI, -0.03 to 0.07]; p=0.3924). CISPCa was detected in 14% of patients by MPMRI-TB and in 25% of patients by TRUS-SB (RD -0.11 [95% CI, -0.15 to -0.06]; p<0.00001). The MRI pathway (TB for PI-RAD 3-5 lesions) enabled biopsy avoidance in 49% of patients and no targeted biopsy in this group's resulted in missing 3% of cases. Meanwhile, TRUS-SB would have over-detected CISPCa in 20% of these patients, according to the authors [2].

Table 4-3 (Q1b) Studies examining detection rates of MPMRI-TB and TRUS-SB in biopsy-naïve patients by different definitions of clinically significant prostate cancer

RCTs						
Study (n)	**MRI Navigation system /+MRI definition**	**Cores**	**CSPCa/CISPCa definition**	**CSPCa MPMRI-TB vs.TRUS-SB**		
				MPMRI-TB DR (95% CI)	**TRUS-SB DR (95% CI)**	**p value**
Kasivisvanathan, 2018 (n=500)	Visual registration or software fusion (≥ 3 of 5 scores) (TR or TP)	TB: Max. 3 areas with max. 4 biopsy cores obtained per areas SB: 12	**CSPCa:** (GS≥3+4)	37.7% (32,44) 95/252	25.8% (20-31) 64/248	0.005
			CISPCa: (GS=3+3)	9.1% (6,13) 23/252	22.2% (17,27) 55/248	0.001
Porpiglia, 2017 (n=212)	Software fusion (≥ 3 of 5 score) TP or TR	TB: 3 to 6 cores from each lesion SB: 12	**CSPCa:** (GS≥7 or max. CCL≥ 5mm)	43.9% (35,53) 47/107	18.1% (11,25) 19/105	0..001
			CISPCa: (GS=3+3 or max. CCL < 5mm)	6.5% (2,11) 7/107	11.4% (5,18) 12/10	0.2113

Cohort Studies								
Study (n)	**MRI Navigation system /+MRI definition**	**Cores**	**CSPCa/CISPCa definition**	**MPMRI-TB DR (95%CI)**	**Missed if TB not done**	**TRUS-SB DR (95% CI)**	**Missed if TRUS-SB not done**	**p-value**
Alberts, 2018 (n=74) non-randomized arm of RCT	Software fusion (TRUS-Bx_fusion) /1 PI-RAD v1 ≥3 of 5	TB: 2 per lesion SB: grp 1 [PSA≥3.0] sextant TRUS-SB +1 core per hypoechoic lesion; Grp 2 [PSA ≥3.0] 12 core blinded for MRI+1 core for each hypoechoic lesion.	**CSPCa:** (GS≥3+4)	18.9% (10,28)	5.4% (1/74)	20.3% (11,29)	6.8% (5/74) MRI- 4/46 MRI+ 1/28	0.8365
			CISPCa: (GS=3+3)	6.8% (1,12)	1.4 (1/74)	33.8% (23,45)	28.4% (21/74) MRI- 17/46 MRI+ 4/28	0.0001
Baco, 2016 (n=86) non-randomized arm of RCT	Software fusion (Image fusion) /PI-RAD v1 ≥3 of 5	TB: Med. 2 (range 1-4) TRUS-SB: 12	**CSPCa:** (GS≥3+4)	38.4% (28,49)	NR	36% (26,46)	NR	0.7532
			CISPCa:	NR	NR	NR	NR	NR
Borkowetz, 2017 (n=133)	Software fusion (fusPbx - TP - combined with TR at one site and TR sysPbx at another site)	TB: Min. 2 per lesion TRUS-SB: 12	**CSPCa:** (GS≥ 7)	40.6% (32,49)	6.8% (9/133)	35.3% (27,43)	2.3% (3/133) MRI- NR MRI+ NR	0.3781

	/PI-RAD v1&2 ≥3 of 5		**CISPCa:** (GS=6)	8.3% (4,13)	NR	6.1% (2,10)	NR	0.4763
Borkowetz, 2018 (n=214)	Software fusion (fusPbx -TP - combined with TR at one site and TR sysPbx at another site) 1&v2 ≥3 of 5	TB: Min. 2 per lesion TRUS-SB: 12	**CSPCa:** (GS≥ 7)	37.9% (31,44)	9.3% (20/214)	34.6% (28,41)	6.1% (13/214) MRI- NR MRI+ NR	0.4822
			CISPCa: (GS=6)	8.9% (5,13)	6.1% (13/214)	7.9% (4,12)	10.3% (22/214)	0.7280
Castellucci, 2017 (n=168)	fusion (≥4 of 5 scores) (n=83), fusion (n=168) / PI-RAD v1 ≥4 of 5	TB: 2 (Mean 2.4 (PI-RAD 3), 2.7 (Pi-RAD 4) TRUS-SB: 12	**CSPCa:** (GS≥3+4)	17.9% (12,24)	NR	19.6% (14,26)	NR	0.6755
			CISPCa: (GS=3+3)	10.7% (6,15)	NR	16.1% (11,22)	NR	0.1513
Filson, 2016 (n=328)	Software fusion / PI-RAD v.2 ≥3 of 5	TB: 1 core per 3mm of the longest ROI axi TRUS-SB: 12	**CSPCa:** (GS≥3+4)	30.5% (26,35)	NR	28.7% (23,33)	NR	0.5491
			CISPCa: (GS=3+3)	13.7% (10,17)	NR	25.6% (21,30)	NR	0.0002
Mannaerts, 2019 (n=294)	Software fusion (MRI-TRUS) / PI-RAD v2 ≥3 of 5	TB: 2 to 4 per lesion depending on lesion size TRUS-SB: 12	**CSPCa:** (GS≥3+4)	32% (27,37)	3.1% (9/294)	39.5% (34,45)	10.5% (31/294) MRI- 24/133 MRI+ 7/161	0.0593
			CISPCa: (GS=3+3)	5.4% (3,8)	4.1% (12/294)	15% (11,19)	13.6% (32/294) MRI- 21/133 MRI+ 11/161	0.0002
Mariotti, 2016 (n=246)	Software fusion (MRI-TRUS(/ PI-RAD (NR) ≥3 of 5	TB: 2 or 3 from each target TRUS-SB: 12	**CSPCa: 5**(GS≥3+4)	45.9% (40,52)	14.2% (35/246)	34.1% (28,40)	2.4% (6/246) MRI-5/113 MRI+1/133	0.0081
			CISPCa: (GS=3+3)	8.1% (5,12)	4.1% (10/246)	24% (19,29)	13.8% (34/246) MRI- 24/113 MRI+ 10/133	0.0000
Meng, 2016 (n=292)	Software fusion MRI-US fusion / PI-RAD (NR) ≥3 of	TB: 4 per lesion TRUS-SB: 12	**CSPCa:** (GS≥7)	30.5% (25,36)	NR	25.3% (20,30)	NR	0.1675
			CISPCa: (GS=6)	11% (7,15)	NR	20.5% (16,25)	NR	0.0016
Preiser, 2019 (n=141)	MRI/ultrasound software fusion-guided TB / PI-RAD v.2 ≥3 of 5	TB: NR TRUS-SB: 12	**CSPCa:** (GS≥3+4)	51.8% (43,60)	NR	53.9% (45,62)	NR	0.7188
			CISPCa: (GS=3+3)	13.5% (8,20)	NR	13.5% (8,20)	NR	1
Rouviere, 2019 (n=251)	TR cognitive or software fused MRI-TBx /PI-RAD v2	206 (198 + 8 from PI-RAD 2)	**CSPCa:** (csPCa-A (GG ≥2)	32.3% (26,38)	7.6% (19/251)	29.9% (24,36)	5.2% (13/251) MRI- 5/45 MRI+ 8/206	0.225

	≥ 3 of 5	TB: 3 to 6 per lesion depending on Likert score TRUS-SB: 12 to 14	**CISPCa:** (ISUP GRADE group 1)	9.2% (6,13)	3.5% (9/251)	22.3% (17,28)	16.3% 42/251 MRI- 8/45 MRI+ 34/206	0.0000
Sakar, 2019 (N=100)	NR /PI-RAD v2 ≥ 4 of 5	TB: Med. 6 cores from ave.. of 2 lesions SB: 8	**CISPCa: (**GS > 3 + 3)	47% (37,57)	NR	39% (29,49)	NR	0.2543
			CISPCa: (GS=3+3)	7% (3,14)	NR	16% (9,25)	NR	0.0466
Van der Leest, 2019 (n=626)	TR in-bore / PI-RAD v2 ≥3 of 5	TB: 2 to 4 per lesion TRUS-SB: 12	**CSPCa:** (G ≥ 2 [GS ≥ 3+4])	25.4% (22,29)	NR	23.3% (20,27)	NR	0.3924
			CISPCa: (not defined)	14.1% (11,17)	NR	24.8% (21,28)	NR	0.0000
Westoff, 2019 (n=307)	Software fusion / PI-RAD v2 ≥3 of 5	TB: Med. 2 (IQR 2-3) SB: 12	**CSPCa:** (GS≥3+4)	37.5% (32,43)	NR	39.4% (34,45)	NR	0.6171
			CISPCa: (GS=3+3)	19.2% (15,24)	NR	26.7% (22,32)	NR	0.0271
Zalesky, 2019 (n=211)	Software fusion / PI-RAD v2 ≥3 of 5	TB: mean 2.21 cores per lesion SB: NR	**CSPCa:** (GS≥7)	30.3% (24,37)	NR	39.8% (33,47)	NR	0.0414
			CISPCa: (GS=6)	4.7% (2,9)	NR	13.2% (9,19)	NR	0.0022
Zhang, 2017 (n=224)	Cognitive fusion (free hand TP MPMRI/TRUS) /PI-RAD v1 ≥2 of 5	TB: mean 3.5 (± 1.84) TRUS-SB: 12	**CSPCa:** (GS≥7)	26.3% (21,32)	NR	15.6% (10,20)	NR	0.0058
			CISPCa: (GS=6)	17.9% (13,23)	NR	19.2% (14,24)	NR	0.7156

*using the 2014 International Society of Urologic Pathology (ISUP) criteria. CCL = cancer core length; CI = confidence interval; CSD = clinical significant disease; CISPCa = clinically insignificant prostate cancer; CSPCa = clinically significant prostate cancer; DR = detection rate; fusPbx = fusion biopsy; grp = group; GS = Gleason Score; ITT = intention to treat; MC = multi-centre; MCCL = maximum cancer core length; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging-Reporting and Data System; PP= per protocol; pt = patient; PSA = prostate-specific antigen; RCT = randomized controlled trial; ROI = region of interest; SB = systematic biopsy; SC = single centre; TRUS-SB = transrectal ultrasound-guided systematic biopsy; TB = targeted biopsy; TR = transrectal; TP = transperineal

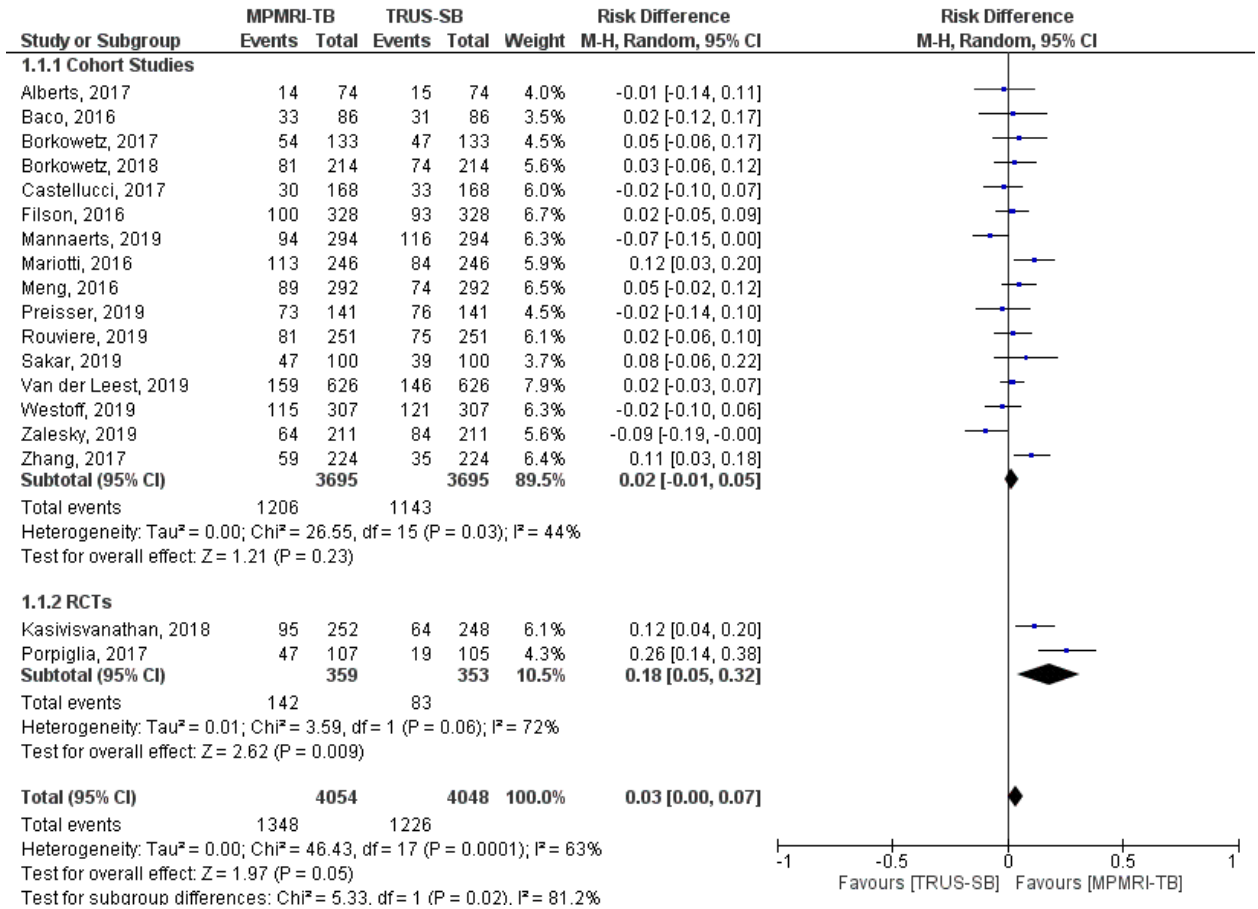

Figure 1.1: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men

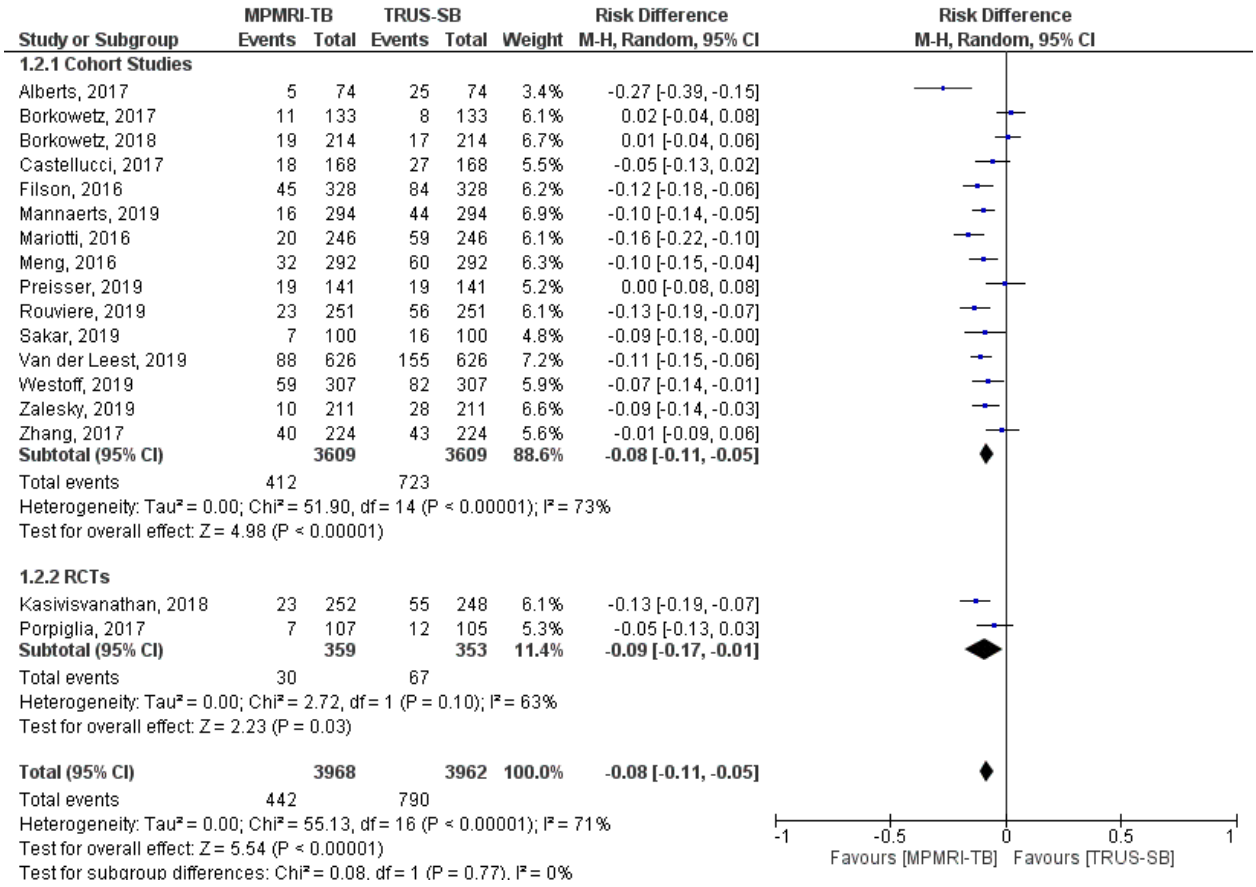

Figure 1.2: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men

Q1c MPMRI-TB plus TRUS-SB vs. MPMRI-TB alone or TRUS-SB alone

Risk of bias assessment for individual studies

Thirteen studies (1 RCT, 12 cohort) compared MPMRI-TB (+TRUS-SB) to either MPMRI-TB alone or TRUS-SB alone. Appendix 5b shows the risk of bias assessment using the Cochrane Risk of Bias tool [60] for the one RCT included for these comparisons. The RCT [25] was assessed at low risk of bias on random sequence generation and whether participant group allocation was concealed. Blinding of participants and direct personnel was not possible in these types of studies and would not likely influence diagnostic outcomes and, thus, was not assessed. The RCT was rated at unclear risk of bias on whether outcome assessor blinding was implemented and whether outcome data reporting was complete. The RCT was rated at low risk of bias in the area of selective reporting.

Appendix 5c shows the risk of bias outcomes for 12 cohort studies using the ROBINS-I tool [61]. All studies were rated at low risk of bias for confounding. Three studies were assessed at high risk of bias for selection of participants, due to their retrospective nature or non-consecutive patient selection [22-24]. Two studies [8,13] were assessed at moderate risk on this domain and the remaining were rated as low. Two studies [1,2] were assessed at low risk of bias on the domain of measurement of intervention and one [13] was assessed as unclear. The remaining studies were assessed as being at moderate risk of bias on measurement of

intervention mainly due to different versions of PI-RAD being used during the study period or lack of clarity regarding measurement. Three studies [8,9,13] were assessed as being at moderate risk of bias for departure from intervention due to lack of clarity of how the intervention was implemented during the study period. The remaining studies were rated as low on this domain. All studies were rated at low risk of bias on the domain of missing data. All studies were assessed as being at moderate risk of bias on measurement of outcome either because it was unclear whether the outcome assessor was blinded to the index test when measuring the reference standard or because no reference standard was used to assess the accuracy of both the MPMRI and TRUS-SB detection. Three of the studies were rated at moderate risk of bias on the domain of selection of reported results [8,9,22]. The remaining studies were rated low on this domain. Overall, two of the cohort studies were assessed as being at low risk of bias [1,2], three were assessed at high risk [22-24] and the remaining were assessed at moderate risk of bias (see Appendix 5).

Confidence intervals were narrow and fell generally in the same direction of effect (Figures 2.1 and 2.2) favouring MPMRI-TB plus TRUS-SB for CSPCa and favouring targeted biopsy alone for CISPCa for studies examining MPMRI-TB plus TRUS-SB versus targeted biopsy alone. Heterogeneity was low for both CSPCa and CISPCa (I^2=0% for both). There were no differences between MPMRI-TB subgroups found for CSPCa and CISPCa (Appendix 8, Figures 2.1 and 2.2).

Confidence intervals were narrow and fell generally in the same direction of effect (Figures 3.1 and 3.2) favouring MPMRI-TB plus TRUS-SB for studies examining MPMRI-TB plus TRUS-SB versus TRUS-SB alone (see Figures 3.1 and 3.2). Heterogeneity was low for both CSPCa and CISPCa (I^2=0% for both) and no significant subgroup difference were detected between cohort and RCTs (I^2=0%). Subgroup differences by type of MPMRI-TB used showed no significant difference (see Appendix 8, Figures 3.1 and 3.2).

The aggregate study evidence certainty for the comparisons was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

Outcomes *(MPMRI-TB plus TRUS-SB vs. MPMRI-TB alone or TRUS-SB alone)*

Table 4-4 shows reported detection rates for studies examining MPMRI-TB plus TRUS-SB versus MPMRI-TB alone and TRUS-SB alone in biopsy-naive patients. Seven studies used software fusion-guided targeted biopsy[7-9,11,22,23,25], three used cognitive fusion [10,14,24], one used in-bore [2], one used either cognitive or software [1], and one did not report the MPMRI-TB technique used [13] (see Appendix 8 for subgroup analysis by type of MPMRI-TB).

TB+TRUS-SB vs. TB.

Figures 2.1 and 2.2 show the overall RD for the studies (including the non-randomized intervention arm of an RCT [25]) comparing MPMRI-TB plus TRUS-SB to targeted biopsy alone, with 0.06 (95% CI, 0.04 to 0.08, p<0.00001 – Figure 2.1) for CSPCa detection and 0.08 (95% CI, 0.06 to 0.10, p<0.00001 – Figure 2.2) for the detection of CISPCa.

TB+TRUS-SB vs. TRUS-SB.

Figures 3.1 and 3.2 show the overall RD for the studies (including one RCT [25] comparing MPMRI-TB plus TRUS-SB to TRUS-SB alone), with 0.08 (95% CI, 0.05 to 0.10, p<0.00001 - Figure 3.1) for CSPCa detection and 0.00 (95% CI, -0.02 to 0.03, p=0.73 – Figure 3.2) for the detection of CISPCa.

Table 4-4. (Q1c) Studies examining detection rates of MPMRI-TB plus TRUS-SB combined and targeted biopsy and TRUS-SB alone in biopsy-naive patients by different definitions of clinically significant cancer

RCT								
			TB+TRUS-SB vs.TB alone			**TB+TRUS-SB vs. TRUS-SB alone**		
Study (n)	**MRI Navigation system (positive MRI definition) / cores**	**CSPCa/CISPCa Definition**	**TB+TRUS-SB detection rate (95% CI)***	**TB alone detection rate (95% CI)**	**p-value**	**TB+TRUS-SB detection rate (95% CI)***	**TRUS-SB detection rate (95% CI)**	**p-value**
Tontilla, 2016 (n=130)	MRI-TRUS fusion (≥3 of 5 scores)	GS >3+3, > 2 positive cores, or MCCL ≥ 3mm	54.7% (41,68) 29/53	NR	NR	54.7% (41,68) 29/53	45% (32,58) 27/60	0.30
		GS = 3+3, ≤ 2 positive cores, or MCCL < 3mm	9.4% (3,21) 5/53	NR	NR	9.4% (3,21) 5/53	12% (5,23) 7/60	0.70
Cohort Studies								
			TB+TRUS-SB vs.TB alone			**TB+TRUS-SB vs. TRUS-SB alone**		
Study (n)	**MRI Navigation system (positive MRI definition) / cores**	**CSPCa/CISPCa Definition**	**TB+TRUS-SB detection rate (95% CI)***	**TB alone detection rate (95% CI)**	**p-value**	**TB+TRUS-SB detection rate (95% CI)***	**TRUS-SB detection rate (95% CI)**	**p-value**
Baco, 2016 (n=86) SC non-randomized arm of RCT	Software fusion (Image) (PI-RAD v1 ≥ 3 of 5) / Med. 2 (range 1-4)	**CSPCa:** GS≥3+4	44.2% (34,55)	38.4% (28,49)	0.4409	44.2% (34,55)	36% (26,46)	0.2792
		CISPCa:	NR	NR	NR	NR	NR	NR
Borkowetz, 2017 (n=133)	Software fusion (fusPbx - scores) (TP - combined with TR at one site and TR sysPbx at another site) (PI-RAD v1&2 ≥2 of 5) /Min. 2 per lesion	**CSPCa:** GS≥7	44.4% (36,53)	40.6% (32,49)	0.5362	44.4% (36,53)	35.3% (27,43)	0.1353
		CISPCa: GS=6	NR	NR	NR	NR	NR	NR
Borkowetz, 2018 (n=214)	Software fusion (fusPbx TP - combined with TR at one site and TR sysPbx at another site) (PI-RAD v1&2 ≥2 of 5) /Min. 2 per lesion	**CSPCa:** GS≥7	43.9% (37,51)	37.9% (31,44)	0.2030	43.9% (37,51)	34.6% (28,41)	0.0490
		CISPCa: GS=6	14% (9,19)	8.9% (5,13)	0.0964	14% (9,19)	7.9% (0,12)	0.0457
Castellucci, 2017 (n=168)	Cognitive fusion (≥2 of 5) (n=83), software fusion (n=168) (PI-RAD v1 ≥ 3 of 5) /2 (Mean 2.4 (PI-RAD 3), 2.7 (Pi-RAD 4)	**CSPCa:** GS≥3+4	24.4% (18,31)	17.9% (12,24)	0.1434	24.4% (18,31)	19.6% (14,26)	0.2938
		CISPCa: GS=3+3	16.7% (11,22)	10.7% (6,15)	0.1144	16.7% (11,22)	16.1% (11,22)	0.8830
Filson, 2016 (n=328)	Software fusion (PI-RAD v2 ≥3 of 5)	**CSPCa:** GS≥3+4	37.5% (32,43)	30.5% (26,35)	0.0589	37.5% (32,43)	28.7 % (23,33)	0.0132

	/1 core per 3mm of the longest ROI axi	**CISPCa:** GS=3+3	21.6% (17,26)	13.7% (10,17)	0.0082	21.6% (17,26)	25.6% (21,30)	0.2330
Preiser, 2019 (n=141)	MRI/ultrasound software fusion-guided TB / PI-RAD v.2 ≥3 of 5	**CSPCa:** GS≥3+4	59.6% (51,68)	51.8% (43,60)	0.1868	59.6% (51,68)	53.9% (45,62)	0.3371
		CISPCa: GS=3+3	NR	NR	NR	NR	NR	NR
Rouviere, 2019 (n=251)	TR cognitive or software fused MRI-TBx (PI-RAD v2 ≥ 3 of 5) /3 to 6 per lesion depending on Likert score	**CSPCa:** csPCa-A (GG ≥ 2 tumours)	37.5% (31,43)	32.3% (26,38)	0.2245	37.5% (31,43)	29.9% (24,36)	0.0739
		CISPCa: ncsPCa (ISUP grade group 1 tumours with a MCCL <6mm)	23.5% (18,29)	9.2% (6,13)	<0.0000	23.5% (18,29)	22.3% (17,28)	0.7490
Sakar, 2019 (N=100)	NR /PI-RAD v2 ≥ 4 of 5	**CISPCa:** GS>3+3	51% (41,61)	47% (37,57)	0.5687	51% (41,61)	39/100	0.08726
		CISPCa: GS=3+3	16% (9,25)	7% (3,14)	0.0466	16% (9,25)	16% (9,25)	1
Tonttila, 2016 (n=53) non-randomized arm of RCT	Software fusion (MRI-TRUS) (PI-RAD (NR) ≥3 of 5) /Max. 2 lesions of any MRI score or size	**CSPCa:** GS≥ 3+4	54.7% (41,68)	41.5% (28,55)	0.1795	54.7% (41,68)	35.8% (23,49)	0.0564
		CISPCa: GS=3+3	22.6% (11,34)	9.4% (2,17)	0.0696	22.6% (11,34)	15.1% (5,25)	0.3253
Van der Leest, 2019 (n=626)	TR in-bore (PI-RAD v2 ≥3 of 5) /2 to 4 per lesion	**CSPCa:** GS≥2 GS≥3+4	30.4% (27,34)	25.4% (22,29)	0.0512	30.4% (27,34)	23.3% (20,27)	0.0052
		CISPCa: G≥2 GS≥3+4	23% (20,26)	14.1% (11,17)	0.0001	23% (20,26)	24.8% (21,28)	0.4662
Westoff, 2019 (n=307)	Software fusion / PI-RAD v2 ≥3 of 5	**CSPCa:** GS≥3+4	46% (41,52)	37.5% (32,43)	0.0271	46% (41,52)	39.4% (34,45)	0.08726
		CISPCa: GS=3+3	25% (21,31)	19% (15,24)	0.0658	25% (21,31)	26.7% (22,32)	0.71138
Zalesky, 2019 (n=211)	Software fusion / PI-RAD v2 ≥3 of 5	**CSPCa:** GS≥7	40.3% (34,47)	30.3% (24,37)	0.0324	40.3% (34,47)	39.8% (33,47)	0.9203
		CISPCa: GS=6	13.3% (9,19)	4.7% (2,09)	0.0222	13.3% (9,19)	11.8% (8,17)	0.6599
Zhang, 2017 (n=224)	Cognitive fusion (free hand TP MPMRI/TRUS) (PI-RAD v1 ≥ 2of 5) / mean 3.5 (± 1.84)	**CSPCa:** GS ≥ 7	28.1% (22,34)	26.3% (21,32)	0.6716	28.1% (22,34)	15.6% (10,20)	0.0016
		CISPCa: GS = 6	22.3% (17,28)	17.9% (13,23)	0.4157	22.3% (17,28)	19.2% (14,24)	0.4157

Abbreviations: CI = confidence interval; CSD = clinically significant disease; CSPCa = clinically significant prostate cancer; CISPCa = clinically insignificant prostate cancer; GS = Gleason Score; ITT = intention to treat; MCCL = maximum cancer core length; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging-Reporting and Data System; PP = per protocol; pt = patient; RCT = randomized controlled trial; RD = risk difference; TB = target biopsy; TP = transperineal; TR = transrectal; TRUS-SB = transrectal ultrasound-guided systematic biopsy.

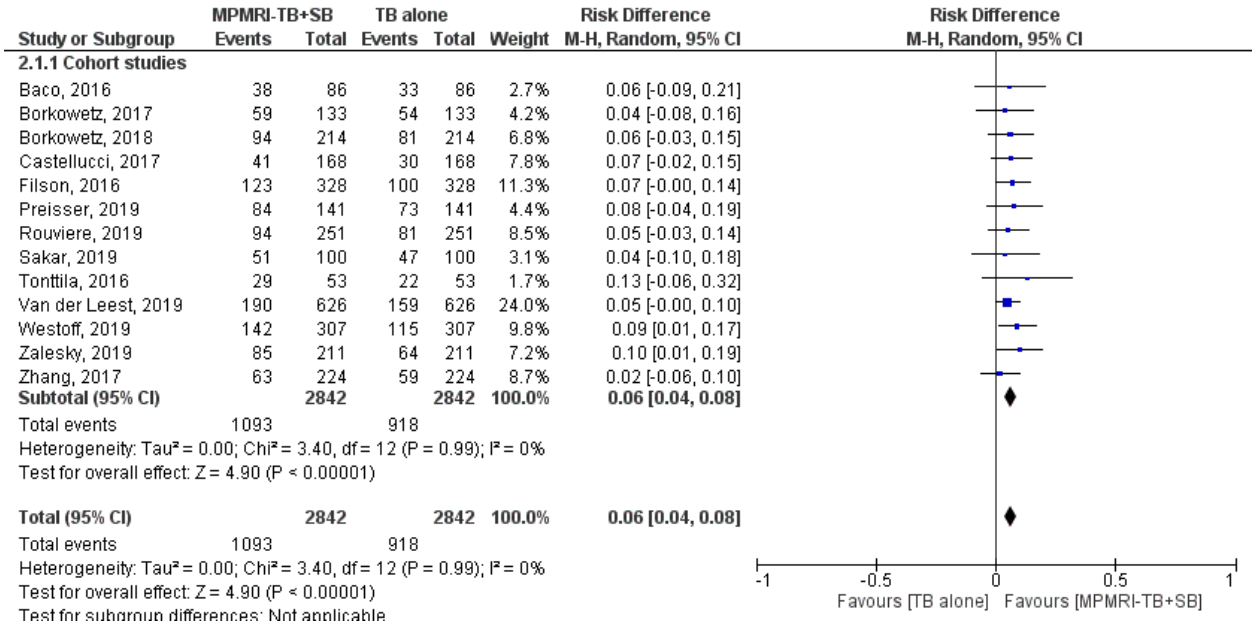

Figure 2.1: (MPMRI-TB+ TRUS-SB vs. MPMRI-TB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men

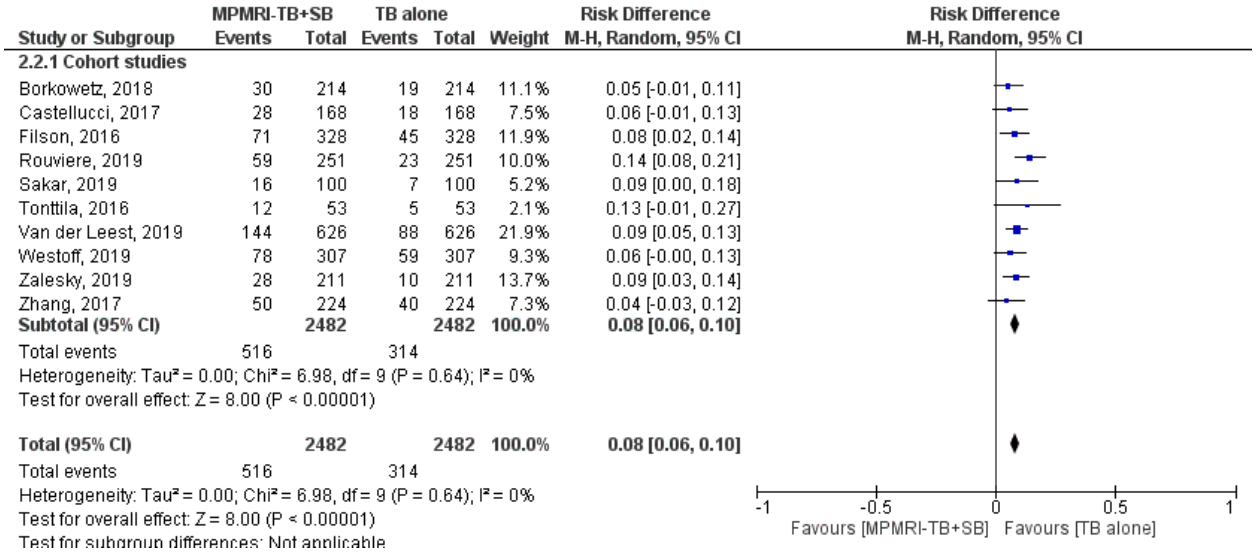

Figure 2.2: (MPMRI-TB+ TRUS-SB vs. MPMRI-TB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men

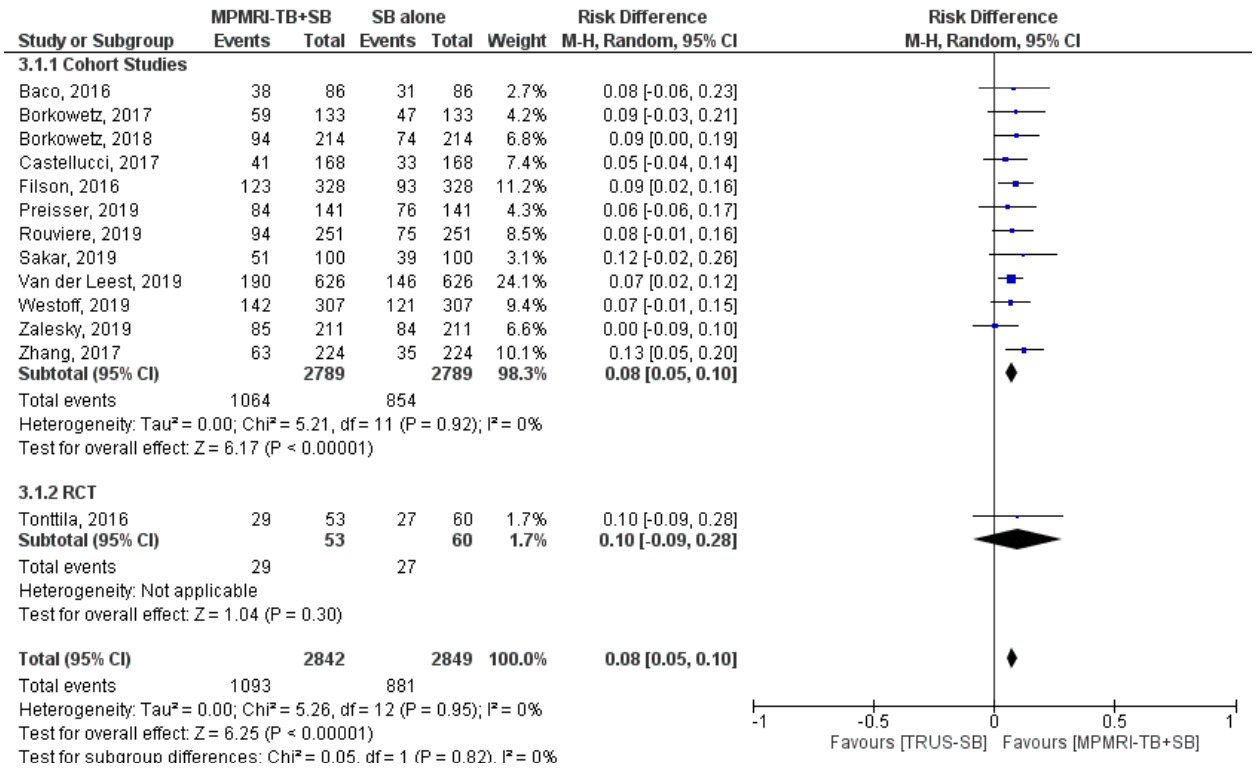

Figure 3.1: (MPMRI-TB+ TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men

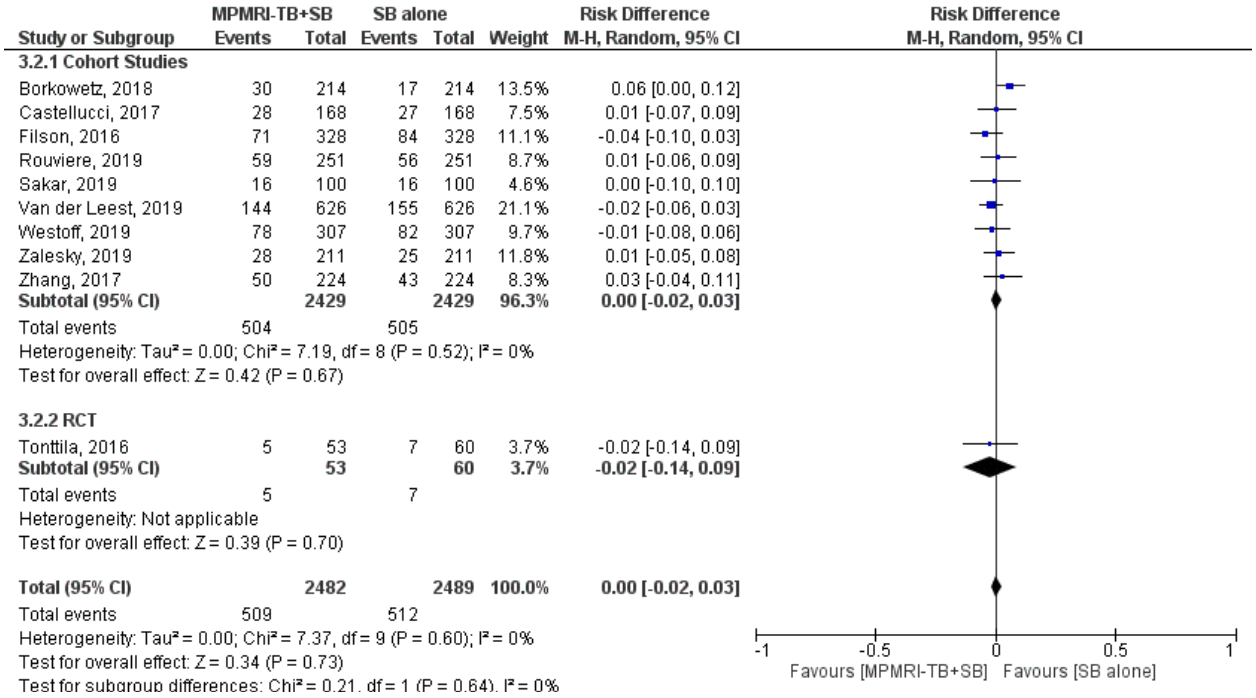

Figure 3.2: (MPMRI-TB+ TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men

Previously negative patients (Question 2)

Q2a MPMRI-TB vs. Reference Standard

Risk of bias assessment for individual studies

Seven studies assessed the diagnostic accuracy of MPMRI (±TB) against the reference standard (TTMB). Appendix 5a shows the risk of bias and applicability using the QUADAS-2 tool [4,5]. Three [5,18,67] of the seven studies were assessed as being at low risk of bias on the domain of patient selection and the remaining studies were assessed as unclear. All studies were rated at low risk of bias on the domain of index testing. One study [5] was assessed as being at moderate risk of bias on the reference standard domain mainly due to lack of blinding of the outcome assessors; the remaining were assessed as either unclear [18,19,31] or low [26,32-34] on risk of bias for this domain. Studies were assessed as either unclear [32-34] or low [5,18,26,31] on risk of bias on the domain of flow and timing. All studies were assessed as being at low risk for the applicability concerns regarding patient selection, index testing and the reference standard. One of the seven articles addressing this question was assessed overall at being at moderate risk of bias [5] on the QUADAS-2 tool and five were assessed overall at being at unclear [18,31-34] risk of bias. The final study was assessed overall at being at low risk of bias on the QUADAS-2 tool [26] (see Appendix 5).

The sensitivities across the seven studies assessing the diagnostic accuracy of MPMRI (±TB) for previously negative patients were somewhat comparable, ranging between 78.2% [34] and 100% [32]. However, specificities varied among the studies, ranging from 39% [18,31] to 100% [32] for MPMRI alone and 30% [26] to 77% [34] for MPMRI-TB (see Table 4-5). The aggregate study evidence certainty for the comparisons was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

***Outcomes** (MPMRI-TB vs. Reference Standard)*

Table 4-5 shows the diagnostic accuracy of MPMRI (±TB) compared with a reference standard for the seven cohort studies [4,5,26,31-34] reporting diagnostic accuracy outcomes for MPMRI (±TB) in previously negative patients. All but one of the studies [32] had a threshold of ≥3 of 5 scores. Four studies compared MPMRI alone to a reference standard [18,31-33] and three compared the reference standard to MPMRI followed by software fusion-guided targeted biopsy[5,26,34]. Reported mean/median age ranged from 62 [26,34] to 66 [31] years and PSA ranged from 6.7 ng/mL [5] to 9.7 ng/mL [31] (see Table 4-1).

MPMRI Alone

In the 2016 Hansen et al. study [18] the prevalence of CSPCa among 295 patients was 27%. Using MPMRI alone, the sensitivity and specificity of MPMRI to detect CSPCa was 90% (95% CI, 84 to 110) and 39% (95% CI, 32 to 45), respectively, indicating that 10% of true CSPCa patients were missed and 61% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 36% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 9% (NPV=91%) were true CSPCa patients (see Table 4-5).

In the 2017 Hansen et al. study [31] the prevalence of CSPCa among 487 patients was 31%. Using MPMRI alone, the sensitivity and specificity of MPMRI to detect CSPCa was 93% (95% CI, 88 to 97) and 39% (95% CI, 34 to 45), respectively, indicating that 7% of true CSPCa patients were missed and 61% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 40% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 8% (NPV=92%) were true CSPCa patients (see Table 4-5).

In the 2015 Pepe et al. study [32] the prevalence of CSPCa among 100 patients was 13%. Using MPMRI alone, the sensitivity and specificity of MPMRI to detect CSPCa was 100% (95% CI, 100 to 100) and 100% (95% CI, 100 to 100), respectively, indicating that 0% of true CSPCa patients were missed and 0% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 0% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 0% (NPV=100%) were true CSPCa patients (see Table 4-5).

In the 2018 Pepe et al. study [33] the prevalence of CSPCa among 1032 patients was 26%. Using MPMRI alone, the sensitivity and specificity of MPMRI to detect CSPCa was 84% (95% CI, 79 to 88) and 72% (95% CI, 69 to 76), respectively, indicating that 16% of true CSPCa patients were missed and 28% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 52% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 7% (NPV=93%) were true CSPCa patients (see Table 4-5).

MPMRI-TB

In the Mortezavi 2018, et al. study [5] the prevalence of CSPCa among 86 patients was 30%. Using MPMRI plus software fusion TB, the sensitivity and specificity of MPMRI to detect CSPCa was 81% (95% CI, 66 to 96), and 52% (95% CI, 39 to 64), respectively, indicating that 19% of true CSPCa patients were missed and 48% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 42% (PPV) had CSPCa; among the MPMRI-negative patients, 14% (NPV=86%) were true CSPCa patients (see Table 4-5).

In the 2017 Pepe et al. study [34] the prevalence of CSPCa among 150 patients was 37%. Using MPMRI plus software fusion TB, the sensitivity and specificity of MPMRI to detect CSPCa was 78% (95% CI, 67 to 89) and 77% (95% CI, 68 to 85), respectively, indicating that 22% of true CSPCa patients were missed and 23% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 66% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 14% (NPV=86%) were true CSPCa patients (see Table 4-5).

In the 2017 Simmons et al. study [26] the prevalence of CSPCa among 249 patients was 41%. Using MPMRI plus software fusion TB, the sensitivity and specificity of MPMRI to detect CSPCa was 94% (95% CI, 89 to 97) and 30% (95% CI, 20 to 41), respectively, indicating that 6% of true CSPCa patients were missed and 70% of patients without CSPCa were falsely diagnosed. Among the MPMRI-positive patients, 73% (PPV) of patients had CSPCa; among the MPMRI-negative patients, 31% (NPV=69%) were true CSPCa patients (see Table 4-5).

Table 4-5. Cohort studies examining (Q2a) MPMRI (±TB) in previously negative patients (compared with reference standard) by different definitions of clinically significant cancer

Study (Prevalence of CSPCa)	Index test	Positive MRI	Reference standard	CSPCa Definition	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
MPMRI Alone								
Hansen, 2016 n=295 (27%)	T2WI+DWI+DCE	PI-RAD v1 ≥3 of 5	24-core TRUS-SB according to the Ginsburg TRUS-SB protocol	GS 7 to 10	90.1% (84,110)	38.8% (32,45)	35.8% (29,42)	91.2% (85,97)
Hansen, 2017 n=487 (31%)	T2WI+DWI+DCE	PI-RAD v1&2 ≥3 of 5	18-24 core TRUS-SB TP according to the Ginsburg TRUS-SB protocol	GS 7 to 10	92.6% (88,97)	39.3% (34,45)	40.2% (35,45)	92.4% (88,97)
Pepe, 2015 n=100 (13%)	T2WI+DWI+ DCE+spectroscopy	PI-RAD v1 ≥4 of 5	TP saturation biopsy	GS ≥7	100% (100,100)	100% (100,100)	100% (100,100)	100% (100,100)
Pepe, 2018 n=1032 (26%)	T2WI+DWI+DCE	PI-RAD v1&2 ≥3 of 5	TP saturation biopsy	GS ≥3+4	83.8% (79,88)	72.4% (69,76)	52.1% (47,57)	92.6% (90,95)
MPMRI-TB								
Mortezavi, 2018 n=86 (30%)	T2WI+ DWI+DCE MPMRI/TRUS fusion guided	PI-RAD (NR) ≥3 of 5	TP TPMB	GS ≥7	80.8% (66,96)	51.7% (39,64)	42% (28,56)	86.1% (75,97)
Pepe, 2017 n=150 (37%)	TRUS/MPMRI TR fusion targeted (software) biopsy (T2WI, DWI, DCE)	PI-RAD v1 ≥3 of 5	TP saturation biopsy	GS ≥3+4	78.2% (67,89)	76.8% (68,85)	66.2% (55,78)	85.9% (78,93)
Simmons, 2017, 2018 n= 249 (41%)	T2WI+DWI+DCE + Image fusion TB	PI-RAD (NR) ≥3 of 5	TP TPMB	GS ≥3 +4 and /or MCCL ≥4 mm	93.5% (89,97)	29.6% (20,41)	73.4% (67,79)	68.6% (51,83)

*using the 2014 International Society of Urologic Pathology (ISUP) criteria

CSPCa = clinically significant prostate cancer; DCE = dynamic contrast enhanced-magnetic resonance imaging; DWI = diffusion weighted imaging; GS = Gleason Score; MCCL = maximum cancer core length; MPMRI = multi-parametric magnetic resonance imagine; MRI = magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging Reporting and Data System; TB = targeted biopsy; TP = transperineal; TPMB = template prostate mapping biopsy; TR = transrectal; TRUS-SB = transrectal ultrasoud systematic biopsy; T2WI = T_2-weighted imaging.

Q2b MPMRI-TB vs. TRUS-SB

Risk of bias assessment for individual studies

Fifteen studies compared MPMRI-TB with TRUS-SB. Appendix 5c shows the risk of bias assessments for the studies using the ROBINS-I Tool [61]. All studies were rated at low risk of bias for confounding. Four studies were assessed at high risk of bias for selection of participants, due to their retrospective nature or to non-consecutive patient selection [22-24,65]; two [8,27] were assessed at moderate on this domain and the remaining were rated as low. Four studies [6,27-29] was assessed at low risk of bias on measurement of intervention and one [65] was assessed at being at high risk of bias; the remaining studies were assessed as being at moderate risk of bias on measurement of intervention mainly due to different version of PI-RAD being used during the study period or lack of clarity regarding measurement. Nine studies [6,11,22-24,27-30] were assessed as being at low risk of bias for departure from intervention; the remaining studies were rated as moderate on this domain due to lack of clarity on measurement. Four studies [6,12,65,66] were assessed as being at moderate risk of bias due to missing data and the remainder was assessed as being at low risk of bias on this domain. All studies measuring detection rates were assessed as being at moderate risk of bias on measurement of outcome either because it was unclear whether the outcome assessor was blinded to the index test when measuring the reference standard or because no reference standard was used to assess the accuracy of both the MPMRI and TRUS-SB detection. Three of the studies [8,22,65] were rated at moderate risk of bias on the domain of selection of reported results and the remaining studies were rated low on this domain. Overall, two [28,29] of the studies were assessed at being at low risk of bias and six [21-24,65,66] were assessed at high risk of bias. The remaining studies were assessed at being at moderate risk of bias (see Appendix 5).

The aggregate study evidence certainty for the comparisons was moderate to low after considering the four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

***Outcomes** (MPMRI-TB vs. TRUS-SB)*

Table 4-6 shows the detection rates of MPMRI-TB versus TRUS-TB for previously negative patients. Fifteen studies with a definition of CSPCa of GG ≥2 reported detection rates for MPMRI-TB versus TRUS-SB in previously negative men. Two were non-randomized interventions arms from RCTs [6,27]. Twelve studies used software fusion-guided targeted biopsy[6,8,11,12,20-24,27,30,65], one used cognitive fusion [66], and two used either software or cognitive fusion targeted biopsy[28,29] (see Table 4-6).

Estimates for CSPCa for the studies of previously negative patients show an overall effect of 0.05 (95% CI, 0.03 to 0.07, p<0.0001) (Figure 4.1). For CISPCa, the overall effect is -0.07 (95% CI, -0.09 to -0.04, p<0.00001) (Figure 4.2).

Table 4-6. Cohort studies examining (Q2b) detection rates of MPMRI-TB and TRUS-SB in previously negative patients by different definitions of clinically significant cancer

Study (n)	MRI Navigation system (positive MRI definition)/+MRI definition (n) /-MRI definition (n)	Cores	CSPCa/CISPCa definition	MRI/TB DR (95% CI)	Missed if not done	TRUS-SB DR (95% CI)	Missed if TRUS-SB not done	p-value
Alberts, 2018 (n=84) non-randomised arm of RCT	Software fusion(TRUS-Bx) /PI-RAD ≥3 of 5	TB: 2 per lesion TRUS-SB: 12	**CSPCa:** (GS≥3+4)	3.6% (0,8)	1.2% (1/84)	4.8% (0,9)	2.4% (2/84) MRI-1/64 MRI+1/20	0.7004
			CISPCa: (GS=3+3)	7.1% (2,13)	4.8% (4/84)	23.8% (20,40)	21.4% (18/84) MRI-17/64 MRI+1/20	0.0003
Arsov, 2015 (n=104) non-randomised arm of RCT	Software fusion (TR or TP) /PI-RAD v1&2 ≥3 of 5	TB: 2 targeted cores from each lesion TRUS-SB: 12	**CSPCa:** (GS≥3+4)	26% (18,34)	6.7% (7/104)	25% (17,33)	5.8% (6/104) MRI- NR MRI+ NR	0.8124
			CISPCa: (GS=3+3)	7.7% (3,13)	2.9% (3/104)	9.6% (4,15)	4.8% (5/104) MRI- NR MRI+ NR	0.6545
Boesen, 2018 (n=289)	Cognitive fusion (n=83), software fusion (n=289) /PI-RAD v1 ≥3 of 5	TB: 1-2 per lesion TRUS-SB: 10	**CSPCa:** (GS≥3+4)	27% (22,32)	10% (29/289)	20.4% (16,25)	3.5% (10/289) MRI- NR MRI+ NR	0.0641
			CISPCa: (GS=3+3)	6.2% (3,9)	2.1% (6/289)	17% (13,21)	12.8% (37/289) MRI- NR MRI+ NR	0.0001
Borkowetz, 2017 (n=445)	Software fusion (fusPbx TP - combined with TR at one site and TR sysPbx at another site) /PI-RAD v1&2 ≥2 of 5	TB: min. 2 per lesion TRUS-SB: 12	**CSPCa:** (GS≥7)	31.2% (27,36)	11.7% (52/445)	23.8% (20,28)	4.3% (19/445) MRI- NR MRI+ NR	0.0136
			CISPCa: (GS=6)	8.1% (6,11)	NR	8.1% (6,11)	NR	0.9028
Exterkate, 2020 (n=152)	Software fusion or cognitive fusion or MRI-TB /PI-RAD v1&2 ≥3 of 5	TB: med. 3 (3-4) TRUS-SB: 10 (8-12)	**CSPCa:** (GS≥3+4)	33.6% (26,41)	19.1% (29/152)	15.8% (11,22)	1.3% (2/152) MRI- NR MRI+ NR	<0.001
			CISPCa: (GS=3+3)	13.2% (9,21)	5.3% (8/152)	16.4% (11,22)	7.9% (12/152) MRI- NR MRI+ NR	0.421
Filson, 2016 (n=324)	Software fusion /PI-RAD v2 ≥3 of 5	TB: 1 core per 3mm of the longest ROI axi TRUS-SB: 12	**CSPCa:** (GS ≥ 3+4)	18.5% (14,23)	NR	14.8% (11,19)	NR	0.2068
			CISPCa: (GS =3+3)	7.1% (4,10)	NR	14.8% (11,19)	NR	0.0018
Lian, 2017 (n=101)	Software fusion /PI-RAD v2, ≥ 3 of 5	TB: at least each one core in axial and sagittal planes TRUS-SB:TB	**CSPCa: (**GS ≥ 3 + 4 or GS 6 with MCCL ≥ 4 mm)	21.8% (14,30)	11.9% (12/101)	12.9% (6,19)	3% (3/101) MRI- NR MRI+ NR	0.097
			CISPCa: (G/S < 3 + 4	8.9% (3,14)	5% (5/101)	13.9% (7,21)	9.9% (10/101) MRI- NR	0.271

Table 4-6. Cohort studies examining (Q2b) detection rates of MPMRI-TB and TRUS-SB in previously negative patients by different definitions of clinically significant cancer

Study (n)	MRI Navigation system (positive MRI definition)/+MRI definition (n) /-MRI definition (n)	Cores	CSPCa/CISPCa definition	MRI/TB DR (95% CI)	Missed if not done	TRUS-SB DR (95% CI)	Missed if TRUS-SB not done	p-value
			or GS 6 with MCCL ≥ 4 mm)				MRI+ NR	
Mannaerts, 2019 (n=159)	Software fusion (MRI-TRUS fusion) /PI-RAD v2 ≥3 of 5	TB: 2 to 4 per lesion TRUS-SB: 12	**CSPCa:** (GS≥3+4)	11.9% (7,17)	3.1% (5/159)	14.5% (9,20)	6.9% (11/159) MRI- 5/65 MRI+ 6/94	0.5086
			CISPCa: (GS=3+3)	3.1% (0,6)	1.3% (2/159)	15.1% (10,21)	13.2% (21/159) MRI- 13/65 MRI+ 8/94	0.0003
Mariotti, 2016 (n=143)	Software fusion (MRI-TRUS fusion) /PI-RAD (NR) ≥3 of 5	TB: 2 or 3 from each target TRUS-SB: 12	**CSPCa:** (GS≥3+4)	22.4% (16,29)	14% (20/143)	12.6% (7,18)	4.2% (6/143) MRI-3/94 MRI+3/49	0.0309
			CISPCa: (GS=3+3)	11.9% (7,17)	5.6% (8/143)	28.7% (21,36)	22.4% (32/143) MRI-21/94 MRI+1149	0.0006
Meng, 2016 (n=172)	Software fusion (MRI-US) /PI-RAD (NR) ≥3 of 5	TB: 4 per lesion TRUS-SB: 12	**CSPCa:** (GS≥7)	16.3% (11,22)	NR	9.3% (5,14)	NR	0.0544
			CISPCa: (GS=6)	8.1% (4,12)	NR	9.3% (5,14)	NR	0.7028
Preiser, 2019 (n=78)	MRI/ultrasound software fusion-guided TB / PI-RAD v.2 ≥3 of 5	TB: NR TRUS-SB: 12	**CSPCa:** (GS≥3+4)	25/78	NR	24/78	NR	0.8650
			CISPCa: (GS=3+3)	5/78	NR	7/78	NR	0.5485
Say, 2016 (n=143)	Software fusion (MRI-US) /PI-RAD v1 ≥3 of 5	TB: at least one biopsy core taken per target TRUS-SB: 12	**CSPCa:** (GS ≥ 3+4)	23.1% (16,30)	9.1% (13/143)	18.2% (12,26)	4.2% (6/143) MRI- 0/22 MRI+ 6/121	0.3850
			CISPCa: (GS =3+3)	11.2% (6,16)	7% (10/143)	16.8% (11,23)	12.6% (18/143) MRI- 3 /22 MRI+ /121	0.1748
Sidana, 2018 (n=779)	Cognitive fusion /PI-RAD v2 ≥3 of 5	TB: 4 per lesion TRUS-SB: 12	**CSPCa:** (GS ≥ 3+4)	26.3% (23,29)	11.8% (92/779)	18.9% (16,22)	4.4% (34/779) MRI- NR MRI+ NR	0.0005
			CISPCa: (GS=3+3)	8.1% (6,10)	4% (31/779)	15.1% (13,18)	11% (86/779) MRI- NR MRI+ NR	0.0000
Westoff, 2019 (n=210)	Software fusion / PI-RAD v2 ≥3 of 5	TB: Med. 2 (IQR 2-3) SB: 12	**CSPCa:** (GS≥3+4)	31% (25,38)	NR	30.5% (24,37)	NR	0.9124
			CISPCa: (GS=3+3)	12.4% (8,18)	NR	20.5% (15,27)	NR	0.0251
Zalesky, 2019 (n=174)	Software fusion / PI-RAD v2	TB: mean 2.21 cores per lesion	**CSPCa:** (GS≥7)	27% (21,34)	NR	25.3% (19,32)	NR	0.7114

Table 4-6. Cohort studies examining (Q2b) detection rates of MPMRI-TB and TRUS-SB in previously negative patients by different definitions of clinically significant cancer

Study (n)	**MRI Navigation system (positive MRI definition)/+MRI definition (n) /-MRI definition (n)**	**Cores**	**CSPCa/CISPCa definition**	**MRI/TB DR (95% CI)**	**Missed if not done**	**TRUS-SB DR (95% CI)**	**Missed if TRUS-SB not done**	**p-value**
	≥3 of 5	SB: NR	**CISPCa:** (GS=6)	6.9% (4,12)	NR	13.8% (9,20)	NR	0.0349

*using the 2014 International Society of Urologic Pathology (ISUP) criteria
CI = confidence interval; CISPCa = clinically insignificant prostate cancer; CSPCa = clinically significant prostate cancer; DR = detection rate; fusPbx = fusion biopsy; GS = Gleason Score; MCCL = maximum cancer core length; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging Reporting and Data System; pop. = population; RCT = randomized controlled trial; ROI = regions of interest; sysPbx = systematic biopsy; TB = targeted biopsy; TP = transperineal; TR = transrectal; TRUS-SB =transrectal ultrasound systematic biopsy; US = ultrasound.

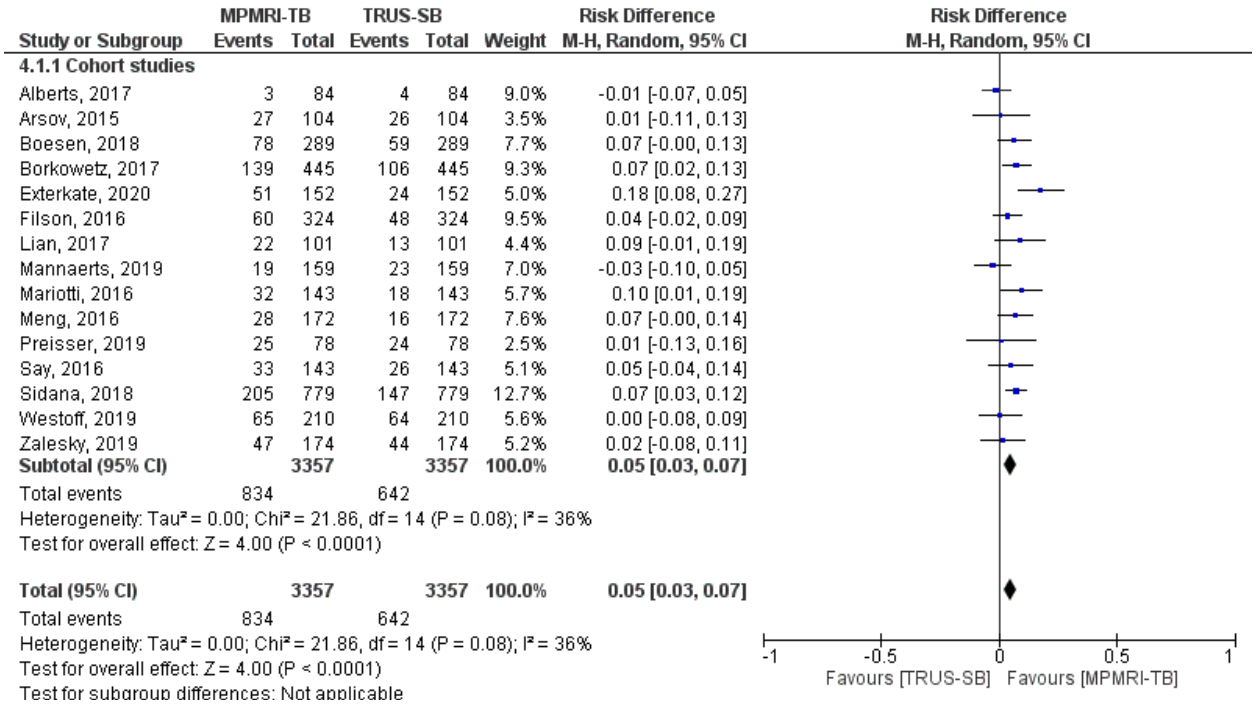

Figure 4.1: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for previously negative men

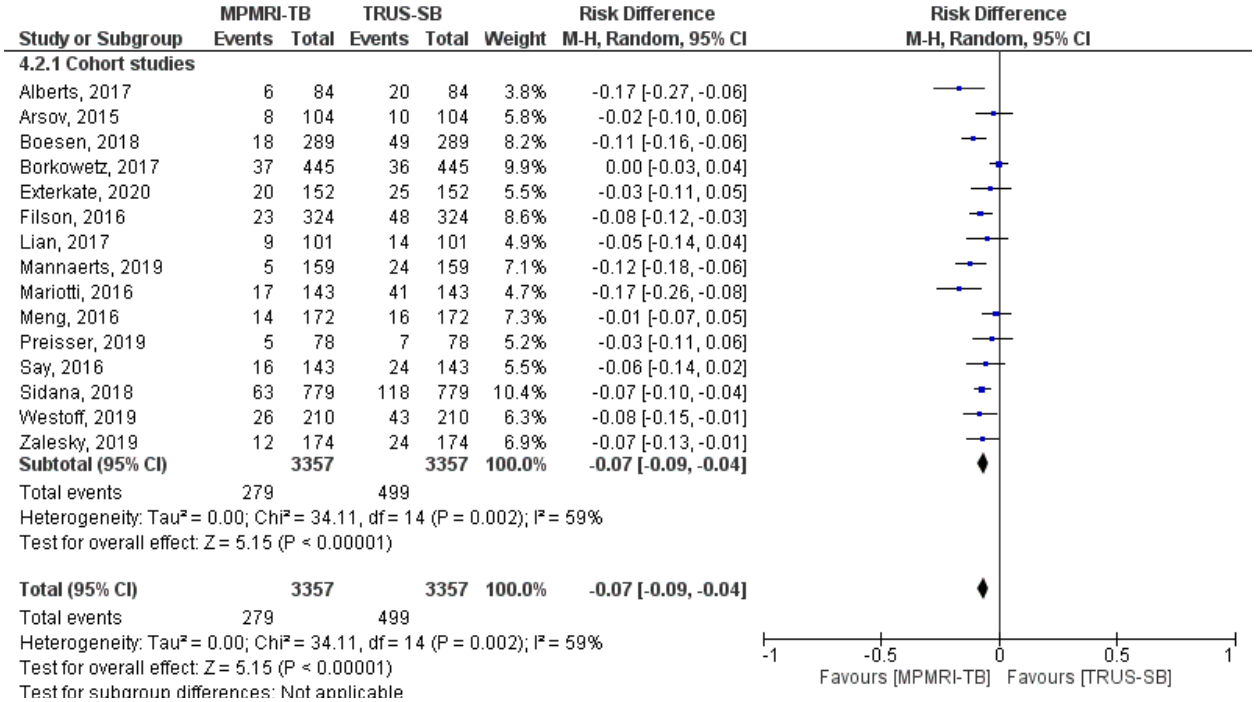

Figure 4.2: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for previously negative men

Q2c – MPMRI-TB vs. MPMRI-TB alone or TRUS-SB alone

Risk of bias assessment for individual studies

Nine cohort studies compared MPMRI-TB with TRUS-SB. Appendix 5c shows the risk of bias assessments for the studies using the ROBINS-I tool [61]. All studies were rated at low risk of bias for confounding. Four studies were assessed at high risk of bias for selection of participants, due to their retrospective nature or to non-consecutive patient selection [22-24,65]; one [8] was assessed at moderate on this domain and the remaining were rated as low. Two studies [28,29] were assessed at low risk of bias on measurement of intervention and one [65] was assessed at being at high risk of bias; the remaining studies were assessed as being at moderate risk of bias on measurement of intervention mainly due to different version of PI-RAD being used during the study period or lack of clarity regarding measurement. Seven studies [11,22-24,28-30] were assessed as being at low risk of bias for departure from intervention; the remaining studies were rated as moderate on this intervention due to lack of clarity on measurement. One study [65] was assessed as being at moderate risk of bias due to missing data and the remainder were assessed as being at low risk of bias on this domain. All studies measuring detection rates were assessed as being at moderate risk of bias on measurement of outcome either because it was unclear whether the outcome assessor was blinded to the index test when measuring the reference standard or because no reference standard was used to assess the accuracy of both the MPMRI and TRUS-SB detection. Three of the studies [8,22,65] were rated at moderate risk of bias on the domain of selection of reported results and the remaining studies were rated low on this domain. Overall, two [28,29] of the studies were assessed at being at low risk of bias and four [22-24,65] were assessed at high risk of bias. The remaining studies were assessed overall at being at moderate risk of bias (see Appendix 5).

Estimates for the studies comparing TB+TRUS-SB to targeted biopsy alone and TRUS-SB alone for previously negative patients show narrow confidence intervals and fall generally in the same direction of effect, with low study heterogeneity for both CSPCa and CISPCa (I^2=0% - see Figures 5.1, 5.2, 6.1, 6.2). Tests for subgroups differences among MRI technologies show no significant differences (I^2=0% – see Appendix 8 for subgroup by type of MPMRI-TB).

The aggregate study evidence certainty for the comparisons was moderate to low after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach (traditional GRADE summary tables not presented) [15].

***Outcomes** (MRI-TB vs. MPMRI-TB alone or TRUS-SB alone)*

Table 4-7 shows the detection rates of CSPCa and CISPCa for the nine studies reporting detection rates for MPMRI-TB plus TRUS-SB versus targeted biopsy alone or TRUS-SB alone. Six studies used software fusion-guided targeted biopsy [8,11,19,22,23,65], one used cognitive fusion [24], and two used cognitive/software fusion [28,29] (see Table 4-1).

TB+TRUS-SB vs.TB

Overall estimates for CSPCa show an overall effect of 0.05 (95% CI, 0.02 to 0.08, p=0.0005) (Figure 5.1). For CISPCa, the overall effect is 0.09 (95% CI, 0.06 to 0.11, p<0.00001) (Figure 5.2).

TB+TRUS-SB vs.TRUS-SB

Overall estimates for CSPCa for the five studies defining show an overall effect of 0.11 (95% CI, 0.08 to 0.14, p<0.00001) (Figure 6.1). For CISPCa, the overall effect is 0.01 (95% CI, -0.02 to 0.04, p=0.40) (Figure 6.2).

Table 4-7. Cohort studies examining (Q2c) detection rates of targeted biopsy plus TRUS-SB combined and targeted biopsy and TRUS-SB alone in previously negative patients by different definitions of clinically significant cancer

Study (n)	MPMRI Navigation system (positive MRI definition)	CSPCa/CISPCa definition	TB+TRUS-SB vs.TB alone			TB+TRUS-SB vs. TRUS-SB alone		
			TB+TRUS-SB detection rate (95% CI)*	TB alone detection rate (95% CI)	p-value	TB+TRUS-SB detection rate (95% CI)*	TRUS-SB alone detection rate (95% CI)	p-value
Boesen, 2018 (n=289)	Cognitive fusion (n=83), software fusion (n=289) /PI-RAD v1&2	**CSPCa:** GS≥3+4	30.4% (25,36)	27% (22,32)	0.3587	30.4% (25,36)	20.4% (16,25)	0.0060
		CISPCa: GS=3+3	19% (15,24)	6.2% (3,9)	0.0000	19% (15,24)	17% (13,21)	0.5164
Borkowetz, 2017 (n=445)	Software fusion (fusPbx TP - combined with TR at one site and TR sysPbx at another site) /PI-RAD v1&2 ≥2 of 5 scores	**CSPCa:** GS≥7	37.1% (33,42)	31.2% (27,36)	0.0668	37.1% (33,42)	23.8% (20,28)	0.0000
		CISPCa: GS=6	NR	NR	NR	NR	NR	NR
Exterkate, 2020 (n=152)	Software fusion or cognitive fusion or MRI-TB /PI-RAD v1&2 ≥3 of 5	**CSPCa:** GS≥3+4	34.9% (27-42)	33.6% (26,41)	0.80927	34.9% (27-42)	15.8% (11,22)	0.21022
		CISPCa: GS=3+3	18.4% (12-25)	13.2% (9,21)	0.2077	18.4% (12-25)	16.4% (11,22)	0.65084
Filson, 2016 (n=324)	Software fusion /PI-RAD v2 ≥ 3 of 5 score	**CSPCa:** GS ≥ 3+4	23.1% (19,28)	18.5% (14,23)	0.1478	23.1% (19,28)	14.8% (11,19)	0.0072
		CISPCa: GS 3+3	14.5% (11,18)	7.1% (4,10)	0.0026	14.5% (11,18)	14.8% (11,19)	0.9116
Lian, 2017 (n=101)	Software fusion /PI-RAD v2, ≥ 3 of 5	**CSPCa:** (GS ≥ 3 + 4 or GS 6 with MCCL ≥ 4 mm)	24.8% (16,33)	21.8% (14,30)	0.618	24.8% (16,33)	12.9% (6,19)	0.03313
		CISPCa: (GS < 3 + 4 or GS 6 with MCCL ≥ 4 mm)	18.5% (11,26)	8.9% (3,14)	0.04437	18.5% (11,26)	13.9% (7,21)	0.34360
Preiser, 2019 (n=78)	MRI/ultrasound software fusion-guided TB / PI-RAD v.2 ≥3 of 5	**CSPCa:** GS≥3+4	29/78	25/78	0.5029	29/78	24/78	0.3953
		CISPCa: GS=3+3	NR	NR	NR	NR	NR	NR
Say, 2016 (n=143)	Software fusion (MRI-US fusion) /PI-RAD v1 ≥ 3 of 5 score	**CSPCa:** GS ≥ 3+4	28% (21,35)	23.1% (16,30)	0.3441	28% (21,35)	18.2% (12,25)	0.0716
		CISPCa: GS = 3+3	23.8% (17,31)	11.2% (6,16)	0.0058	23.8% (17,31)	16.8% (11,23)	0.1436
Westoff, 2019 (n=210)	Software fusion / PI-RAD v2 ≥3 of 5	**CSPCa:** GS ≥ 3+4	38.1% (32,45)	31% (25,38)	0.1239	38.1% (32,45)	30.5% (24,37)	0.101
		CISPCa: GS = 3+3	18.6% (14,25)	12.4% (8,18)	0.0801	18.6% (14,25)	20.5% (15,27)	0.6241
Zalesky, 2019 (n=174)	Software fusion / PI-RAD v2 ≥3 of 5	**CSPCa:** GS≥7	35.1% (28-43)	27% (21,34)	0.1052	35.1% (28-43)	25.3% (19,32)	0.0466
		CISPCa: GS=6	13.2% (9,19)	6.9% (4,12)	0.05	13.2% (9,19)	13.8% (9,20)	0.8729

*usi using the 2014 International Society of Urologic Pathology (ISUP) criteria

CI = confidence interval; CISPCa = clinically insignificant prostate cancer; CSPCa = clinically significant prostate cancer; DR = detection rate; fusPbx = fusion biopsy; GS = Gleason Score; MCCL = maximum cancer core length; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; PI-RAD = Prostate Imaging Reporting and Data System; sysPbx = systematic biopsy; TRUS-SB = transrectal ultrasound systematic biopsy; TB = targeted biopsy; TR = transrectal; TP = transperineal, US = ultrasound

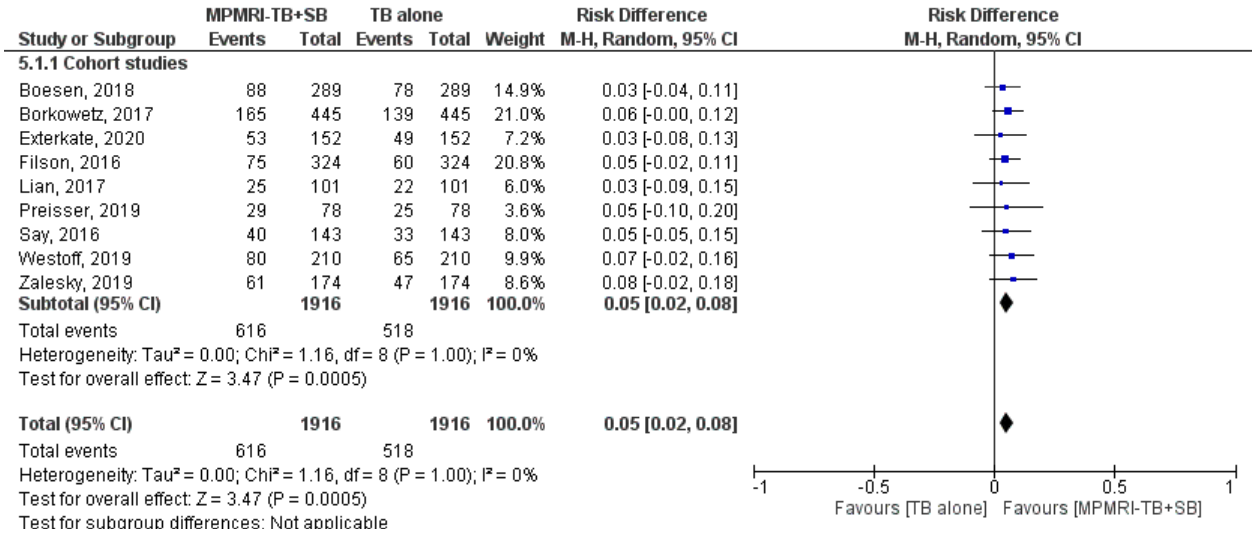

Figure 5.1: (MPMRI-TB+TRUS-SB vs. MPMRI-TB) Risk differences in detection of clinically significant prostate cancer for previously negative men

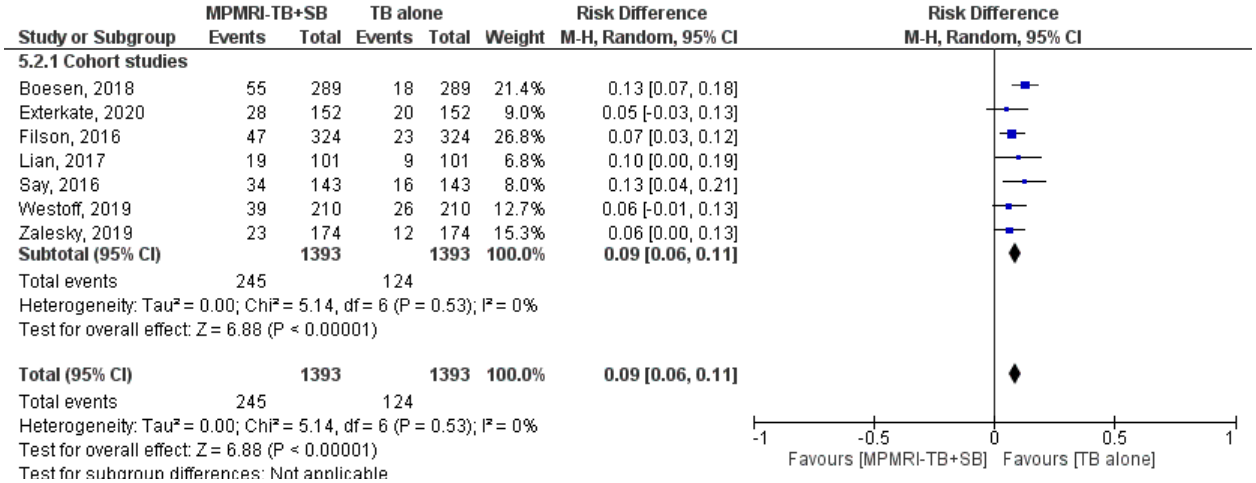

Figure 5.2: (MPMRI-TB+TRUS-SB vs. MPMRI-TB) Risk differences of clinically insignificant prostate cancer for previously negative men

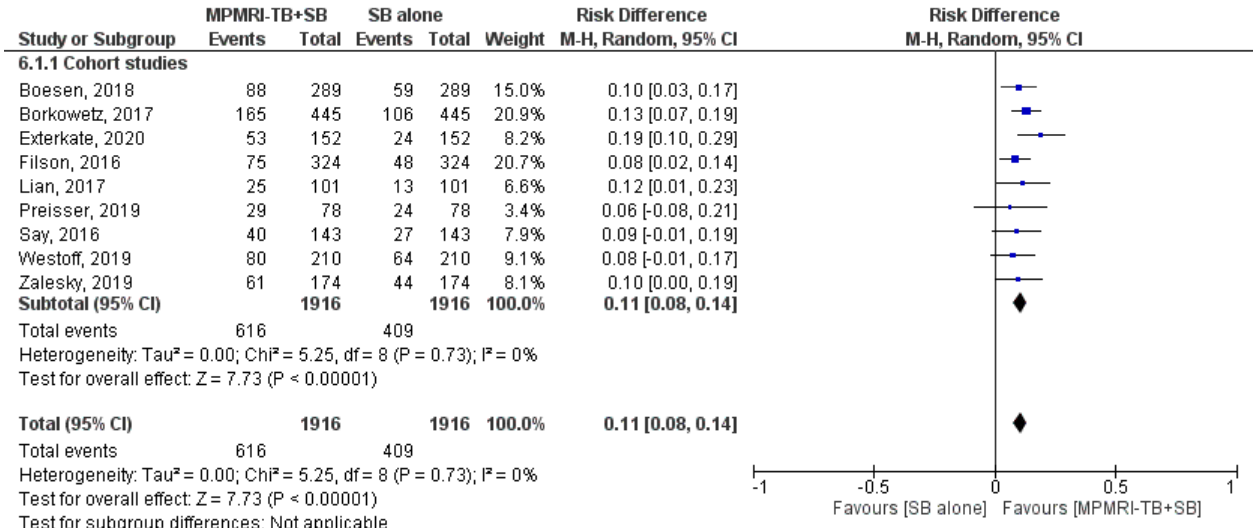

Figure 6.1: (MPMRI-TB+TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for previously negative men

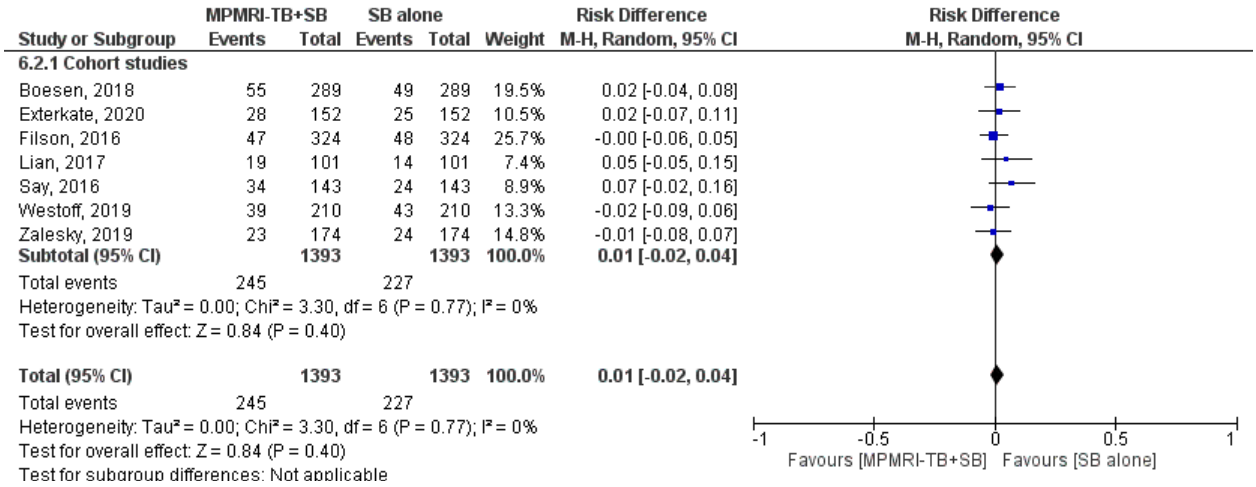

Figure 6.2: (MPMRI-TB+TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for previously negative men

Q3a Comparison between PI-RAD and non-PI-RAD Likert scales

Only one of the 36 studies reported data on the comparison between PI-RAD and non-PI-RAD Likert scales in the detection of prostate cancer. Rouviere [1] reported on 293 concordant biopsy decisions for 321 lesions (91%) among 215 patients.

Q3b Expertise of operators, MPMRI-TB techniques, optimal number of cores

Expertise of operators

None of the 36 studies compared level of reader experience and its effect on target biopsy yields. Three studies did present reader agreement scores [2,3,16], but did not relate them to reader's experience (mostly compared readings between study centres). However, this was not an outcome of interest to the study.

MPMRI-TB techniques

Table 4-8 shows the three RCTs comparing MPMRI-TB approaches/technologies. Baco et al. [7] randomized 175 biopsy-naïve men (median age 65 years, median PSA 7.3 ng/mL) to assess and compare the outcomes of two-core prostate targeted biopsy guided by computer-assisted fusion of MRI/TRUS images of suspicious lesions followed by 12 core TRUS-SB (MRI group) with that of both two-core targeted biopsy for abnormal digital rectal examination and/or TRUS-suspicious lesions and 12 core TRUS-SB (control group). Clinically significant cancer was defined as GS ≥3+4. The detection rate for CSPCa for the MRI group and control groups were 44% versus 49% (RD, -0.05 [95% CI, -0.20 to 0.10], p=0.49) and for CISPCa 15% versus 5% (RD 0.11 [95% CI, 0.02 to 0.19], p=0.02).

Arsov et al. [27] randomized 210 men to either in-bore targeted biopsy alone (study arm A: median age 66 years, median PSA 10.0 ng/mL) or software fusion-guided targeted biopsy plus TRUS-SB (study arm B: median age 68 years, median PSA 10.8 ng/mL) in patients with at least one prior negative TRUS-SB. The detection rates for CSPCa for two study arms were 29% (in-bore) versus 32% (fusion-guided targeted biopsy plus TRUS-SB) (RD -2.5 [95% CI, -0.15 to 0.10], p=0.70) and for CISPCa 8% versus 8% (RD -0.00 [95% CI, -0.07 to 0.07], p=0.97).

Wegelin et al. [58] randomized 665 patients to either of three MRI-based targeted biopsy techniques. The authors found no significant differences in detection rate of CSPSC among the three MRI-based targeted biopsy techniques (fusion-guided TB vs. cognitive registration MRI-transrectal ultrasound-TB vs. MRI-TB) (see Table 4-8). Differences in CSPCa detection rates were 2% between fusion-guided targeted biopsy and MRI-TB (p=0.8), 1% between fusion-guided targeted biopsy and cognitive registration MRI-transrectal ultrasound targeted biopsy (p>0.9), and 1% between cognitive registration MRI-transrectal ultrasound-TB and MRI-TB (p>0.9).

Optimal number of cores per target

None of the 36 studies reported on the optimal number of cores per target.

Table 4-8. (Q3b) RCTs comparing patients randomized to different MPMRI targeted biopsy approaches/technologies for biopsy-naïve and previously negative patients

Study	CSPCa/ CISPCa definition	MPMRI navigational system (positive definition)	Sample size	Biopsy cores/pt	CSD detection rate (95% CI)	Sample size	Biopsy cores/pt	CSD detection rate (95% CI)	Difference (95% CI) P-value
Biopsy Naïve		**FUS-TB plus TRUS-SB**				**TB (abn. DRE, TRUS-susp. Lesions) + TRUS-SB**			
Baco, 2016 (n=175)	GS ≥3+4	Image fusion (≥3 of 5 scores) (transperineal)	86 MRI-TB plusTRUS-SB vs. TRUS-SB + TB (palable lesion/TRUS suspicous	12 TRUS-SB plus med. 2-core TB, range 1-4	44% (38/86)	89	12 TRUS-SB plus 2-core TB for abnormal DRE and/or TRUS suspicious lesions	49% (44/89)	-0.05 (-20 to 0.10, p=0.49
	GS 3+3				15% (13/86)			5% (4/89)	0.11 (0.02 to 0.19), p=0.02
Previously Negative			**In-bore TB**			**FUS-TB plus TRUS-SB**			
Arsov, 2015 (n=210)	GS ≥3+4	Software fusion and in-bore (≥3 of 5 scores) (transrectal or transperineal)	106	2 from each lesion	29.2% (31/106)	104	12 plus 2 from each lesion	31.7% (33/104)	-2.5 (-15 to 10) p=0.7
	GS 3+3				7.5% (8/106)			7.7% (8/104)	-0.00% (-.07 to .07) P=0.97

Previously Negative		FUS-TB (n = 79)		COG-TB (n = 78)		MRI-TB (n = 77)		P-value
Study	**CSPCa/ CISPCa definition**	**Med. biopsy cores/pt**	**Detection rate of csPCa, n (%)**	**Med. biopsy cores/pt**	**Detection rate of csPCa, n (%)**	**Med. biopsy cores/pt**	**Detection rate of csPCa, n (%)**	**Pearson chi-square**
Weglin, 2019 (n=665)	GS ≥3 + 4	4 (IQR 3–5)	27 (34.2)	3 (IQR 3-4)	26 (33.3)	2 (IQR 2-3)	25 (32.5)	>0.9
	GS 3+3		NR		NR		NR	NR

Abbreviations: abn.= abnormal; CI = confidence interval; COG-TB = cognitive registration MRI-transrectal ultrasound; CSD = clinically significant disease; CSPCa = clinically significant prostate cancer; CISPCa = clinically insignificant prostate cancer; DRE = abnormal digital rectal examination; FUS-TB = MRI-transrectal ultrasound fusion; GS = Gleason score; IQR = interquartile range; MCCL = maximum cancer core length; Med. = median; MPMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; NR = not reported; pt = patient; RCT = randomized controlled trial; TB = target biopsy; TRUS-SB = transrectal ultrasound-guided systematic biopsy; TRUS-susp = MRI-transrectal ultrasound-suspicious lesions.

Adverse Events and Other Study Outcomes

MPMTI-TB reported adverse events included sepsis (0.4%), prostatitis (1.2%) [16], prostatitis (1%) [1], complicated urinary tract infection (3%), lower urinary tract symptoms (3%), and bleeding (1.5%) [2]. See Appendix 6 for a complete list of reported adverse events.

No patient outcomes regarding a positive change in patient management or survival were reported in the included studies.

ONGOING, UNPUBLISHED, OR INCOMPLETE STUDIES

Table 4-9 includes ongoing studies and studies that have reported an interim analysis, but are not yet complete. Studies that have closed, but have not yet been published, are also included.

Table 4-9. Ongoing Studies

Protocol ID(s)	Title and details of study
NCT03960112	**Official title:** Multicentric Evaluation of the True Negative Predictive Value of Multiparametric MRI for the Detection of Prostate Cancer Using Cystoprostatectomy Specimen as Reference Standard **Study type: Treatment groups:** MPMRI vs. Reference Standard **Estimated enrolment:** 150 **Start date:** May 1, 2020 **Date trial summary last modified:** Jan. 10, 2020 **Estimated primary completion date:** July 1, 2022 **Status:** Not yet recruiting **Primary results reported:** none
NCT03572946	**Official title:** Targeted Biopsy or Standard Biopsy for Clinical Significant Prostate Cancer Detection **Study type: Treatment groups:** MPMRI vs. TRUS-SB **Estimated enrolment:** 400 **Start date:** Oct. 9, 2018 **Date trial summary last modified:** Oct. 14, 2019 **Estimated primary completion date:** Oct. 14, 2019 **Status:** Recruiting **Primary results reported:** none
NCT02936258	**Official title:** PRostate Evaluation for Clinically Important Disease: MRI vs.Standard Evaluation Procedures **Study type: Treatment groups:** MPMRI vs. TRUS-SB **Estimated enrolment:** 450 **Start date:** Nov., 2016 **Date trial summary last modified:** Feb. 22, 2018 **Estimated primary completion date:** Nov., 2019 **Status:** Unknown **Primary results reported:** none
NCT02678481	**Official title:** MR-targeted vs. Random TRUS-guided Prostate Biopsy **Study type: Treatment groups:** MPMRI vs. TRUS-SB **Estimated enrolment:** 90 **Start date:** Nov., 2014 **Date trial summary last modified:** Aug. 22, 2016 **Estimated primary completion date:** Aug., 2016 **Status:** Unknown **Primary results reported:** none
NCT02450266	**Official title:** Study Comparing MRI/Ultrasound Fusion-guided Prostate Biopsy Versus Systematic Transrectal Ultrasound-guided Biopsy **Study type: Treatment groups:** MPMRI vs. MPMRI **Estimated enrolment:** 586 **Start date:** Feb., 2015 **Date trial summary last modified:** May 21, 2015 **Estimated primary completion date:** Feb., 2018

	Status: Unknown **Primary results reported:** none
NCT02138760	**Official title:** Comparison of MRI Fusion Biopsy Techniques in Men With Elevated PSA and Prior Negative Prostate Biopsy **Study type: Treatment groups:** MPMRI vs. MPMRI **Estimated enrolment:** 400 **Start date:** Aug., 2014 **Date trial summary last modified:** May., 2014 **Estimated primary completion date:** Dec., 2015 **Status:** Unknown **Primary results reported:** none

DISCUSSION

This report updates a previous systematic review evaluating MPMRI in the diagnosis of CSPCa. The current evidence summary includes 36 studies examining the research questions, seven of which were RCTs [6,7,16,17,25,27,58], with the remainder being cohort studies.

Based on the evidence, for biopsy-naïve patients at elevated risk of CSPCa, MPMRI is recommended prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer. In five studies [3-5,18,19] where TTMB was the reference standard, sensitivity of MPMRI was reasonable at 87-96%, while NPVs were as high as 92%.

Two RCTs [16,17] compared CSPCa detection rates of MPMRI-TB versus TRUS-SB for biopsy-naïve men. In a 25-centre, non-inferiority trial (PRECISION), 500 biopsy-naïve men were randomized to either MPMRI + MPMRI-TB, if a lesion was detected, or TRUS-SB. MPMRI-TB detected significantly more CSPCa compared with TRUS-SB (38% vs. 26%, p=0.005). MPMRI-TB detected significantly less CISPCa than TRUS-SB (9 vs. 22% p<0.001) [16]. Porpiglia et al. [17] randomized 212 men to either MPMRI-TB or TRUS-SB. MPMRI-TB detected significantly more CSPCa compared with TRUS-SB (44% vs. 18%, p<0.001) in this study. Thus, MPMRI when combined with MPMRI-TB reduces CISPCa detection rates, without an overall reduction in CSPCa detection rates while reducing the number of men undergoing biopsy. The PRECISE trial [81] was a third multicentre RCT for biopsy-naïve men performed in Canada. This trial was published just at the time of writing of this guideline. The study design was similar to the PRECISION trial and involved five Canadian centres, three of which were in Ontario. MPMRI-TB and TRUS-SB were compared for 453 biopsy-naïve men. As with the PRECISION trial, the PRECISE trial showed non-inferiority of the MPMRI-TB . Biopsy was avoided in over one-third of men with a reduction in the diagnosis of CISPCa from 22% to 10%. In addition, there were fewer biopsy-related complications in the MRI arm [81].

Sixteen cohort studies [1,2,6-14,20,21,23,24] presented detection rates comparing MPMRI-TB to TRUS-SB for biopsy-naïve men and, of these, two [1,2] were prospective MCTs. A paired diagnostic study (MRI-FIRST) [1] enrolled 251 patients. Patients received both TRUS-SB and MPMRI-TB. There were no significant differences in detection of CSPCa in MPMRI-TB versus TRUS-SB (32% vs. 30%). However, MPMRI-TB detected significantly less CISPCa than TRUS-SB (6% vs. 20%, p<0.0001). Five percent of CSPCa was detected by TRUS-SB that was missed by MPMRI-TB and 8% was detected by MPMRI-TB and missed by TRUS-SB. Thus, detection of CSPCa was improved by combining both TRUS-SB and MPMRI-TB [1]. Another prospective MCT enrolled 646 men to receive MPMRI followed by TRUS-SB and in-bore MPMRI-TB [2]. This study showed similar CSPCa detection rates (25% vs. 23%); however, CISPCa was detected in significantly fewer patients by MPMRI-TB than in TRUS-SB (14% vs. 25%, p<0.0001). MPMRI-TB enabled biopsy avoidance in 49% of patients while missing only 35 cases with CSPCa. Meanwhile, TRUS-SB would have over-detected CISPCa in 20% of patients [2]. In summary, TRUS-SB does detect additional CSPCa when combined with MPMRI-TB but the principal advantage of MPMRI in this population,

which is biopsy avoidance, would be lost if all patients still underwent TRUS-SB. This recommendation of TRUS-SB combined with MRI-TB was made for MPMRI-positive patients in these guidelines

Based on the evidence, in patients who had a prior negative TRUS-SB and demonstrated an increased risk of having CSPCa, MPMRI should be performed. The overall improvement across studies in CSPCa detection for MPMRI-TB plus TRUS-SB compared with TRUS-SB alone was 11% (95% CI, 8 to 14%, p<0.00001) (Section 4 - Figure 6.1). Recent estimates suggest that between 0% [32] and 31% [34] of patients with CSPCa may be missed if patients with a negative MPMRI are not biopsied. Seven studies reported on the diagnostic accuracy of MPMRI for previously negative patients [4,5,26,31-34]. As a group, the seven studies showed sensitivities of 78%-100%, specificities of 30%-100%, PPVs of 36%-100%, and NPVs of 69%-100% (Table 4-5). The overall improvement in CSPCa detection rate for the 15 cohort studies comparing MPMRI-TB alone to TRUS-SB was 5% (95% CI, 3 to 7%, p<0.0001) (Section 4 - Figure 4.1) with a reduction of CISPCa detection of 7% (95% CI, 4 to 9%, p<0.0001) (Section 4 - Figure 4.2). The overall improvement in CSPCa detection for the five cohort studies comparing MPMRI-TB plus TRUS-SB to MPRMRI-TB alone was 5% (95% CI, 2 to 8%, p=0.0005) (Section 4 - Figure 5.1). In comparison to the biopsy-naïve population there is a consistent improvement in CSPCa detection when performing MPMRI-TB compared with TRUS-SB.

Recommendation 3 is based on expert opinion and is an essential component of the successful implementation of these guidelines. Further work is needed in the development of quality assurance standards for MPMRI to be successfully implemented across the province.

Study limitations

There are several limitations in the literature examining MPMRI in the diagnosis of prostate cancer. First, the definitions of clinically significant cancer varied across studies. To combat this, we focused on studies with a definition of CSPCa of GG ≥2 (GS ≥3+4). Likewise, the definition of MPMRI-positive results varied; although most studies used a score ≥3 of 5, a few used scores of ≥4 of 5 [10,32] and ≥2 of 5 [8,9,14]. A lower threshold of the PI-RAD score may result in a higher sensitivity and fewer true CSPCa patients will be missed, with the trade-off being more non-clinically significant patients will have an unnecessary biopsy after MPMRI because of a lower specificity. Fourth, MPMRI techniques differed among studies, and subgroup analysis was performed to combat this (see Appendix 8). However, this made for smaller sample sizes when examining these groups. Fifth, and most notably, when comparing detection rates of CSPCa and CISPCa between MPMRI (±TB) and TRUS-SB, for many of the studies no pre-planned reference standards were used to confirm the results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy. Thus, we do not know the true rate of false negative and false positives for either biopsy technique (MPMRI-TB and TRUS-SB). Finally, no patient outcomes were reported regarding positively changing patient management or survival outcomes.

CONCLUSIONS

Based on the existing evidence, the guideline Working Group recommends MPMRI prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer. The recommendation for performing MPMRI in patients with prior negative biopsy remains unchanged from the prior guideline. Performing MPMRI and MPPRI-TB according to the current PI-RADS standard is a requirement. Finally, the establishment of a quality assurance program will be essential for implementation across the province.

Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the nine members of the GDG Expert Panel, eight members voted and one abstained, for a total of 89% response in August 2020. Of the eight who voted, seven approved the document (88%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Expert Panel emailed comments	Working Group comments
• The studies have shown that TRUS in addition to MRI-TB detected an additional 6% of CSPCa. Although there was an associated increase of 8% of CISPCa, the benefits of detecting additional CSPCa in men already undergoing biopsy (MRI-TB) outweighs the risk of detecting additional CISPCa, which was not much more than the increased detection rate for CSPCa. This is nicely explained in the justification section and feel that it is justified. This can be changed later if subsequent evidence does no longer supports this. • In the qualifying statements in Recommendation 1, I would include focal therapies in the statement on treatment in addition to surgery and radiation. • I agree with the authors on these recommendations. We also have our own Canadian multicentre study support to this. Undoubtedly, this will result in a large increase in the volume of prostate MRIs leading to many radiologists needing to train and interpret these studies. Thus, quality assurance is critical as this becomes standardized use and I strongly agree with inclusion of the statement in Recommendation 3 about having a local quality assurance method in place, until a formal provincial one is available. From this, I hope a formal quality assurance program becomes a priority and is established as soon as possible in the near future. I also understand that with the limited MRI resources in Canada, there is pressure for sites (mine included) to perform BPMRI to meet the demands of these exams. This further adds to the importance of implementation of a formal quality assurance program.	PRECISE trial results were added to the Discussion. We cannot add it to the formal review as this will require a complete reanalysis and literature search to update with all recent studies. This is beyond the current time constraints. Removed specification of radiation therapy and surgery leaving the door open to focal therapy or other curative intent therapies in the future.
With respect to the additional requests: • Regarding Recommendation 1, I would classify the strength of this recommendation as "Recommendation to use the diagnostic tool" (benefits of the diagnostic tool in the target patients clearly outweigh the harms for nearly all patients and the group is confident to support the recommended action).	No action required

• Regarding Recommendation 2, I would again classify the strength of this recommendation as "Recommendation to use the diagnostic tool" (benefits of the diagnostic tool in the target patients clearly outweigh the harms for nearly all patients and the group is confident to support the recommended action). • I would suggest that the Table on page 1, Section 1 does not really apply to the collection of recommendations listed under Recommendation 3. These recommendations pertain less to *whether* a diagnostic tool should be used and rather more to *how* the diagnostic tool that is being recommended in Recommendations 1 and 2 (i.e., MPMRI) should be implemented.	
• "the use of MPMRI-TB plus TRUS-SB or MPMRI-TB alone for patients who have had a prior negative TRUS-S"; To a large extent depends upon time interval since last SB. If >2 years since last biopsy but rising PSA, then repeat SB with TB (many urologists would send patient for SB biopsy irrespective of negative MRI or (PSA density if >2 years with increasing PSA volume, which makes it difficult to justify TB only if longer duration since last biopsy). Also as targeted focal therapy evolves and is brought into standard of care options, it is imperative that disease outside of the targets is also ruled out • The minimum acceptable standards in the acquisition, interpretation and reporting of MPMRI and the minimal acceptable standards for performance of MPMRI-TB. Strongly support this statement. Need to have means of auditing the quality and reporting of prostate MPMRI. There should be means to capture the NPV of MRI reads as well, else there will be tendency of calling only the definite lesions (PI-RADS 4/5)	No action required
• The Precise data likely would not influence the recommendations, but they should be incorporated into the evidence discussion. I realize that this would mean re-doing many of the Forest plots and data summaries. I strongly recommend, however, that this be done. This was a major trans-Canadian initiative, co-funded by the Ontario Institute for Cancer Research, whose goal was to influence funding for prostate MRI in Canada. I have indicated in the edited version which plots would require revision. But for COVID, it would have been presented at major spring meetings this year and therefore be in the public domain. • Obviously the issue of the role of systematic biopsies in men having targeted biopsy is not black and white. If the objective is to maximize diagnosis, they are clearly required. But another objective is to minimize morbidity and reduce number of cores. In the lower-risk patient, the NPV in the regions of the gland where the MRI is negative is sufficiently high (90%, according to the Moldaver paper) that systematic biopsies may be omitted. Therefore I believe the concept of risk stratification as the basis for decision making should be addressed in the document more than it is. • Treatment alternatives in Recommendation 1 should be expanded beyond surgery and radiation, (i.e., to include partial gland ablation and energy-based technologies). The statement implying that radiation and surgery are the only curative options is outdated. Suggest including 'partial gland ablation' as a	PRECISE trial results have been added in the Discussion. We will await publication of results as e-pub or abstract before releasing this document. Removed specification of radiation therapy and surgery leaving the door open to focal therapy or other curative intent therapies in the future. *"Therefore I believe the concept of risk stratification as the basis for decision making should be addressed in the document more than it is."* We have not further delved into risk stratification as this is a extensive and complex topic and beyond the scope of this document. A change has been made to the target population definition as follows: "Patients with an elevated risk of CSPCa (defined as International Society of Urologic Pathology (ISUP) Grade Group (GG) ≥2) as estimated by available clinical information and

treatment option. (This is not to endorse partial gland ablation, but only to acknowledge they are approved options that are often offered to patients). • I have some serious concerns about the wording of Recommendation 2. In particular, the statement 'In patients who had a prior negative TRUS-SB and demonstrate a high or an increasing risk of having CSPCa in whom curative management is being considered: MPMRI should be performed. The problem with this strategy is the risk of overdiagnosis**.** This is a complex topic. There are two key studies that are not referenced in the document that should be, and the implications discussed**. First,** the ESRPC study by Schröder et al., " Eleven-year outcome of patients with prostate cancers diagnosed during screening after initial negative sextant biopsies ". These men received repeat PSAs at four and eight years, with repeat biopsy if PSA remained elevated. The results were that prostate cancer mortality was extremely low in men with negative biopsy: seven deaths in the 3056 patients with negative biopsy, an 11-year probability of 0.03%, about 10-fold lower than the population average. Second, the NCI study of concurrent MRI and TRUS (Ahdoot et al.) is also very relevant to this question. The study reports the results of MRI biopsy in 999 men with negative TRUS biopsy: 791 had benign findings on MRI-targeted biopsy, but 208 were diagnosed with cancer, 134 of whom had high-grade disease, with 37 with the very highest risk cancers, Grade Group 4 or 5. • The message of the Schröder et al. study is that men with a negative systematic biopsy have very low prostate cancer mortality. The NCI study shows that in men with a negative systematic biopsy, an MRI and targeted biopsy-based strategy results in a lot of cancer diagnosis (20%, and 13% significant cancer). The very significant concern is that finding these additional cases will have little or no effect on prostate cancer mortality, i.e., a very high NND, particularly in the non-high-risk patient. • So, I am not sure that an evidence-based approach justifies a recommendation that MRI and targeted biopsy should be done in men with a negative biopsy. Therefore, in addition to including the above in the evidence discussion, Recommendation 2 should be modified to take out the phrase 'increasing risk' so that it is confined to high-risk men only. 'Increasing risk' is not defined and too inclusive.	tools such as risk calculators and nomograms" The principal role for MRI in biopsy naïve patients is complete biopsy avoidance to reduce the risk of over-diagnosis. This is the primary advantage of the strategy and produces the largest reduction in overdiagnosis. Once a decision to perform a biopsy is made because of a positive MRI it is assumed that there is also an intent to pursue curative intent therapy. MPMRI-TB combined with TRUS-SB in MRI-positive patients still allows for overall reduction in TRUS-SB in those patients who are MPMRI negative with only a slight increase in CISPCa detection (8%) while increasing CSPCa detection by 6%. This also provides a backstop for varying quality and experience in MPRMI reading and targeted biopsy quality.

RAP Review and Approval

Three RAP members reviewed this document in August 2020 The RAP approved the document on August 5, 2020. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
• Why did the group not include a patient representative?	All edits incorporated. Patient representatives were consulted

• Implications: Not sure if there is a way to quantify the patient's anxiety to a false negative or a false positive and need for unnecessary biopsies. • I know the tables are already busy but the false positive and missed cancer rates are helpful. They are in the text but not in the tables.	during the project plan and recommendation phases.
• Although PEBC has it structure for its documents, this reviewer found it helpful to start in Section 4 in order to understand the technology, the issues and the multitude of acronyms. Would it possible to add a sentence near the beginning of the document that could direct others to this section if they need grounding in the issues related to MPMRI.	All edits incorporated. A list of definitions has been added to document.
• Recommendations 1 and 2 - Not recommending TRUS-SB for patients that have already been diagnosed with CSPCa using TB: the reviewers commented that it seems like an extra biopsy (SB) for a group that have already been confirmed using TB, but they acknowledge (but do not know whether) it is easier to bring all MPMRI-positive patients in at the same time for both biopsies (PEBC staff review). • Recommendation 1 - Suggesting TRUS-SB for MPMRI-negative and MPMRI-TB-negative biopsy-naive patients. For biopsy-naive patients 11.3% of MPMRI-negative patients and 7.5% of MPMRI-TB-negative would have been missed if TRUS-SB in studies reporting the data – this seemed like a lot of potential missed cases to the reviewers. These percentages were lower for previously negative patients.	Recommendation 1: The issue of how TB alone should be interpreted in overall whole gland Gleason scoring has not been resolved in the care community. TB+SB is believed to be necessary if MPRI is positive in biopsy-naïve patients as multifocality and positive biopsy in other regions not seen by MRI is important in clinical decision making and treatment planning given the use of focal dose escalation therapies. Once you bite the bullet and decide for a biopsy you want the whole picture. In addition, the risk of severe complications such as hospital admission for urosepsis does not go up when you go from target to targeted plus systematic biopsy although minor complications do. A par like this can be added to the document if needed. **The patients that gain the most in the biopsy-naïve group are the MRI-negative patients.** The primary goal is safe avoidance of CISPCa detection (over-detection) in this cohort. Although the miss rate if no biopsy is performed seems high it is no higher than SB alone so we leave it to the discussion of the patient and the urologist <u>with a commitment to follow-up</u> if biopsy is not being done of prime importance. If we insist on SB in all MPMRI-negative patients who are biopsy naïve then there is no point in doing the MRI up front, we should do it after the SB and then we are back to Rec 2 – prior negative SB. We will also still have a high CISPCa rate and lose a principal advantage

	of biopsy avoidance. This is the core controversy of Recommendation 1 and will be an ongoing point of contention. Recommendation 2: If there has been a long interval since last SB then they should have both SB and TB but if not then it is not necessary. Therefore, we offer the discretion of SB to the oncologist in this group of patients.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group.

Comments	Responses
• Patients expressed concerns re: accessibility of MPMRI (and related expertise) in their areas.	Explanation regarding accessibility explained in text.
• Patients were concerned about Recommendation 3 and if there are any quality assurance measure in place in Ontario for the administration of MPMRI.	Issue of quality assurance addressed in Section 2 of report.
• Generally, the patient representatives thought the recommendations were well written.	No action required.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Five targeted peer reviewers from Ontario and other Canadian Jurisdictions (Quebec and Alberta) who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group and the MPMRI in the Diagnosis of Clinically Significant Prostate Cancer GDG. Two agreed to be the reviewers (Appendix 2). Two responses were received. Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=2)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.					2
2. Rate the guideline presentation.				2	
3. Rate the guideline recommendations.				2	
4. Rate the completeness of reporting.					2
5. Does this document provide sufficient information to inf orm your decisions? If not, what areas are missing?					2

6. Rate the overall quality of the guideline report.				1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				1	1
8. I would recommend this guideline for use in practice.				2	
9. What are the barriers or enablers to the implementation of this guideline report?	Access outside tertiary centres. Access to MRI facilities, and especially experienced Radiology for reporting, and targeted biopsies is limited. Therefore, making standard of care recommendations is likely to provoke some issues especially for rural patients.				

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
One thing that I was uncertain of is the nature of a "negative biopsy" (i.e., no prostate cancer seen or does a negative biopsy include GG=1 prostate cancer). It might be worthwhile to make a disclaimer that this guideline is not addressing the use of MPMRI for men diagnosed with CISPCa on previous biopsies. I wonder if a quick sentence to clarify that in the "Target Population" section may ensure clinicians are not expecting recommendations on the use of MPMRI in patients on active surveillance.	We have added a phrase in "Target populations": Patients with an elevated risk of CSPCa (defined as ISUP GG ≥2), as estimated by available clinical information and tools such as risk calculators and nomograms, of who are A) biopsy-naïve or B) have had a prior negative TRUS-SB *defined as no prostate cancer on biopsy of any grade group.* A definition has been added under qualifying statements for recommendation 2: *•Prior negative TRUS-SB is defined as no cancer of any grade group on prior biopsy*

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All radiation oncologists and urologists in the PEBC database were contacted by email to inform them of the survey (n=202). Twelve (5.9%) responses were received. Eighteen stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 12 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number 12 (5.9%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				6	6
	Strongly	(2)	(3)	(4)	Strongly Agree (5)

	Disagree (1)				
2. I would make use of this guideline in my professional decisions.			2	3	7
3. I would recommend this guideline for use in practice.		1		5	6
4. What are the barriers or enablers to the implementation of this guideline report?	Lack of access to MRI and fusion biopsy technology is mentioned as an issue in IMPLEMENTATION CONSIDERATIONS section of the Discussion, A sentence has been added: "The lack of ready access to computer-aided fusion biopsy systems may require the use of cognitive fusion biopsy in many centres which will require additional operator training."				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
If MRI becomes insured in biopsy-naïve patients, then their delay for study will go from 2-3 months now to 6 months because the hospitals do not have the capacity. Also the stipend for MRI-fusion biopsy and increase significantly, because of the extra planning time and procedural time compared to standard TRUS-biopsy. Finally, there are very few doctors- radiologists or urologists that are doing fusion biopsies, because of the exorbitant costs of the machines and the disposables. How will that be addressed?	No action required.
Will need to look at accessibility and wait times for the whole province. Congratulations on this great guideline!	No action required.
• Please do not use CSPCa as a short form in the context used. Most readers will naturally interpret that as castrate-sensitive prostate cancer as it is so deeply engrained in genitourinary language. I continually reverted back to the more standard meaning while reading this, even though it is clearly stated otherwise at the start of the text. • The target population is not exactly clear. Presumably patients "at elevated risk" are those with a nodule and/or elevated PSA but the parameters do not seem to be stated - certainly not up front. I also recognize that patient populations differ within the literature. • What about the use of MRI in active surveillance of low-risk patients who have a previous positive (but low-risk) biopsy?	We have added a list of acronyms into the Appendices A sentence has been added to the Introduction of Section 4 as follows: "The scope of these recommendations does not include the use of MRI in active surveillance."

MPMRI is not widely available everywhere and, where it is available, there are often significant restrictions for use and/or potentially long wait times. It is also highly dependent on operator and reader expertise and should not be performed unless that expertise exists. However, the authors already stress this fact in their very well written document.	No action required.
Barriers might include inability to get a MPMRI and/or MPMRI-TB in a timely fashion as well as consistent reporting of these MRI's by radiologists.	No action required.
Barriers: -Lack of access to MRI or lack of timely access. -Funding concerns for the institution, there is conflicting information around whether institutions can get paid for this. -Does not address PSA, so normal MRI and high PSA should be addressed.	No action required.
I think some mention of PSA is indicated (also maybe DRE abnormalities) The report at face value indicates that a normal MPMRI should lead to a shared decision but implies a biopsy is not needed. I think this is very different for a patient with a PSA of 8 versus a PSA of 25, (or a DRE abnormality perhaps) or a very high PSA density. I do not see these items addressed.	These points are well taken; however, specific recommendations on how risk should be assessed are difficult and beyond the scope of this Guideline.
I agree with the recommendations regarding management of MPMRI-positive patients, but have unease about recommending no biopsy for MPMRI-negative patients. This could involve missing clinically significant cancer in over 20% of patients, which I think is too high. I would be interested in lay/ patient opinion on this.	No action required.
Page 2 (Recommendation 1) - "Between 8% to 24% of patients….missed by a negative MPMRI". Warning, this sentence suggests that up to 24% of CSPCa may be missed by MPMRI. In fact, this result is based on the NPV and should be only interpreted for negative MPMRI population instead of the whole population who had MPMRI result. It could also be useful to specify what you mean by a negative MPMRI result (PIRADS 1-2). Page 3 (Recommendation 1) - Bullet point #1: Wrong information about PROMIS study "...if MPMRI-TB was the only biopsy performed, …". There was no MPMRI-TB in this study. The reference test was TPM-biopsy by TRUS-biopsy. - Bullet point #2: "The principal value of MPMRI in biopsy-naïve… avoidance with up to a 49% reduction…". You should be cautious with this result based on the Van de Leest results. Furthermore, this result is not justified in the	• All suggested edits have been addressed in the text. • Regarding the PROMIS study, we have corrected this. For PROMIS we have changed some of the wording in the Key Evidence section for Recommendation 1 and in the Discussion. • The review by Drost did not meet our study criteria and, thus, was not used (did not separate biopsy naive and previously negative men according to our inclusion criteria). • The Australian Guideline was not included because it did not adequately separate biopsy-naïve and previous negative patients • Changed the term “diagnose” to “help diagnose” in the text as suggested. • Edits have been added to the text to address the reviewer’s comments regarding the content of the discussion.

section "Biopsy-naïve patients (Question 1) of the guideline. Many studies are available to estimate the number of biopsy avoidance based on a negative MPMRI result among the biopsy-naïve patients (see Cochrane review Drost FH et al. 2019). - Bullet point #3: same comment about "...MPMRI may miss between 8% to 24%". In this section, you should more strongly emphasize the goal of added MPMRI in the clinical diagnosis pathway in biopsy-naïve population; biopsy avoidance and safe avoidance of CISPCa. Results in this section of the guideline and Section 3 may be more explicit to justify this objective. Bullet points#2,#3,#4: Very interesting information but few results to support them in the section "Justification for Recommendation 3" and on page 49 (Q3a, Q3b). Data issued from Recommendations 1 and 2 should be more explicit to justify these bullet points. Page 11 (Introduction) 3rd paragraph: "Over the past several years,...MPMRI as a non-invasive tool to diagnose and localize CSPCa". The use of "to diagnose" seems inappropriate to the clinical context. The diagnosis is based on biopsy result and pathological analysis and not the MPMRI result itself. So, MPMRI can help to diagnose. page 13 (Study selection criteria and process) Bullet point #3: For Q1a and Q2a, the reference test TTMB is not intended only for MPMRI-positive patients but also for MPMRI-negative patients. Page 14 (Results): " No systematic review met the inclusion criteria". It is unclear why the systematic review by Drost et al. 2019 (Cochrane collaboration) did not meet the inclusion criteria. Barriers: - Clinical criteria for the referral biopsy-naïve patients to MPMRI? - Primary objective: MPMRI as a tool to biopsy avoidance or targeted biopsy? - Who is in charge of referring patients to MPMRI, Urologists, family physicians? - Budget impact of introducing MPMRI into the diagnosis pathway? - Is it cost-effective? Depending on the objective (biopsy avoidance or target biopsy) and the measures to follow negative-MPMRI patients? - Impact to the accessibility to MRI in general? - What are the measures to the follow-up of negative-MRI patients (e.g. PSA, MRI)?	

Enablers: - Level of biopsy avoidance (25%?, 30%?, 49%?) in biopsy-naïve patients and the positive impacts on over diagnosis and overtreatment of PCa - Bringing together MPMRI expertise in a few hospital centres. - Support from international guidelines in uro-oncology - Demonstration of cost-effectiveness - Improving patient experience - Shared-decision making with respect to MPMRI results	
No significant barriers other than resource limitations (MRI and experienced operators) in Ontario. Much of this report is directed toward indications for prostate MRI which is most relevant to referring clinicians. Dissemination to urologists and GPs in Ontario would be beneficial.	No action required.
More guidance on what constitutes "experienced" operators would be helpful. More specific guidance on who can apply PBMRI would also be helpful; we have considered switching to BPMRI to expedite MRI exams given our long wait-times, however we decided not to given our uncertainty about the trade-offs and the experience level of our radiologists	This is out of scope and will have to come from further discussions with Ministry/CCO.
-Provincial access to MRI will be a problem -Costs of MRI will be high, so that will pose a problem as well -The need for a quality assurance program may impede widespread implementation unless it is rolled out in a timely manner	No action required.
While a quality assurance program before widespread adoption is beyond the scope of this document, such a program along with widespread MRI utilization may become a huge strain on resources. Are there recommendations to increase the number of magnets in the province? How many MRI's of the prostate do you estimate will occur once widely adopted. The quality assurance program will also be a huge initial step and resource prohibitive	Beyond scope.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Definitions and Abbreviations

BPMRI = bi-parametric MRI

CI = confidence interval

CISPCa = clinically insignificant prostate cancer

CSPCa = clinically significant prostate cancer

MCT = multicentre trial

DCEMRI = dynamic contract enhanced MRI

MPMRI = multiparametric magnetic resonance imaging

MPMRI-TB = MPMRI-informed biopsy of MPMRI-positive lesions with no biopsy performed if the MPMRI shows no lesions. This can be performed using TRUS with cognitive fusion with MPMRI images, software assisted fusion with MPMRI images, or under direct MRI guidance in the bore of the MRI.

NPV = negative predictive value

PI-RAD = Prostate Imaging-Reporting and Data System

PPV = positive predictive value

PSA = prostate-specific antigen

RCT = randomized controlled trial

TRUS = transrectal ultrasound

TRUS-SB = TRUS-guided systematic biopsy (Note: although the high level evidence was based on trials using TRUS, systematic transrectal biopsy is roughly equivalent in cancer detection to systematic transperineal biopsy)

TTMB = template transperineal mapping biopsy

Appendix 2: Affiliations and Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, MPMRI in the Diagnosis of CSPCa Expert Panel, and internal and external reviewers were asked to disclose potential conflicts of interest.

Name	Affiliation	Declarations of interest
Working Group		
Judy Brown	Health Research Methodologist McMaster University, Department of Oncology, Program in Evidence-based Care, Hamilton< Ontario	None declared
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MPMRI in the Diagnosis of Clinically Significant Prostate Cancer Expert Panel (Expert Panel)		
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Sylvia Chang Radiologist	Vancouver General Hospital Vancouver, BC	None declared
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Sangeet Ghai, Radiologist	Toronto General Hospital Toronto, ON	See below
Laurence Klotz, Urologist	University of Toronto, Sunnybrook Health Sciences Centre Toronto, Ontario, Canada	See below
Scott Morgan, Radiation Oncologsist	Radiation Oncology University of Ottawa	See below
Bobby Shayegan, Urologist	St. Joseph's Healthcare Hamilton, McMaster University	See below

	Hamilton, Ontario, Canada	
Report Approval Panel		
William Evans	Oncosynthesis Consulting Inc, Hamilton	None declared
Lorraine Elit	Juravinski Cancer Centre, Hamilton	None declared
Targeted Peer Review		
Bryan Donnelly	Urologist, Calgary Health Region Clinical Associate Professor, University of Calgary Co-Founder & Chairman, Prostate Cancer Institute, Calgary, ON	None declared
Ryan Carlson	Health Sciences North Regional Cancer Program Sudbury, ON	See below

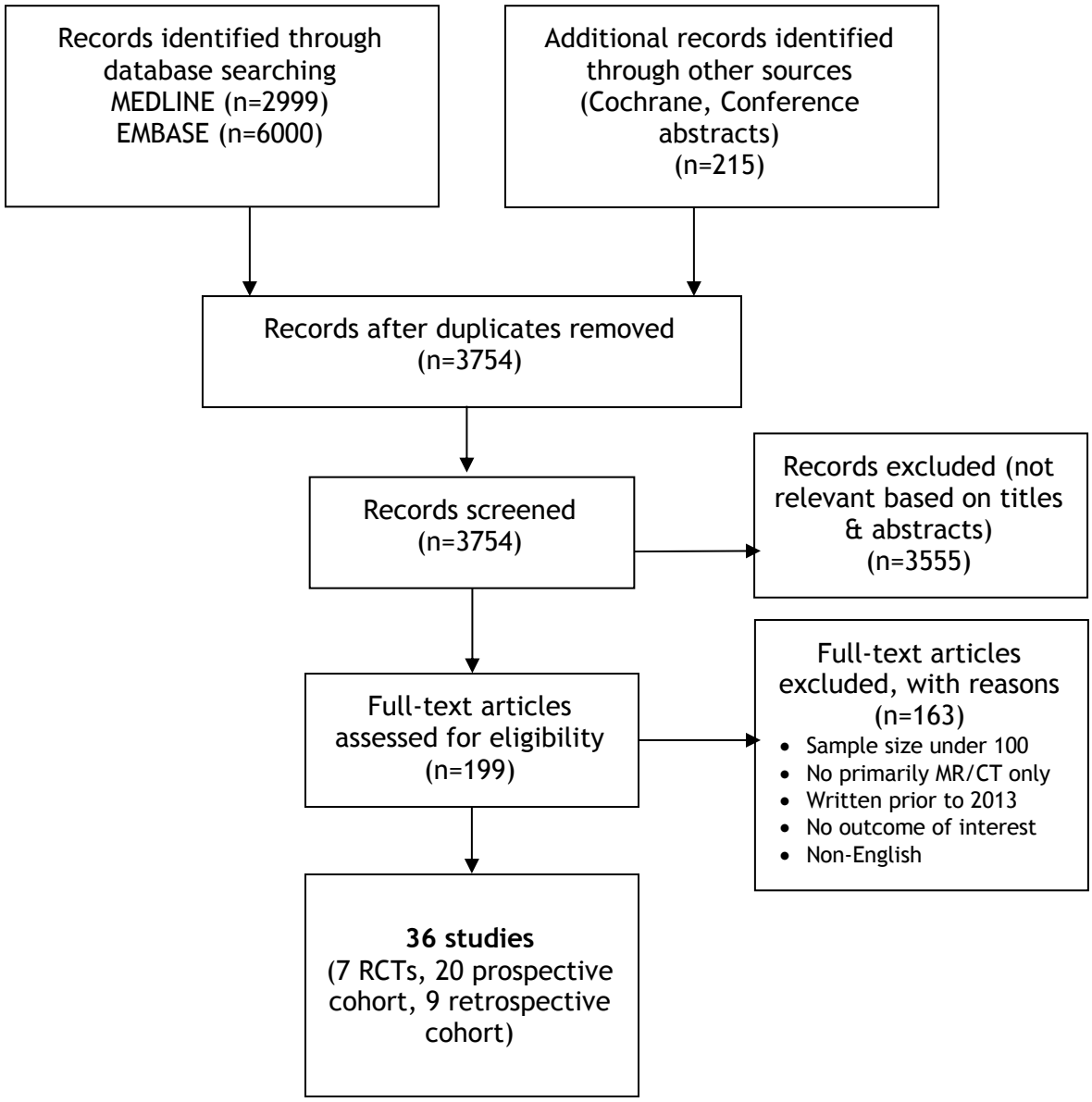
(M. Haider) Have read prostate MRI in clinical practice so will see increase demand and work/revenue if this is approved; PI on Multiple trials in mpMRI. Can review my CV if you wish a full list; Author on relevant publications 1: Padhani AR, Haider MA, Villers A, Barentsz JO. Multiparametric Magnetic Resonance Imaging for Prostate Cancer Detection: What We See and What We Miss. Eur Urol. 2019 May;75(5):721-722. doi: 10.1016/j.eururo.2018.12.004. Epub 2018 Dec 16. PubMed PMID: 30563723. 2: Barentsz JO, Weinreb JC, Verma S, Thoeny HC, Tempany CM, Shtern F, Padhani AR, Margolis D, Macura KJ, Haider MA, Cornud F, Choyke PL. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol. 2016 Jan;69(1):41-9. doi: 10.1016/j.eururo.2015.08.038. Epub 2015 Sep 8. PubMed PMID: 26361169 (part of PI-RAD committee); PubMed Central PMCID: PMC6364687 reviewed his declaration and the professional publications noted by Dr. Haider (re publications: The PEBC do not find that the opinions expressed represent a clear conflict with respect to this project, and waive the requirement preventing him from being the lead author).
(A. Loblaw) received grants from Sanofi, Paladin; PI on two clinical trial (ASIST, PRECISE) looking at MRI in active surveillance and prediagnosis; Gave advice/guidance to multiple news agencies about prostate cancer treatment and side effects.
(G. Bauman) Invited speaker for Bayer; DOD grant investigating mpMRI and PSMA PET in localized prostate cancer, co-PI; Publications: Multi-modality Imaging (PCa) Using Sodium MRI and PSMA PET in Men Pre-prostatectomyNCT04053842, PET/MRI for Men Being Considered for Radiotherapy for Suspected Prostate Cancer Recurrence Post-ProstatectomyNCT02131649, Advanced Prostate Imaging of Recurrent Cancer After RadiotherapyNCT02793284, Multi-modality Prostate Cancer Image Guided InterventionsNCT04009174,Prospective Study Using Hybrid PET/MRI to Evaluate Men With Suspected Recurrence Following Treatment for Prostate Cancer NCT0180423; Published editorial: 1: Trabulsi EJ, Rumble RB, Jadvar H, Hope T, Pomper M, Turkbey B, Rosenkrantz AB; My primary research focus is on advanced prostate cancer imaging applications including PET and MRI.
(L. Klotz) Research support for clinical trial from Exact Imaging Inc.,
(S. Morgan) Consultation provided to Astellas: advisory board member,Bayer: advisory board member, Janssen: advisory board member, consulting (Genitourinary Research Consortium)
(S Chai) I have received honorarium from Exact Imaging in 2016 to speak at Milan, Italy EMUC meet; received grants from Insightec Ltd, Haifa, Exact Imaging, Markham; Prinicap investigaor for MR guided focal laser ablation MR guided FUS therapy; publications: Comparison of mpMRI to high resolution TRUS (29MHz) for detecting PCa in biopsy naiive Area: My main area of clinical and research interest is prostate imaging and intervention, from TRUS Bx, high resolution US to mpMRI and Focal therapy under MRI guidance.
(B Shayagen) My focus in clinical practice and research is principally in prostate cancer. However, none of my activities or interests conflict in any way with this document
(R Carlson) On Janssen and Ferring advisory boards. Travel for conferences (Jansen)

Appendix 3: Literature Search Strategy

#	Medline
1	(prostat$ adj2 (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or malig$ or tumo?r$)).mp.
2	(magnetic resonance imag$ or magnetic resonance spectroscop$).mp.
3	(dynamic adj4 (MRI or magnet$)).mp.
4	(diffusion weight$ adj3 (MRI or magnet$)).mp.
5	Magnetic Resonance Imaging/ or Magnetic Resonance Spectroscopy/ or Nuclear Magnetic Resonance Imaging/
6	(MRI or MRSI or DWI-MRI or DW-MRI or DCE-MRI).mp.
7	((T1-weighted or T2-weighted) adj3 imag$).mp.
8	(nmr imaging or MRS).mp.
9	((NMR adj3 imag$) or NMRI).mp.
10	((MR adj3 imag$) or (MR adj3 spectroscop$)).mp.
11	or/2-10
12	(case report$ or editorial$ or comment$ or letter$).pt.
13	(comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
14	or/12-13
15	(1 and 11) not 14
16	Animal/ not Human/
17	15 not 16
18	limit 15 to (english language and yr="2013 -Current")
19	remove duplicates from 18

#	Embase
1	(prostat$ adj2 (cancer$ or neoplasm$ or adenocarcinom$ or carcinom$ or malig$ or tumo?r$)).mp.
2	exp prostate cancer/ or exp prostate tumor/
3	1 or 2
4	(magnetic resonance imag$ or magnetic resonance spectroscop$).mp.
5	(dynamic adj4 (MRI or magnet$)).mp.
6	(diffusion weight$ adj3 (MRI or magnet$)).mp.
7	(MRI or MRSI or DWI-MRI or DW-MRI or DCE-MRI).mp.
8	(nmr imaging or MRS).mp.
9	((NMR adj3 imag$) or NMRI).mp.
10	((MR adj3 imag$) or (MR adj3 spectroscop$)).mp.
11	((T1-weighted or T2-weighted) adj3 imag$).mp.
12	or/4-11
13	3 and 12
14	(case report$ or editorial$ or comment$ or letter$).pt.
15	(editorial or note or letter erratum or short survey or abstract).pt. or abstract report/ or letter/ or case study/
16	14 or 15
17	13 not 16
18	Animal/ not Human/
19	17 not 18
20	limit 19 to (english language and yr="2013 -Current")

Appendix 4: PRISMA Flow Diagram



Appendix 5: Risk of Bias Assessments

a) Quality assessment using QUADAS-2 - diagnostic Studies comparing MPMRI(±TB) with reference standard (TTMB)

	Risk of Bias				Applicability Concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference Standard
Ahmed, 2017 (Q1a)	Low	Low	Low	Low	Low	Low	Low
Hansen, 2016 (Q1a, Q2a)	Low	Low	Unclear	Low	Low	Low	Low
Hansen, 2017 (Q2a)	Unclear	Low	Unclear	Low	Low	Low	Low
Hansen, 2018 (Q1a)	Low	Low	Moderate	Low	Low	Low	Low
Mortezavi, 2018 (Q1a, Q2a)	Low	Low	Moderate	Low	Low	Low	Low
Pepe, 2015 (Q2a)	Unclear	Low	Low	Unclear	Low	Low	Low
Pepe, 2017 (Q2a)	Unclear	Low	Low	Unclear	Low	Low	Low
Pepe, 2018 (Q2a)	Unclear	Low	Low	Unclear	Low	Low	Low
Simmons, 2018 (Q2a)	Low	Low	Low	Low	Low	Low	Low
Thompson, 2016 (q1a)	Low	Low	Unclear	Unclear	Low	Low	Low

b) Quality assessment for RCTS using the RISK OF BIAS Tool.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Comments
Kasivisvanathan, 2018 (Q1b)	Low	Low	NA	Low	Low	Low	
Porpiglia, 2017 (Q1b)	Low	Low	NA	Unclear	Unclear	Low	
Tonttila, 2016 (Q1c)	Low	Unclear	NA	Low	Unclear	Low	
Weglin, 2019 (Q3b)	Low	Low	NA	Low	Low	Low	

c) Quality Assessment For Non-randomized studies using ROBINS (ACROBAT-NRSI) Risk of Bias Tool for Non-randomized Studies (Intervention Studies).

Study	Overall rating*	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results
Alberts, 2017 (Q1b,Q2b)	Moderate	Low	Low	Low	Low	Moderate (large # missing data)	Moderate (no RS)	Low

Study	Overall rating*	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results
Arsov, 2015 (Q2b)	Moderate	Low	Moderate	Low	Low	Low	Moderate (no RS)	Low
Baco, 2016 (Q1bc)	Moderate	Low	Low	Moderate	Low	Low	Moderate (no RS)	Low
Boesen, 2018 (Q2bc)	Low	Low	Low	Low	Low	Low	Moderate (no RS)	Low
Borkowetz, 2017 (Q1bc,Q2bc)	Moderate	Low	Moderate (unclear if consecutive)	Moderate (different PI-RAD evaluations)	Moderate	Low	Moderate (outcome assessor not blinded, no RS)	moderate
Borkowetz, 2018 (Q1bc)	Moderate	Low	Low	Moderate (different PI-RAD evaluations)	Moderate	Low	Moderate (outcome assessor not blinded, no RS)	Moderate
Castelluci, 2017 (Q1bc)	Moderate	Low	Low	Moderate (PI-RAD V.1 used)	Low	Low	Moderate (Unclear if outcome assessors blinded, no RS)	Low
Exterkate, 2020 (Q2bc)	Low	Low	Low	Low	Low	Low	Moderate (no RS)	Low
Filson, 2016 (Q1bc,Q2bc)	Moderate	Low	Low	Moderate	Low	Low	Moderate (no RS)	Low
Lian, 2016 (Q2bc)	Moderate	Low	Low	Moderate	Low	Low	Moderate (no RS)	Low
Mannaerts, 2019 (Q1b,Q2b)	Moderate	Low	Low	Moderate	Moderate	Moderate	Moderate (Unclear whether outcome assessors blinded)	Low

Study	Overall rating*	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results
Mariotti, 2016 (Q1b,Q2b)	High	Low	High (retrospective)	Moderate	Moderate	Low	Moderate (unclear if RS separate from index)	Low
Meng, 2015 (Q1b,Q2b)	High	Low	High (retrospective)	Moderate	Moderate	Low	Moderate (Unclear whether outcome assessors blinded)	Low
Preisser, 2019 (Q1bc,Q2bc)	High	Low	High (retrospective)	Moderate	Low	Low	Moderate (no RS)	Mopderate
Rouviere, 2019 (Q1bc)	Low	Low	low	Low	Low	Low	Moderate (no RS)	Low
Sakar, 2019 (Q1bc)	Moderate	Low	Moderate	unclear	Moderate	Low	Moderate (no RS)	Low
Say, 2016 (Q2bc)	High	Low	High (retrospective)	High (Unclear if TB done without knowledge of TRUS-SB)	Moderate	Moderate	Moderate (no RS)	Moderate
Sidana, 2018 (Q2b)	High	Low	High (retrospective, unclear if consecutive)	Moderate	Moderate	Moderate	Moderate (no RS)	Low
Van der Leest, 2018 (Q1bc)	Low	Low	Low	Low	Low	Low	Moderate (no RS)	Low
Westoff, 2019 (Q1bc,Q2bc)	High	Low	High (retrospective)	Moderate	Low	Low	Moderate (no RS)	Low
Zalesky, 2019 (Q1bc,Q2bc)	High	Low	High (retrospective)	Moderate	Low	Low	Moderate (no RS)	Low

Study	Overall rating*	Confounding	Selection of participants	Measurement of interventions	Departure from intervention	Missing data	Measurement of outcomes	Selection of reported results
Zhang, 2017 (Q1bc)	Moderate	Low	Low	Moderate	Low	Low	Moderate (no RS)	Low
*If only one “moderate” rating and the rest low, the study received a “low” rating. If two or more “moderate” ratings, studies received overall “moderate” rating. If one or more “high” assessment, the study received an overall “high” rating.								

Appendix 6: Adverse Events

Author, year	Procedure	Side effect [missing data]	Number (%)
Ahmed, 2017	MPMRI	Pain. Discomfort	2% (11/561)
		Allergic reaction to contrast medium	<1% (1/560)
	Combined biopsy procedures (TRUS-SB & TPM)	Pain/discomfort	64% (362/563)
		Dysuria	46% (256/559)
		Hematuria	67% (380/565)
		Hematospermia	55% (291/525)
		Erectile dysfunction (requiring medication, injection therapy or devices)	14% (76/528)
		Urinary tract infection (only if confirmed by a lab test)	6% (32/565)
		Systemic urosepsis	1% (8/568)
		Acute urinary retention	10% (58/564)
		Symptoms associated with general/spinal anesthetic	4% (19/533)
Alberts, 2018 GRP 1 (n=179) Grp 2 (n=158)	Biopsy complications (6-core TRUS-Bx [Grp 1] MRI, 12-core TRUS-Bx, and fusion TBx [Grp 2])	Postbiopsy fever	5.6% (19/337)
		Hospital admission for of postbiopsy fever	3.3% (11/337)
		Hospital admission for urosepsis	Grp 1 4% (6/179), Grp 2. 3.2% (5/158)
		Hospital admission for urinary retention	Grp 1 <1% (1/179)
		Hospital admission for transient ischemic attack 1 day post-biopsy	Grp 2 <1% (1/158)
Arsov, 2015 [G1 104, G2 106])	Major complication rate post biopsy (IB-GB alone [Grp 1] and FUS-GB + TRUS-GB [Grp 2])	Febrile prostatitis requiring hospitalization and intravenous antibiotic therapy.	Grp 1.9% (2/104), Grp 2 1.0% (1/106)
		No prostatic abscess, major bleeding, or other sever adverse events requiring surgical intervention occurred.	---
Castellucci, 2017 (BN=168)	"No major complications were reported after the procedure."		
Kasivisvanathan, 2019	MPMRI±TB (BN=224) Patient-reported immediate post-intervention complications	Discomfort Med. (IQR)	2 (0-4)
		Pain Med. (IQR)	1 (0-3)
	MPMRI±TB (BN=212) Patient-reported 30-day post-intervention complications	Fever	4.2% (9/212)
		Blood in urine	30.2% (64/212)
		Blood in semen	32.1% (68/212)
		Blood in the stools or from the back passage	14.2% (30/212)
		Acute urinary retention	1.4% (3/212)
		Erectile dysfunction	10.8% (23/212)
		Urinary incontinence	6.1% (13/212)
		Urinary tract infection	2.4% (5/212)
		Pain at site of procedure	12.7% (27/212)
		Men for whom another procedure would be a major problem	0.9% (2/212)
		Serious adverse events	1.6% (4/212)

Author, year	Procedure	Side effect [missing data]	Number (%)
	MPMRI±TB (BN=2I2) Investigator-reported Adverse events	Adverse events	0.8 (2/212)
		Sepsis related to intervention	0.4% (1/212)
		Prostatitis related to intervention	1.2% (3/212)
		Pulmonary embolism, unrelated to intervention	0.4% (1/212)
		Death (secondary to pulmonary metastasis of known squamous cell carcinoma)	0.4% (1/212)
Mannaerts, 2019	MPMRI-TBx+TRUS-SB (N=242)	Prostatitis	4.7% (10/2121)
		Urinary retention	0.4% (1/212)
		Gross rectal bleeding	0.4% (1/212)
		Gross hematuria	0.4% (1/212)
Pepe, 2018	"No patient had significant complications (Clavien-Dindo grade I) of prostate biopsy which needed hospital admission. Moreover, the mpMRI procedure was well tolerated and successfully performed in all case."		
Porpiglia, 2017	"The study is ongoing to examine the remaining secondary end points."		
Rouviere, 2019	MPMRI-TB+TRUS-SB (n=NR) Immediate post intervention	Grade 3 prostatitis	3
		Grade 3 urinary retention with hematuria	1
Simmons, 2017	TTPM adverse events (assessed med. 38±56 post biopsy (n=236) (No serious adverse events resulting from mpMRI)	Serious adverse events	3.6% (9/236)
		Hematuria	93.2% (220/236)
		Poor urine flow Urinary retention	45.8% (108/236) 23.7% (56/236)
		Urinary tract infection	9.8% (23/236)
		Perineal skin infection	3.4% (8/236)
		Rectal pain	25.1% (59/236)
		Perineal pain Perineal bruising	40.3% (95/236) 57.6% (136/236)
		De novo erectile dysfunction	20.8% (49/236)
Tonttila, 2016	MPMRI-TRUS fusion	One patient collapsed after the biopsy procedure and experienced a minor head injury.	
VanderLeest, 2016	Transrectal in-bore (n=626) (50% [20/41] in patients TRUSGB only in the nonsuspicious mpMRI group, including 2.9% (nine of 309) with complicated UTI/urosepsis).	Complicated urinary tract infection (UTI/urosepsis)	3% (20/626)
		Lower urinary tract symptoms	1.5% (9/626)
		Bleeding	1.3% (8/626)
		Vasovagal episode	<1% (3/626)
		Transient ischemic attack after discontinuation of anticoagulant medication	<1% (1/626)
Zhang, 2017	MPMRI/TRUS fusion+TRUS-SB	"No serious post-biopsy complication (including acute urinary retention, infection, etc.) was noted in all patients with biopsy."	
Adverse events not presented: Baco, 2016; Boesen, 2017; Boesen, 2018; Borkowetz, 2018; Borkowetz, 2017a; Borkowetz, 2017b; Dal Moro, 2019; Delongchamps, 2016; Filson, 2016; Hansen, 2016; Hansen, 2018; Hansen, 2017; Lian, 2017; Mariotti, 2016; Meng, 2016; Mortezavi, 2018; Peltier, 2015; Pepe, 2015; Pepe, 2017; Say, 2016; Schouten, 2017; Sidana, 2018; Thompson, 2016			

Appendix 7: Supplementary Data (pre-2015 added)

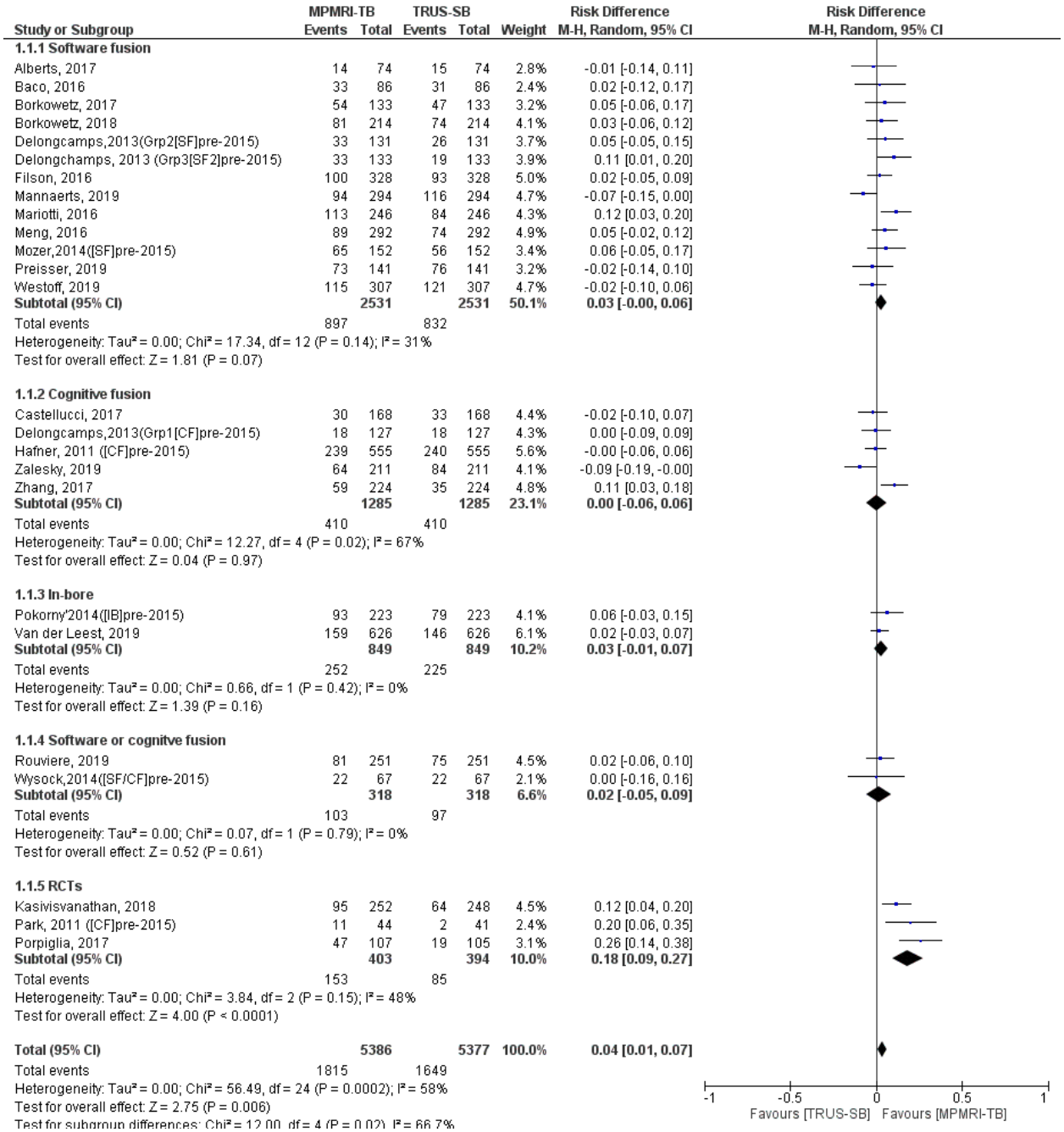
Diagnostic Accuracy of MPMRI alone (compared to reference Standard) by definitions of clinically significant prostate cancer (pre-2015 and updated study data) for biopsy-naïve patients – Q1a

Diagnostic Accuracy of MPMRI (alone) in biopsy naïve patients (compared with reference standard)								
Study (prevalence of CSPCa)	**Index test**	**Positive MRI**	**Reference standard**	**CSPCa definition**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Update study data GS≥ 3+4 – biopsy naïve								
Hansen, 2016 n=107 (39%)	T2W1+ DWI+ DCE	PI-RAD v1 ≥3 of 5	24-core systematic biopsy according to the Ginsburg TRUS-SB protocol	GS 7 to 10	92.9% (85,101)	29.2% (18,40)	45.9% (35,56)	86.4% (72,101)
Hansen, 2018 n=807 (49%)	T2W1+ DWI+ DCE (ALL)	PI-RAD v1 ≥3 of 5	18-24 core systematic TP biopsy according to the Ginsburg TRUS-SB protocol	GS 7 to 10	87.8% (85,91)	45.3% (41,50)	60.2% (56,64)	79.7% (75,85)
Pre-2015 studies GS≥ 3+4 - biopsy-naïve								
Komai 2013 (24%) [70]	T2WI+DWI+DCE for 270 pts; T2WI +DWI for 54 pts	≥3 of 5 scoreTRUS-SB	26-core biopsy (12 transrectal +14 transperineal)	GS ≥4+3 or CL ≥5 mm	86% (78—94)	72% (67—78)	50% (41—58)	94% (91—98)
Abd-Alazeez, 2014 (21%)	T2WI+ DWI+DCE (258 half prostates from 129 pts)	≥3 of 5 scoreTRUS-SB		GS ≥7	93% (86—100)	21% (15—27)	24% (18—29)	91% (84—99)

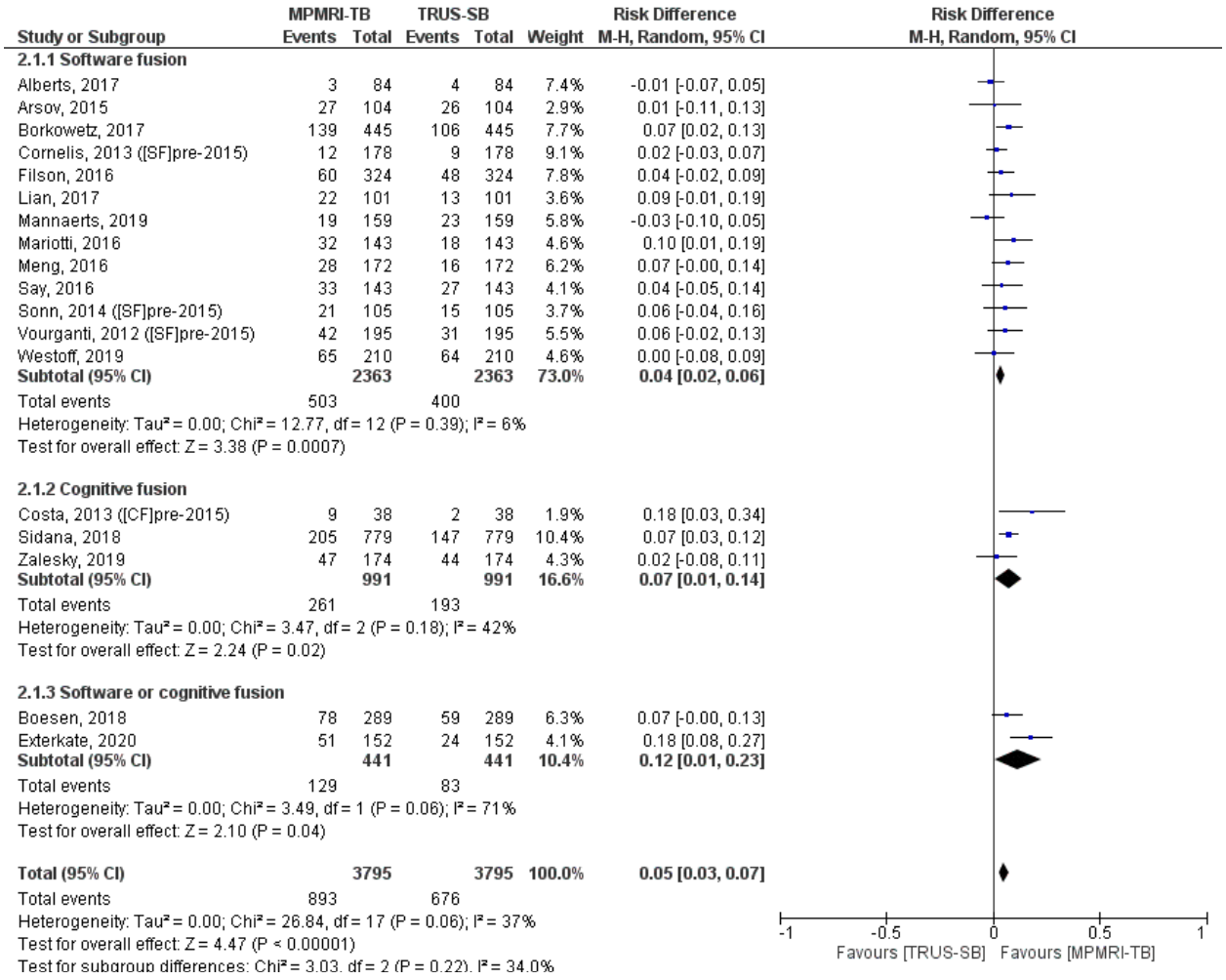
Diagnostic Accuracy of MPMRI alone (compared with reference Standard) by definitions of clinically significant prostate cancer (pre-2015 and updated study data) for previously negative patients – Q2a

Study (prevalence of CSPCa)	**Index test**	**Positive MRI**	**Reference standard**	**CSPCa definition**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**
Update study data GS≥ 3+4 – previously negative								
Hansen, 2016 n=295 (27%)	T2W1+ DWI+ DCE	PI-RAD v1 ≥3 of 5	24-core TRUS-SB according to the Ginsburg TRUS-SB protocol	GS 7 to 10	90.1% (84,110)	38.8% (32,45)	35.8% (29,42)	91.2% (85,97)
Hansen, 2017 n=487 (31%)	T2W1+ DWI+ DCE	PI-RAD v1&2 ≥3 of 5	18-24 core TRUS-SB TP according to the Ginsburg TRUS-SB protocol	GS 7 to 10	92.6% (88,97)	39.3% (34,45)	40.2% (35,45)	92.4% (88,97)
Pepe, 2015 n=100 (13%)	T2W+ DWI+ DCE+spectroscopy	PI-RAD v1 ≥4 of 5	TP saturation biopsy	GS ≥7	100% (100,100)	100% (100,100)	100% (100,100)	100% (100,100)
Pepe, 2018 n=1032 (26%)	T2W1+DWI+DCE	PI-RAD v1&2 ≥3 of 5	TP saturation biopsy	GS≥ 3+4	83.8% (79,88)	72.4% (69,76)	52.1% (47,57)	92.6% (90,95)
Pre-2015 studies GS≥ 3+4 - previously negative								

Study (prevalence of CSPCa)	Index test	Positive MRI	Reference standard	CSPCa definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Pepe 2013 (18%) [73]	T2WI DWI DCE MRSI Combination	T2WI: low signal intensity; DCE: early and intense enhancement; MRSI: choline/ Citrato ≥3 SD above mean healthy value	28 saturation core biopsy + 3—4 core MRI-TB	GS ≥7	100% (100—100)	50% (38—62)	30% (17—44)	100% (100—100)
Abd-Alazeez and Ahmed 2014[a] [80] (21%)	T2WI+ DWI+DCE (108 half prostates from 54 pts)	≥3 of 5 scoreTRUS-SB	5mm template prostate mapping biopsy + MRI software MRI-US fusion (≥20 cores)	GS ≥7	87% (73—100)	42% (32—53)	29% (18—40)	92% (84—100)

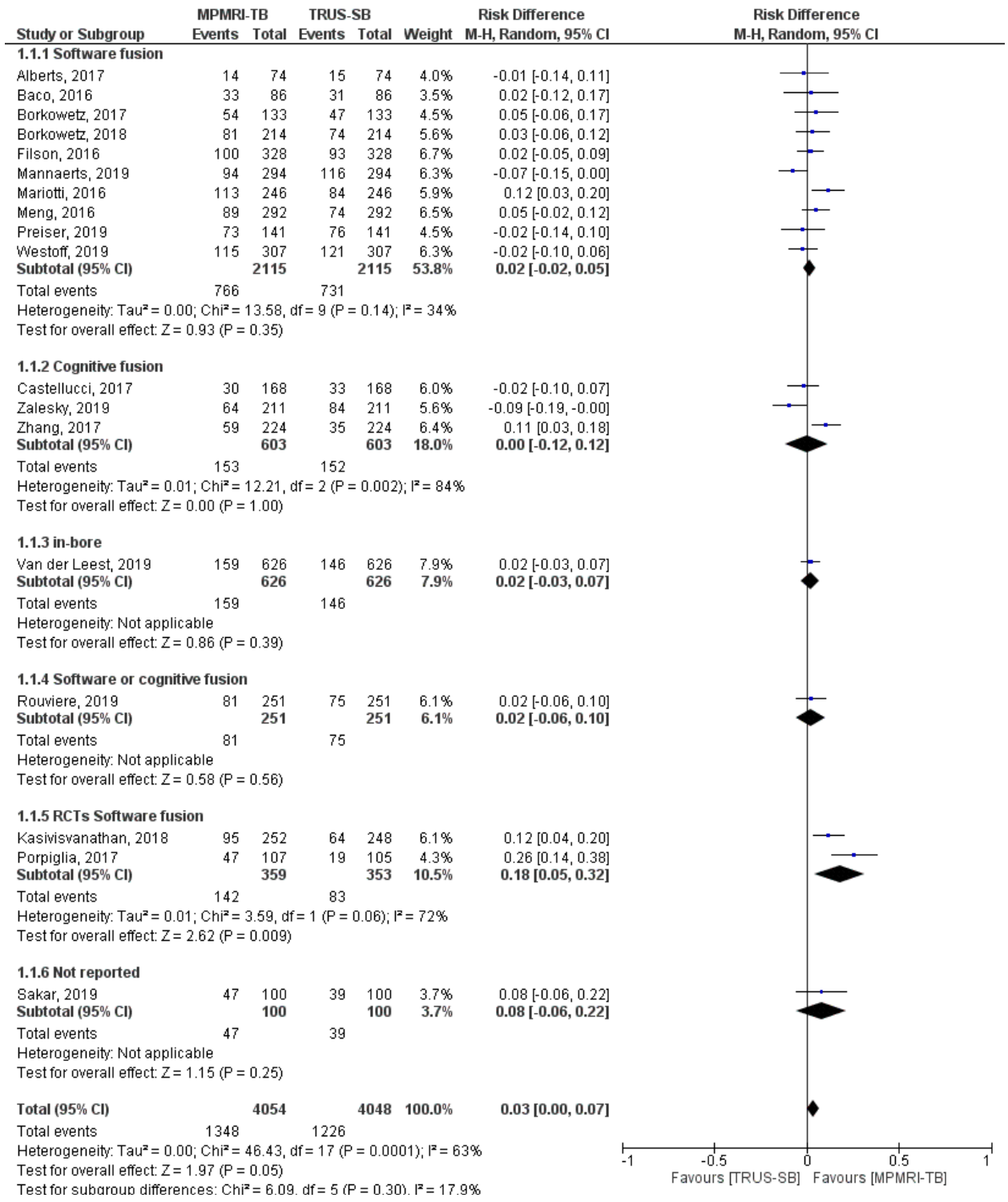


Appendix 7 - Figure 2.1: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men

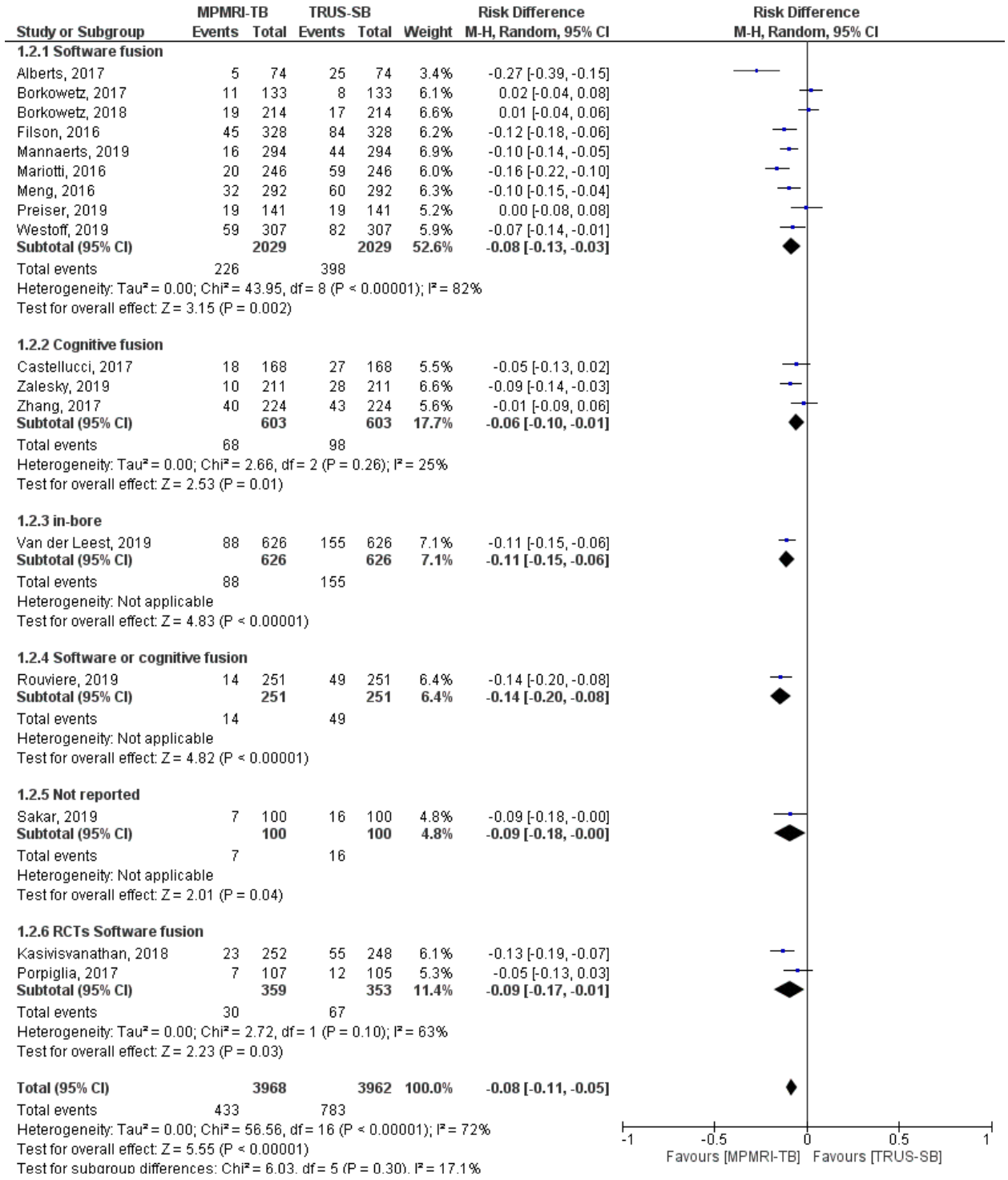


Appendix 7 - Figure 2.2: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for previously negative men

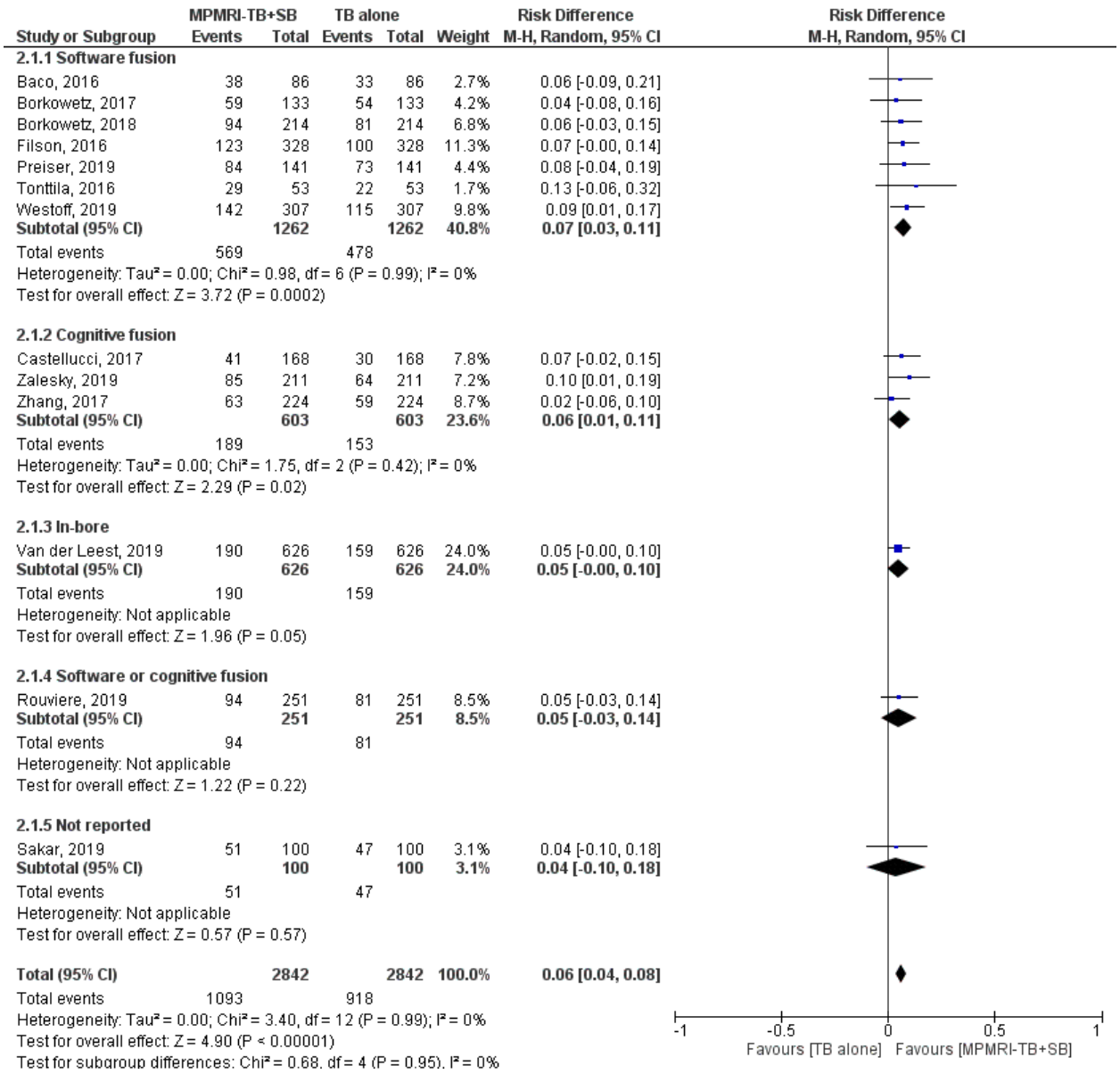
Appendix 8: Subgroup Analysis (by type of TB)



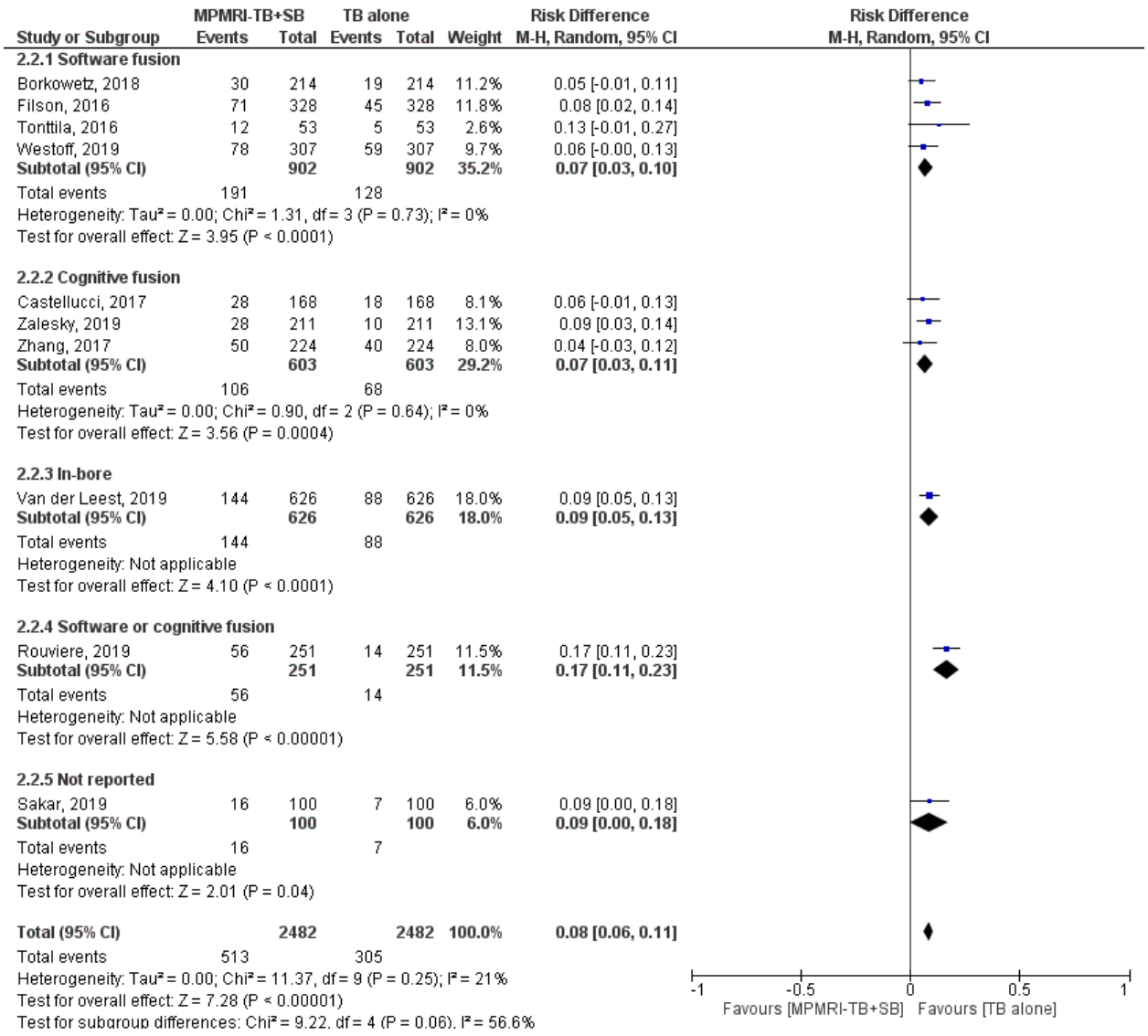
Appendix 8 - Figure 1.1: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men



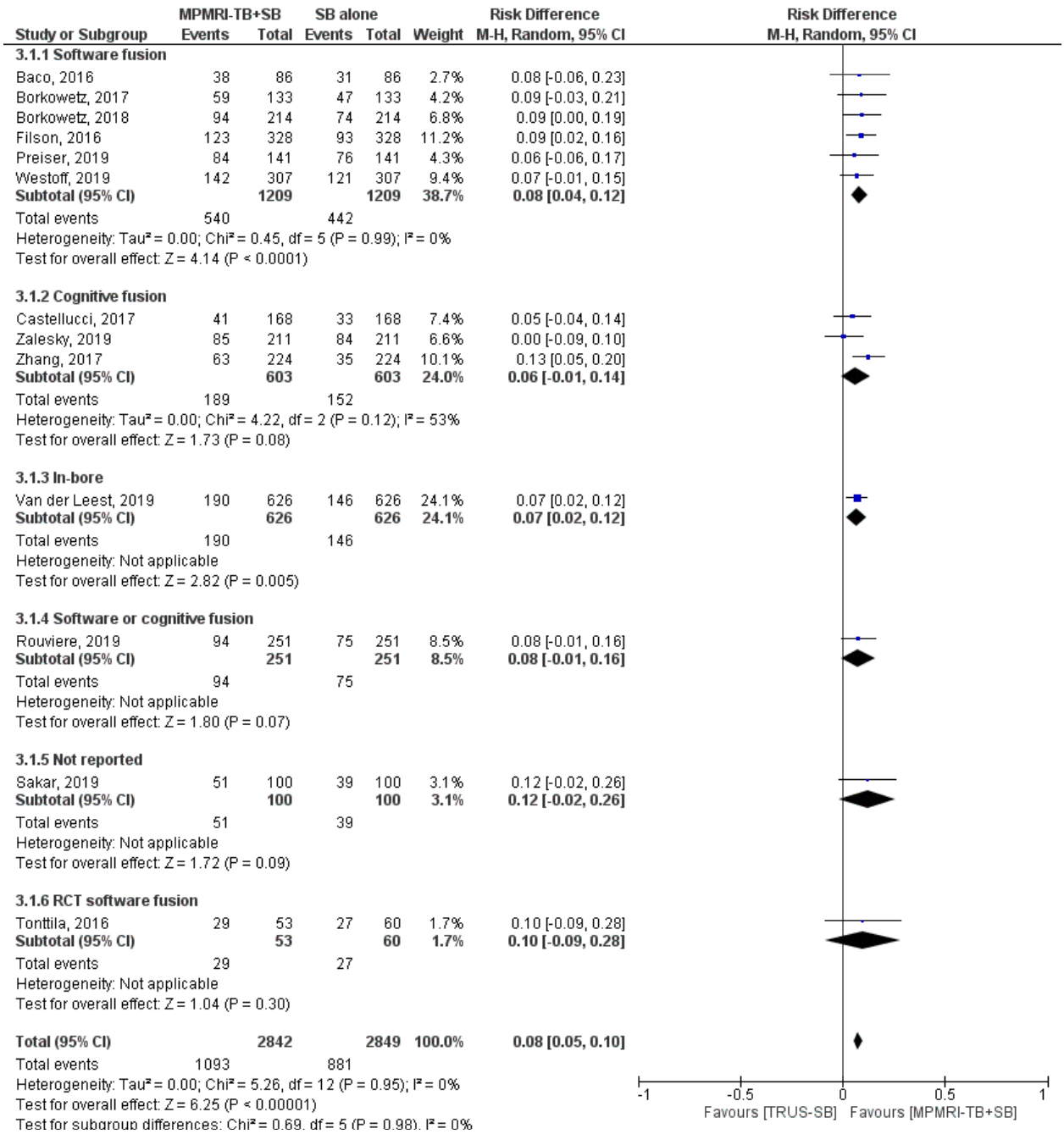
Appendix 8 - Figure 1.2: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men



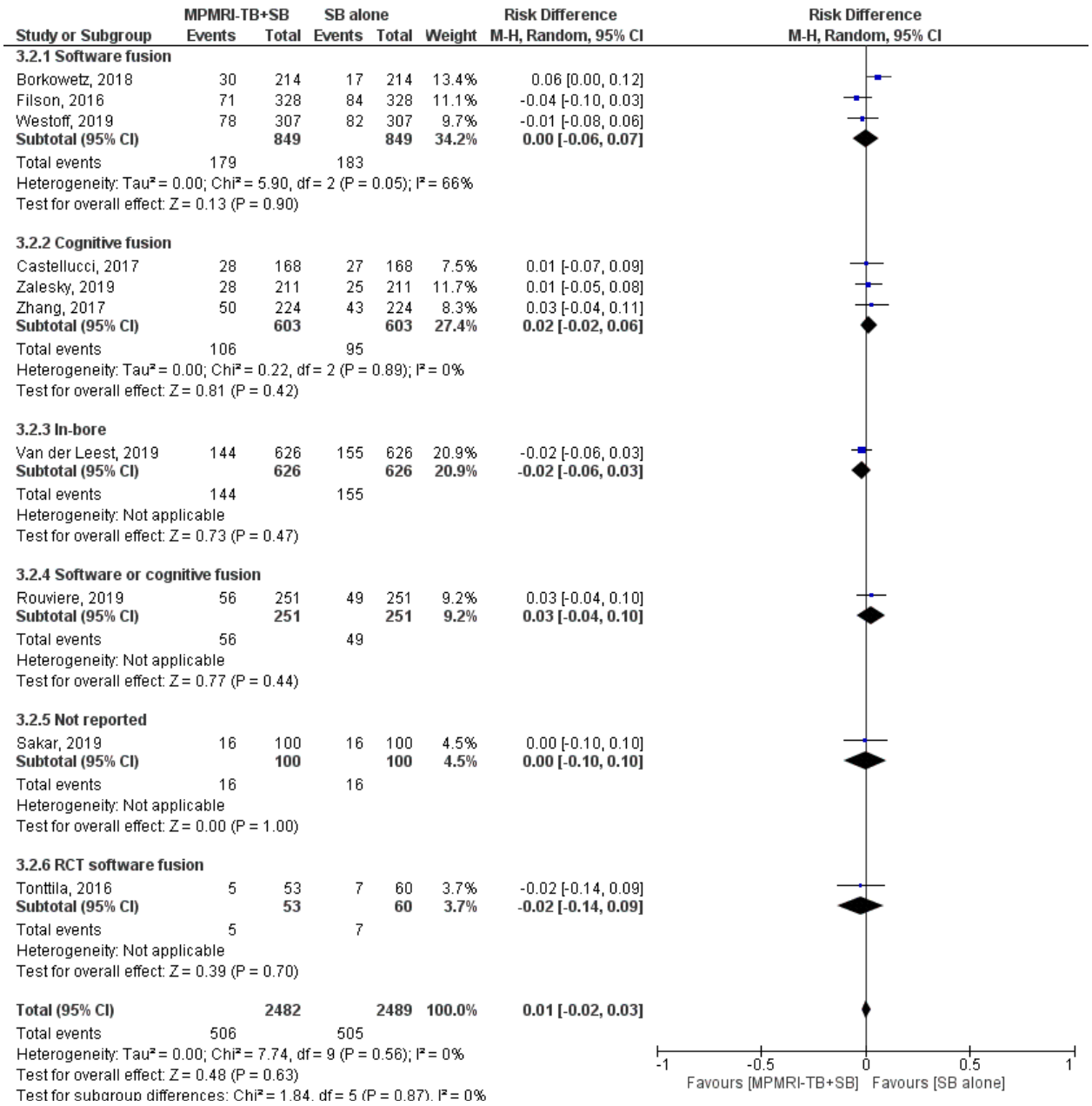
Appendix 8 - Figure 2.1: (MPMRI-TB+ TRUS-SB vs. MPMRI-TB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men



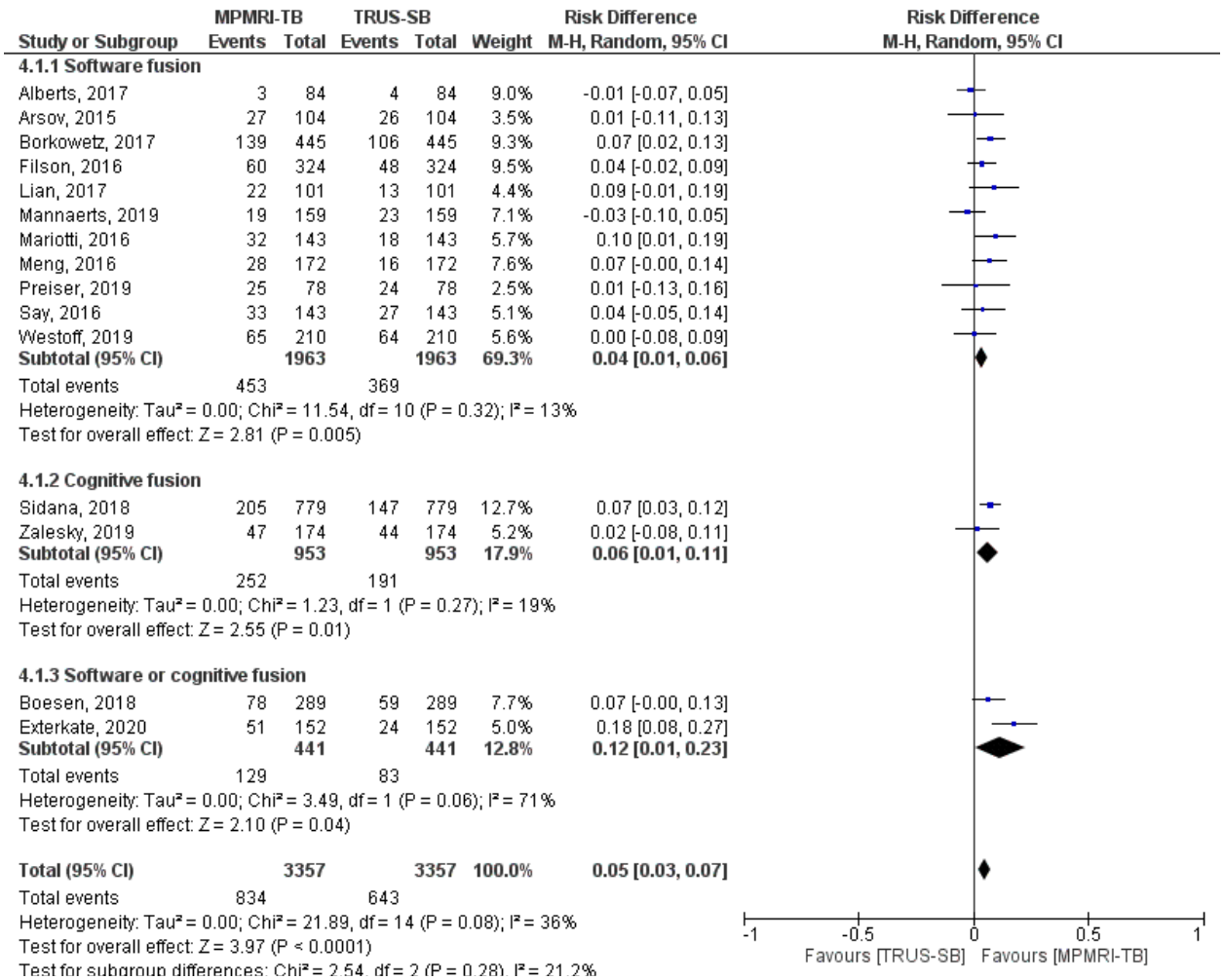
Appendix 8 - Figure 2.2: (MPMRI-TB+ TRUS-SB vs. MPNRI-TB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men



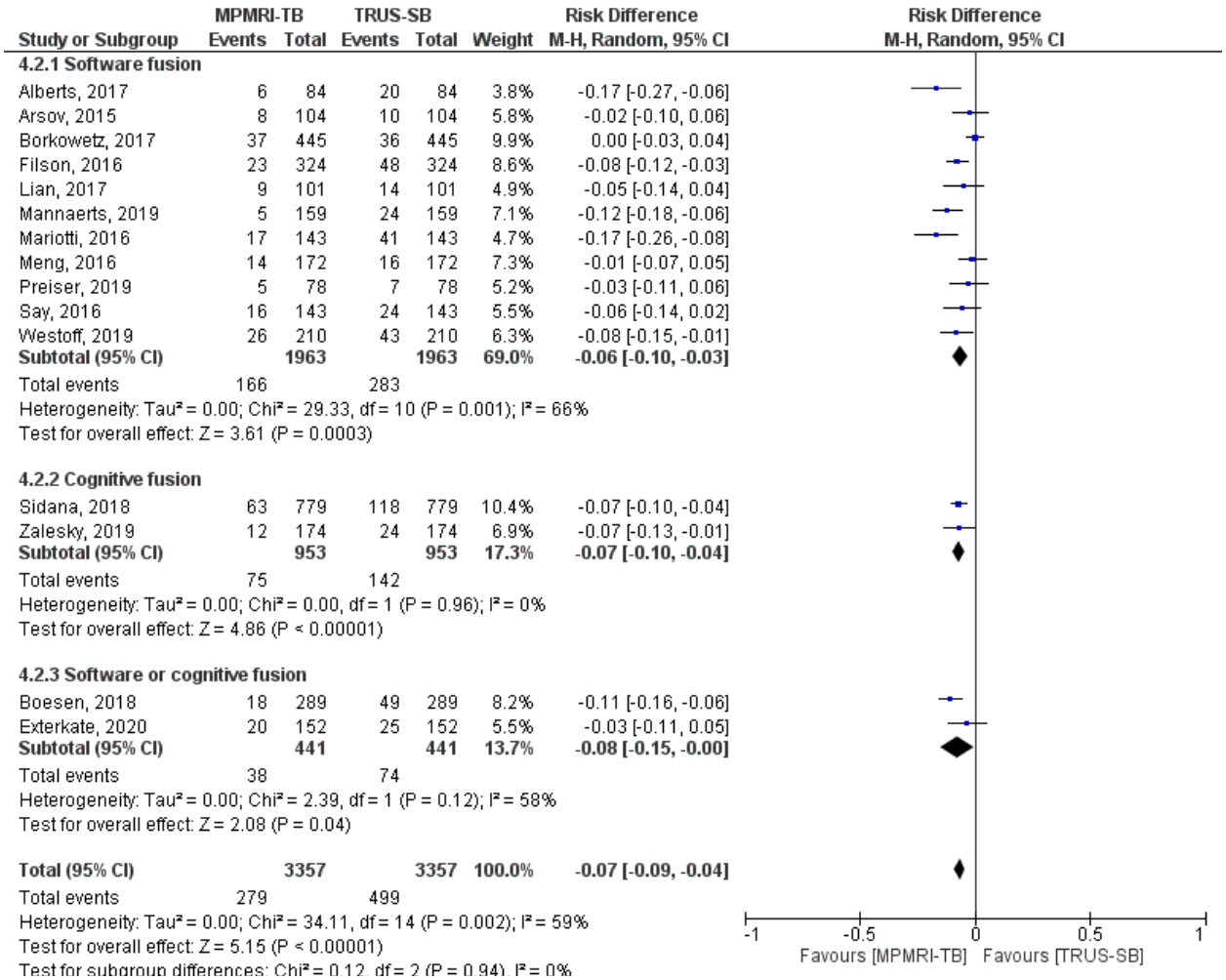
Appendix 8 - Figure 3.1: (MPMRI-TB+ TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for biopsy-naïve men



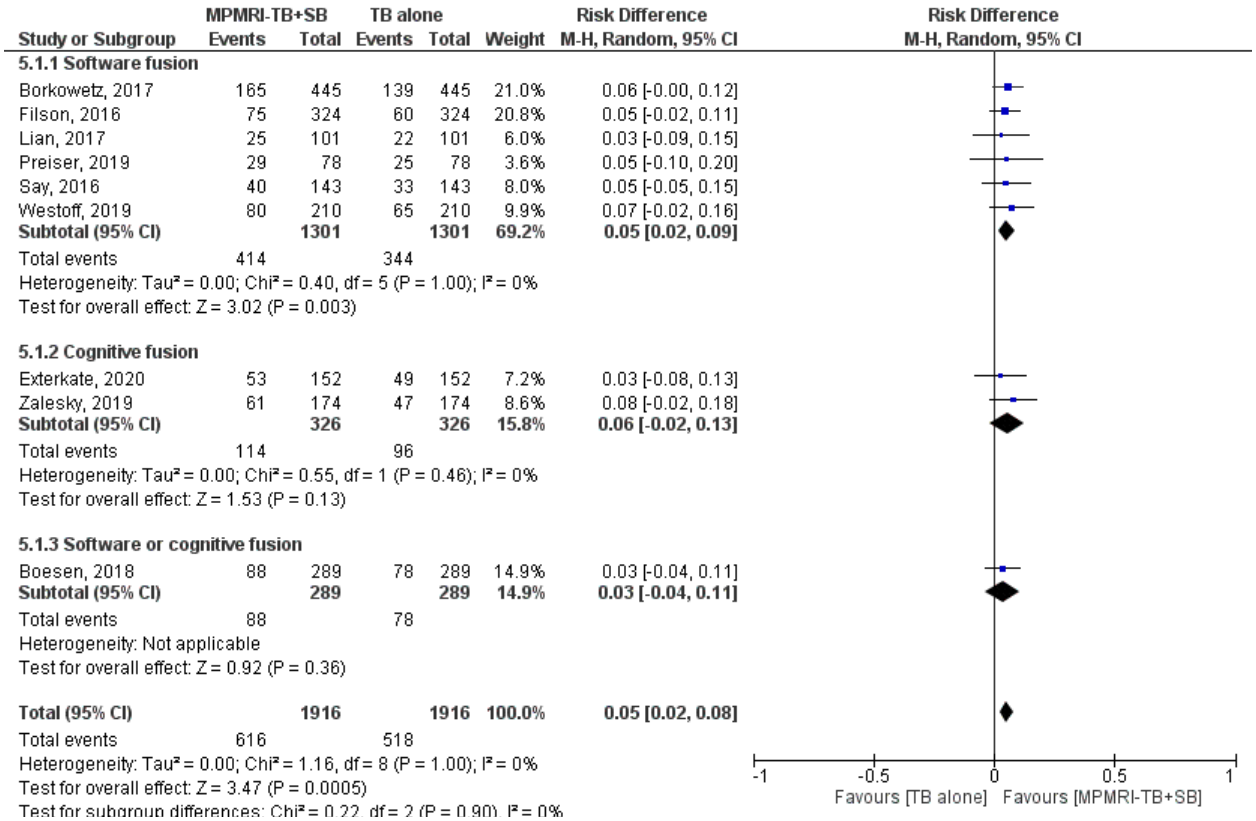
Appendix 8 - Figure 3.2: (MPMRI-TB+ TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for biopsy-naïve men



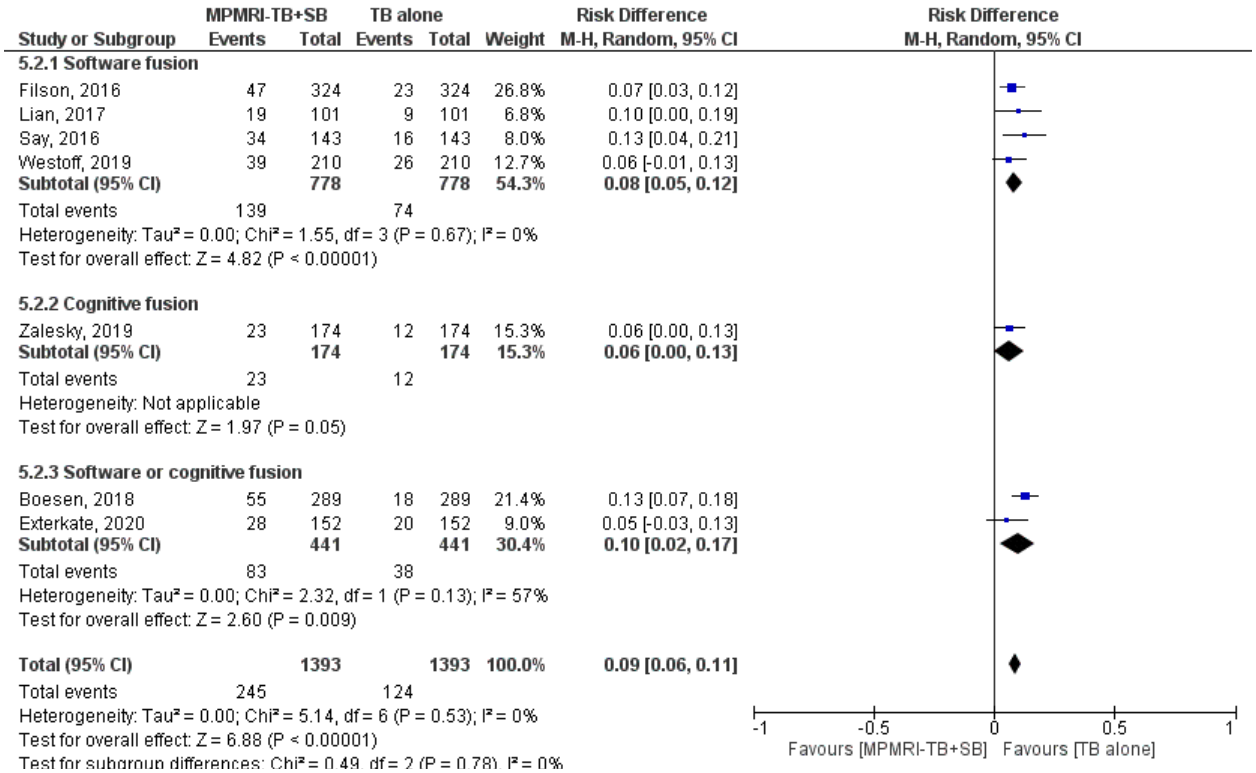
Appendix 8 - Figure 4.1: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for men with prior negative biopsy for cancer



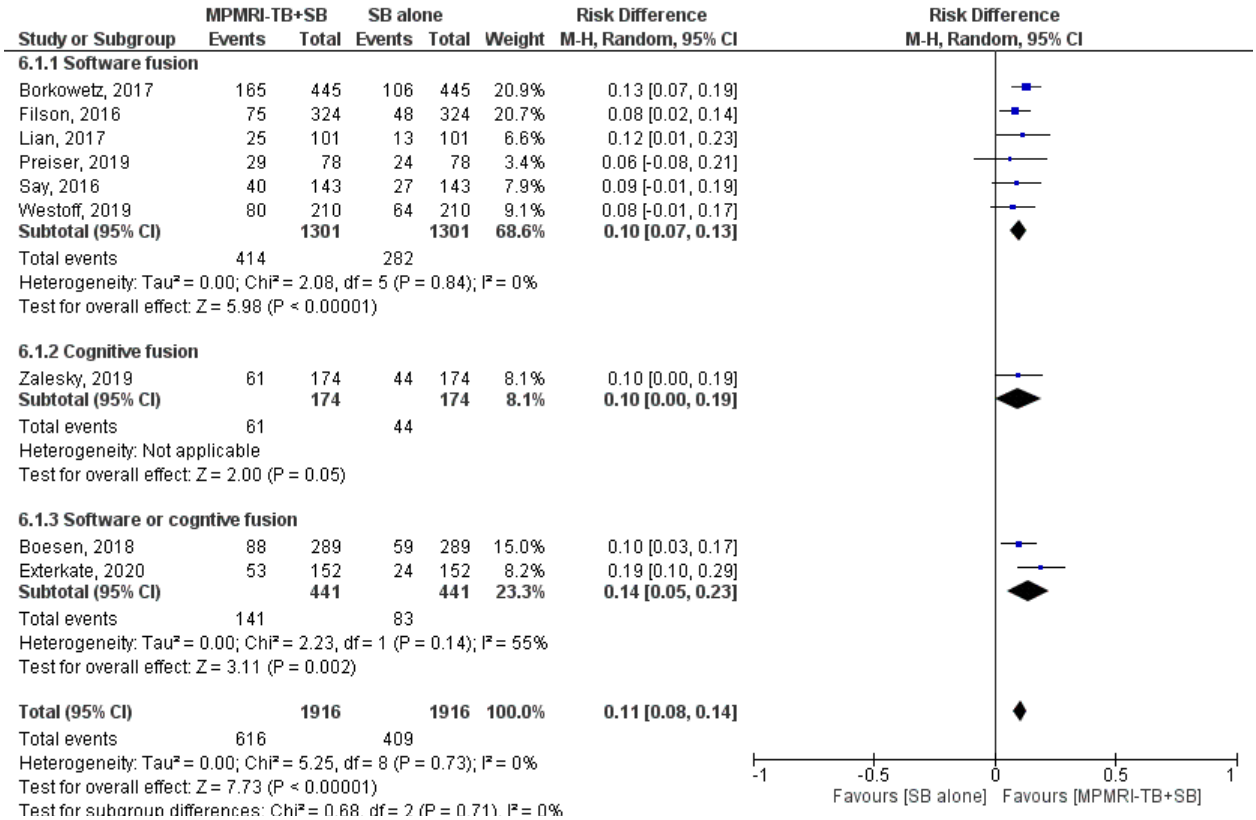
Appendix 8 - Figure 4.2: (MPMRI-TB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for for men with prior negative biopsy for cancer



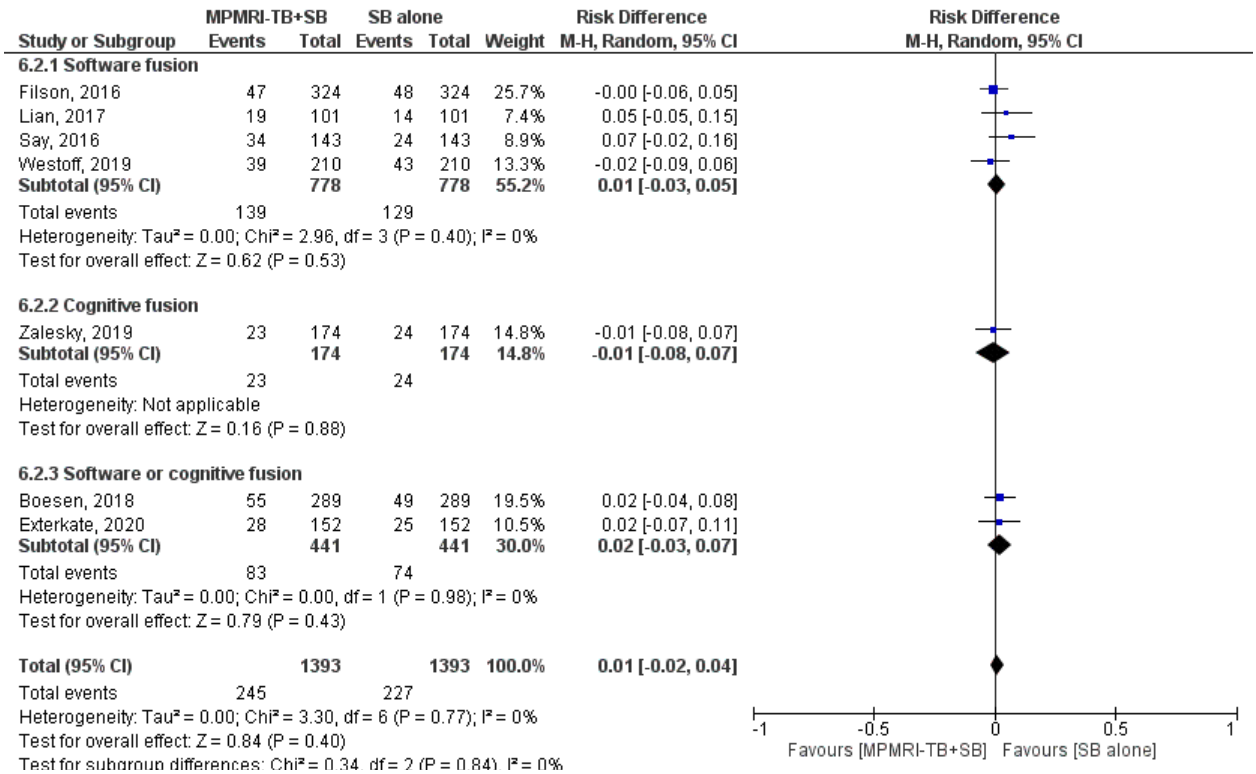
Appendix 8 - Figure 5.1: (MPMRI-TB+TRUS-SB vs. MPMRI-TB) Risk differences in detection of clinically significant prostate cancer for for men with prior negative biopsy for cancer



Appendix 8 - Figure 5.2: (MPMRI-TB+TRUS-SB vs. MPMRI-TB) Risk differences of clinically insignificant prostate cancer for men with prior negative biopsy for cancer



Appendix 8 - Figure 6.1: (MPMRI-TB+TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically significant prostate cancer for men with prior negative biopsy for cancer



Appendix 8 - Figure 6.2: (MPMRI-TB+TRUS-SB vs. TRUS-SB) Risk differences in detection of clinically insignificant prostate cancer for men with prior negative biopsy for cancer