Ontario
Cancer Care Ontario
Action Cancer Ontario

Guideline #27-2 BEING UPDATED

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

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

M.A. Haider, X. Yao, D.A. Loblaw, A. Finelli, and the MRI in Prostate Cancer Guideline Development Group

Report Date: August 5, 2015

CAUTION

As of March 2019, recent evidence indicates that Recommendation 1 requires revision. An updated version of this guideline is in progress.

It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 27-2 is comprised of 3 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/281

Section 1:	**Guideline Recommendations**
Section 2:	**Evidentiary Base**
Section 3:	**Guideline Development Methods and Review Process**

For information about this document, please contact Dr. Haider and Dr. Loblaw, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Guideline Citation (Vancouver Style):
Haider MA, Yao X, Loblaw DA, Finelli A, and the MRI in Prostate Cancer Guideline Development Group. Multiparametric MRI in the Diagnosis of clinically significant Prostate Cancer. Toronto (ON): Cancer Care Ontario; 2015 Aug 5 [Being Updated 2018 Dec]. Program in Evidence-based Care Guideline No.: 27-2 BEING UPDATED.

PEBC Guideline Related Journal Citations:
Haider MA, Yao X, Loblaw A, Finelli A. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer: A Systematic Review. Clin Oncol (R Coll Radiol). 2016;28:550-67.

Haider MA, Yao X, Loblaw A, Finelli A. Evidence-based guideline recommendations on multiparametric magnetic resonance imaging in the diagnosis of prostate cancer: A Cancer Care Ontario clinical practice guideline. Can Urol Assoc J. 2017;11:E1-7.

Guideline #27-2

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

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

Table of Contents

Section 1: Guideline Recommendations 1

Section 2: Evidentiary Base 6

Section 3: Guideline Development Methods and Review Process 33

Guideline #27-2: Section 1

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

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

M. A. Haider, X. Yao, D.A. Loblaw, A. Finelli, and the MRI in Prostate Cancer Guideline Development Group

Report Date: August 5, 2015

GUIDELINE OBJECTIVES

1. To make recommendations with respect to the use of multiparametric magnetic resonance imaging (MPMRI) in the diagnosis of clinically significant prostate cancer in patients with an elevated risk of clinically significant prostate cancer (according to prostate-specific antigen [PSA] level and/or nomograms) who are biopsy-naïve.
2. To make recommendations with respect to the use of MPMRI in the diagnosis of clinically significant prostate cancer in patients with a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA) who had a negative transrectal ultrasound-guided (TRUS-guided) systematic biopsy.

TARGET POPULATION

Patients with an elevated risk of clinically significant prostate cancer (according to PSA level and/or nomograms) who are biopsy-naïve or have a prior negative TRUS-guided systematic biopsy.

INTENDED USERS

Radiologists, family physicians, oncologists, urological surgeons, and other clinicians who provide care for patients defined by the target population.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

Recommendation 1

In patients with an elevated risk of clinically significant prostate cancer (according to PSA level and/or nomograms) who are biopsy-naïve:

- MPMRI followed by targeted biopsy (biopsy directed at cancer-suspicious foci detected with MPMRI) should not be considered the standard of care.
- Data from future research studies are essential and should receive high-impact trial funding to determine the value of MPMRI in this clinical context.

Key evidence and quality

- Eight studies [1-8] that met our preplanned study selection criteria addressed the first objective. The quality of evidence was poor to moderate (for details see Appendices II

and III in Section 2). Meta-analyses of the study results were not feasible because of high clinical heterogeneity among studies using different definitions for clinically significant prostate cancer and for positive MPMRI results, and different MPMRI navigational systems and MPMRI techniques.

- In two studies [4,6] with a prevalence of clinically significant prostate cancer of 21% to 30%, the ranges of sensitivity, specificity, positive predictive value, and negative predictive value of MPMRI to detect clinically significant prostate cancer were 68% to 94%, 21% to 72%, 24% to 50%, and 83% to 94%, respectively.
- Clinically significant prostate cancer detected by MPMRI followed by targeted biopsy but not by TRUS-guided systematic biopsy ranged from 2% to 13% and clinically significant prostate cancer detected by TRUS-guided systematic biopsy but not by MPMRI followed by targeted biopsy ranged from 0% to 7% in five studies with a total of 1388 patients [1,3,5,7,8].
- A randomized controlled trial (RCT) by Park et al [2] found that MPMRI followed by targeted biopsy plus TRUS-guided systematic biopsy identified more clinically significant prostate cancer patients than TRUS-guided systematic biopsy alone in 85 patients (11 of 44 = 25% versus two of 41 = 5%, p = 0.01; but 10 of 11 clinically significant prostate cancer patients were detected by TRUS-guided systematic biopsy alone in the combination group of MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy).
- Pokorny et al [8] (using radical prostatectomy for confirmation) reported that four patients (5%) were upgraded to clinically significant prostate cancer category and 11 (15%) were downgraded to non-clinically significant prostate cancer category by MPMRI followed by targeted biopsy; four patients (5%) were upgraded to clinically significant prostate cancer and 18 (24%) were downgraded to non-clinically significant prostate cancer by TRUS-guided systematic biopsy.
- Pokorny et al [8] reported that 0.9% of patients developed urosepsis, and 0.4% required admission for hematuria after TRUS-guided systematic biopsy; and 0.7% experienced a vasovagal episode after MPMRI followed by targeted biopsy.
- No patient outcomes regarding a positive change in patient management or survival were reported.

Justifications (considering and balancing clinical benefits and harms)

The Working Group (the guideline authors) does not recommend MPMRI followed by targeted biopsy as a standard care in Ontario for the target population because of the following reasons:

- The quality of evidence was poor to moderate;
- Specificity and positive predictive value of MPMRI were not high;
- The detection rates from MPMRI followed by targeted biopsy were not consistently higher than TRUS-guided systematic biopsy in the eligible studies;
- Although cost-effectiveness and resource allocation issues are beyond the scope of this Program in Evidence-Based Care (PEBC) guideline, the Working Group was sensitive to the fact that there are limited MRI resources in Ontario and that these recommendations address a large target population: patients with an elevated risk of clinically significant prostate cancer (according to PSA level and/or nomograms) who are biopsy-naïve.

Although an RCT [2] reported that MPMRI followed by targeted biopsy plus TRUS-guided systematic biopsy detected a statistically significant higher rate of clinically significant prostate cancer than TRUS-guided systematic biopsy alone, the study quality was low (no details of randomization methods, no expected effect, power, and sample size calculation, etc.) and TRUS-guided systematic biopsy alone in the combination group detected

significantly more patients with clinically significant prostate cancer than the TRUS-guided systematic biopsy group. The Working Group was therefore concerned regarding reproducibility of these data until another properly designed and powered RCT was to be completed.

Other consideration

Patient preference: The patients should be informed of the possibility of false-negative results from TRUS-guided systematic biopsy, and the potential complications from biopsy.

Recommendation 2

In patients who had a prior negative TRUS-guided systematic biopsy and demonstrate a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA levels):

- MPMRI followed by targeted biopsy may be considered to help in detecting more clinically significant prostate cancer patients compared with repeated TRUS-guided systematic biopsy.

Key evidence and quality

- Seven studies [9-15] that met our preplanned study selection criteria addressed the second objective. The quality of evidence was poor to moderate (for details see Appendix II in Section 2). Meta-analyses of the study results were not feasible because of high clinical heterogeneity among studies using different definitions for clinically significant prostate cancer and for positive MRI results, and different MRI navigational systems and MRI techniques.
- In three studies (n = 570) [9,13,14] with a prevalence of clinically significant prostate cancer of 18% to 34%, the ranges of sensitivity, specificity, positive predictive value, and negative predictive value of MPMRI to detect clinically significant prostate cancer were 68% to 100%, 41% to 91%, 29% to 87%, and 79% to 100%, respectively.
- MPMRI followed by targeted biopsy detected more clinically significant prostate cancer patients than repeated TRUS-guided systematic biopsy in all four studies with total 516 patients [10-12,15], but only one small sample size study reached a statistically significant difference [12] (n = 38) (24% versus 5%, p = 0.02). Clinically significant prostate cancer detected by MPMRI followed by targeted biopsy but not by repeated TRUS-guided systematic biopsy ranged from 2% to 21% and clinically significant prostate cancer detected by repeated TRUS-guided systematic biopsy but not by MPMRI followed by targeted biopsy ranged from 0% to 5% in four studies.
- The Hoeks et al 2012 study [9] stated 0.4% of patients had sepsis and 1.5% experienced a vasovagal reaction after MRI-guided targeted biopsy. No patients had significant complications that needed hospital admission from saturation biopsy in the Pepe et al 2013 study [13].
- No patient outcomes regarding positively changing patient management or survival outcomes were reported.

Justifications (considering and balancing clinical benefits and harms)

For patients who had a prior negative TRUS-guided systematic biopsy and continue to have a growing risk of clinically significant prostate cancer, although the quality of evidence was poor to moderate and specificity and positive predictive value of MPMRI were not high, all the eligible studies supported the notion that MPMRI followed by targeted biopsy detected a higher number of clinically significant prostate cancer when compared with repeated TRUS-guided systematic biopsy. However, most studies did not reach a statistical difference. Furthermore, the variability in definitions of MPMRI-positive results and clinically significant prostate cancer, and the variability of MPMRI techniques (including different magnet

strength, sequences, MPMRI navigational system, etc.) and radiologists' clinical experience, added more uncertainty to using MRI in the diagnosis of clinically significant prostate cancer. Thus, the Working Group members recommend that MPMRI followed by targeted biopsy may be considered to aid in detecting more clinically significant prostate cancer patients compared with repeated TRUS-guided systematic biopsy in the target population, but should not be a reflexive next step in this population. It should be considered only for those patients who demonstrate a growing risk over time after the first negative biopsy.

Other considerations

Patient preference: Patients and their care providers are faced at times with a rising PSA level and a previous negative biopsy(s). Clinicians together with patients should decide whether MPMRI followed by targeted biopsy should be offered in conjunction with re-TRUS-guided systematic biopsy after weighing the potential benefit of improved detection rates of clinically significant prostate cancer against the extra cost and potential side effects associated with more biopsy cores than re-TRUS-guided systematic biopsy or MPMRI followed by targeted biopsy alone. Patients should be informed of the possibility of false-negative and false-positive results with MPMRI followed by targeted biopsy and/or repeated TRUS-guided systematic biopsy, and the potential complications of prostate biopsy.

Resource use: Cost-effectiveness is beyond the scope of the PEBC guideline; the Working Group leaves resource consideration to other decision makers.

Before MRMRI is used in the clinical practice, diagnostic performance in each centre should be assessed and physicians should be familiar with current international prostate MRI performing and reporting standards [16].

RELATED PEBC GUIDELINES

1. #17-9 Active surveillance for the management of localized prostate cancer (https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2286)
2. #27-3 Magnetic resonance imaging in staging for prostate cancer (https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/606)

UPDATING

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. This is described in the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true

FUNDING

The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

Guideline #27-2: Section 2

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

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

M.A. Haider, X. Yao, D.A. Loblaw, A. Finelli, and the MRI in Prostate Cancer Guideline Development Group

Report Date: August 5, 2015

INTRODUCTION

As one of the most common cancers in men (excluding non-melanoma skin cancers), prostate cancer is the third leading cause of death in Canadian male cancer patients [17]. Although some low-risk prostate cancers grow slowly and may need minimal or no treatments, intermediate- or high-risk prostate cancers can be life-threatening. It is estimated that on average, 11 Canadian men will die from prostate cancer every day in 2014 [17]. Considering this, early and accurate diagnosis for clinically significant prostate cancer in patients with an elevated risk is important to determine optimal managements and thereby improve their quality of life and/or extend their lives. There is no consistent definition for clinically significant prostate cancer in the world. It is defined as a Gleason score (GS) of ≥ 7 in some centres, but in other centres, the definition is combined GS and/or tumour size. The current standard method to diagnose clinically significant prostate cancer is transrectal ultrasound (TRUS)–guided systematic biopsy (10 to 12 cores) [7]. Because TRUS-guided systematic biopsy samples areas from the prostate and not a specific imaged target, this biopsy technique can over-diagnose clinically insignificant prostate cancer and miss clinically significant lesions in patients in the first biopsy setting or the repeated biopsy setting [3,15]. The template transperineal mapping biopsy or saturation biopsy technique should be more diagnostic than TRUS-guided systematic biopsy to detect clinically significant prostate cancer because in that technique, the prostate is divided into ≥ 20 regions in 5 mm increments and a specimen is taken from each region [18]. However, for a walnut-sized prostate, the template transperineal mapping biopsy or saturation biopsy technique is more invasive and resource intense than TRUS-guided systematic biopsy.

In the past few years, there has been growing interest in the use of multiparametric magnetic resonance imaging (MPMRI) to localize clinically significant prostate cancer. When an MPMRI is performed, different tissue properties can be highlighted by manipulating the way the image is obtained. T2-weighted imaging (T2WI), diffusion weighted imaging (DWI), dynamic contrast-enhanced T1 weighted magnetic resonance imaging (DCE-MRI), and proton spectroscopy (MRSI) are performed and imaging features from at least three of these data sets are combined to determine the location of a cancer as part of the MPMRI examination. MPMRI followed by targeted biopsy means biopsy is performed directly at cancer-suspicious foci detected with MPMRI.

Recently, there have been several publications regarding MPMRI techniques in improving the diagnostic accuracy of clinically significant prostate cancer and a growing adoption of MPMRI internationally [1,2,13]. Thus, there is a need for making recommendations with respect to the use of MPMRI in the diagnosis of clinically significant prostate cancer in patients with an elevated risk of clinically significant prostate cancer who are either biopsy-naïve or who have a previous negative TRUS-guided biopsy. Thus, the Working Group (the guideline authors, including one radiologist, one radiation oncologist, one urologist, and one methodologist) of the MRI in Prostate Cancer Guideline Development Group in association with the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario, conducted a systematic review to summarize the relevant papers 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 systematic review has been registered on the website of the international prospective register of systematic reviews (www.crd.york.ac.uk/prospero) as CRD42013004255.

RESEARCH QUESTIONS

1. For biopsy-naïve patients with an elevated risk of clinically significant prostate cancer (according to prostate-specific antigen [PSA] levels and/or nomograms):
   (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer (diagnostic accuracy outcomes including sensitivity, specificity, predictive value, and upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy), positively change patient management, or improve patient outcomes (including side effects and survival outcomes)?
   (2) Is MPMRI followed by targeted biopsy better than TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and the other above patient outcomes?
2. For patients who had a previous negative TRUS-guided systematic biopsy (at least eight cores) with a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA):
   (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer (diagnostic accuracy outcomes including sensitivity, specificity, predictive value, and upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy), positively change patient management, or improve patient outcomes (including side effects and survival outcomes)?
   (2) Is MPMRI followed by targeted biopsy better than repeated TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and the other above patient outcomes?

METHODS

The evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

(1) Search and evaluation of existing guidelines based on a systematic review or existing systematic reviews: if one or more existing guidelines, or systematic reviews (defined as describing search databases, search time period, search terms, and study selection criteria; and having at least one eligible article meeting our study selection criteria for original studies) were identified that addressed the research questions and were of reasonable quality, then those guidelines or systematic reviews would form the core of the evidentiary base.

(2) Systematic review of the primary literature: this review would be conducted if no existing guidelines or systematic reviews were located and/or accepted.

Search for Guidelines and Existing Systematic Reviews

The following resources were checked for existing practice guidelines and systematic reviews that were relevant to the research questions and published from 2010 to October 9, 2013: National Guideline Clearinghouse, National Health and Medical Research Council (Australia), New Zealand Guidelines Group, American Society of Clinical Oncology (ASCO), National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), European Society of Radiotherapy & Oncology (ESTRO), European Association of Urology (EAU), Canadian Urological Association (CUA), American College of Radiology (ACR), European Society of Urogenital Radiology (ESUR), National Institute for Health Research, and the Standards and Guidelines Evidence Directory of Cancer Guidelines (www.cancerview.ca/sage). In addition, the MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews databases were searched from 2004 to April 23, 2014 to identify existing relevant systematic reviews and meta-analyses.

Primary Literature Systematic Review

If no eligible guidelines or systematic reviews were identified, a primary search of the literature was performed and described below.

Literature Search Strategy

A literature search was performed using the Ovid search engine from January 1, 1997 to April 23, 2014 using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews. The literature search of the electronic databases combined alternatives of "prostate cancer" terms along with "MRI" terms (Appendix I). In addition, the proceedings of the meetings of the ASCO, CUA, AUA, ASTRO, ESTRO, and Radiological Society of North America were searched for relevant abstracts in the years 2011 to 2014 if they were accessible from their websites by April 2014.

Study Selection Criteria and Protocol

Inclusion Criteria

Articles or abstracts were eligible for inclusion in this systematic review if they met all the following preplanned criteria:

1. Full texts, or abstracts that were randomized controlled trials (RCTs) or prospectively analyzed ≥ 30 patients.
2. Patients should be those who had an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms).
3. For research questions 1 (1) and 2 (1), reference standards should be post-operational pathological report, template transperineal mapping biopsy/saturation biopsy (≥20 cores) for MPMRI-positive patients or MPMRI followed by targeted biopsy-positive patients, or clinical follow-up for negative results from MPMRI or MPMRI followed by targeted biopsy.
4. Outcomes included accuracy of diagnosis for clinically significant prostate cancer (i.e., sensitivity, specificity, predictive value, and upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy), change in patient management, or patient clinical outcomes (including side effects and survival outcomes).

Exclusion Criteria

Articles or abstracts were excluded if they met any of the following preplanned criteria:

1. Studies or abstracts were published in a language other than English.
2. They were published in the form of letters, editorials, commentaries, or non-systematic review or non-meta-analysis.
3. All the patients had diagnosis of prostate cancer at baseline.
4. For research questions 1 (1) and 2 (1), the reference standards were MPMRI followed by targeted biopsy or MPMRI plus TRUS-guided systematic biopsy.

A research methodologist (XY) reviewed the titles and abstracts that resulted from the search. For those items that warranted full-text review, XY reviewed each item and discussed with the other Working Group members (MH, AL, AF) to confirm the final study selections. A second independent auditor (WH) audited all extracted data. An assessment of study quality was performed for all the included evidence by one methodologist (XY).

Synthesizing the Evidence

If there is no clinical heterogeneity for patient characteristics, MPMRI techniques, etc., for each outcome from three or more studies, meta-analyses were planned assuming a two-sided significance level of $\alpha = 0.05$ and to be performed with the software StataIC 11. To keep consistent, all the outcomes in Tables were calculated by using the same software (Stata/IC 11).

RESULTS

Search for Existing Guidelines and Systematic Reviews

No clinical practice guidelines based on a systematic review were found. A total of 12 systematic reviews [19-30] were relevant and met the preplanned inclusion criteria. However, none of these systematic reviews covered both of the two research questions or used the same study selection criteria as ours. Thus, a systematic review by the PEBC was launched and these 12 reviews were not discussed further. However, a check of the included studies in these systematic reviews was performed to identify extra eligible studies for our systematic review.

Primary Literature Systematic Review

Literature Search Results

Of 8,663 citations identified from the MEDLINE and EMBASE searches and the Cochrane Clinical trial Register, 8,301 articles were excluded after reviewing the titles and abstracts, and 52 met our preplanned study selection criteria after reviewing the full texts [1-15,31-67]. Of these, 15 were analyzed in this systematic review and their reference lists were hand-searched and no further eligible papers were found [1-15]; 37 were not extracted for the following reasons: articles only reported overall prostate cancer outcomes without a subgroup analysis for clinically significant prostate cancer; the same outcomes from the same patient population were reported in duplicate (only the latest paper with the largest sample analyzed was included in the current review); papers did not report clear data to calculate diagnostic accuracy outcomes or detection rates; and papers mixed biopsy-naïve patients and patients with previous negative TRUS-guided systematic biopsy together but did not report outcomes for different target patients separately.

A check of conference abstracts yielded 28 abstracts that met the study selection criteria. Because conference abstracts did not describe the details of study methods and some data were unclear, the Working Group decided not to summarize them to make

recommendations. Fourteen abstracts had been published as full texts and were included in our literature search [68-81]. Another 14 abstracts will require follow-up in updated versions of this guideline in the future [82-95].

The PRISMA flow diagram (http://www.prisma-statement.org/statement.htm) of studies considered in this systematic review was modified and shown in Figure 1.

Study Design and Quality

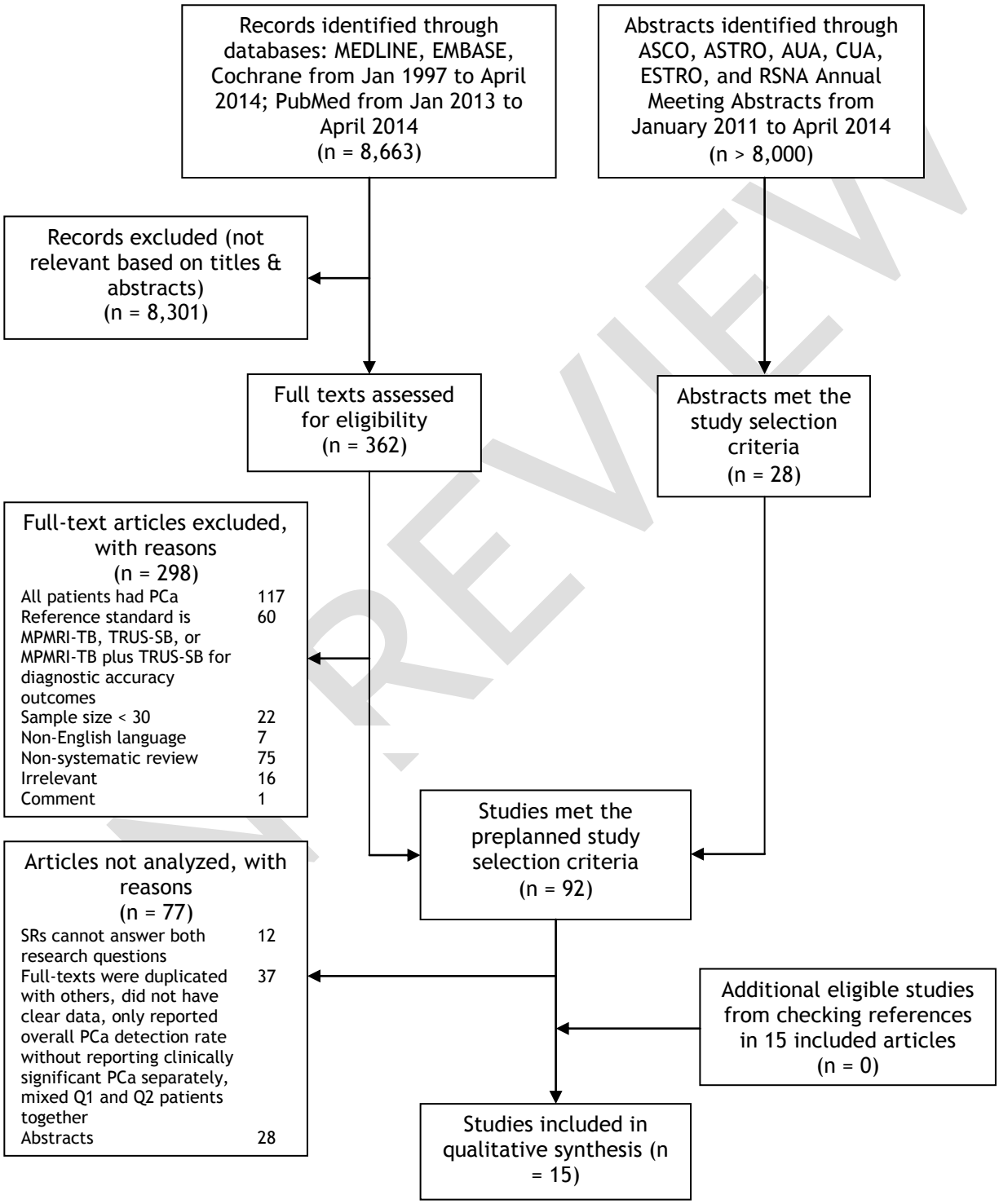
Among the 15 studies, one was an RCT [2], five were prospective studies [3-5,8,13], six were retrospective studies [7,9-12,15], and three articles did not report their study designs [1,6,14] (Table 1).

The study quality was assessed using the QUADAS-2 tool [96] (Appendix II). For the five studies that reported diagnostic accuracy outcomes, the overall quality was from low to moderate [4,6,9,13,14]. Two studies excluded patients with PSA > 20 ng/mL [4,6]. One study did not state the definition of positive MPMRI results [9]. The MPMRI test was blinded to the results of the reference standard in the five studies, but the interpretations of the reference standards were not blinded to the MPMRI results. All the reference standards in the five studies met the preplanned inclusion criteria, but two studies treated MPMRI followed by targeted biopsy as a part of reference standard for some patients [13,14]. The preplanned reference standards were post-operational pathological reports or template transperineal mapping biopsy/saturation biopsy (≥ 20 cores) for MPMRI-positive patients or MPMRI followed by targeted biopsy-positive patients; and clinical follow-up for MPMRI-negative patients or MPMRI followed by targeted biopsy-negative patients. However, the template transperineal mapping biopsy/saturation biopsy (≥ 20 cores) in four studies [4,6,13,14], was a surrogate of post-operational pathological report, and might upgrade or downgrade the final diagnosis for some patients. Additionally, the mean follow-up time for negative MPMRI/MPMRI followed by targeted biopsy patients was less than one year in the fifth study [9], which was not long enough to confirm the final diagnosis. Thus, the risk of bias was marked high for these five studies in Appendix II. Although surgical pathological results should be the ideal reference standard, this is generally not practical or feasible for all the patients. Therefore, the concern question from the QUADAS-2 tool regarding "target condition as defined by the reference standard does not match the review question" was low.

For the 10 studies that compared the detection rates of clinically significant prostate cancer between MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy, the overall quality was from low to moderate [1-3,5,7,8,10-12,15]. The main limitation in these studies was that no patients with negative results from MPMRI, MPMRI followed by targeted biopsy, or TRUS-guided systematic biopsy were followed up to confirm the diagnosis. However, for the purpose of comparing the detection rates of clinically significant prostate cancer between MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy, only the outcomes of patients with positive results needed to be analyzed. Except for the RCT [2], every patient received both MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy in all nine studies. Therefore, concerns regarding applicability were low. For the QUADAS-2 patient selection domain, four studies only recruited patients with positive MPMRI results; this overestimates the diagnostic outcomes of MPMRI followed by targeted biopsy because it is assumed that all patients with negative MPMRI results are free from clinically significant prostate cancer [5,7,10,11]. Three studies excluded patients with PSA > 10 ng/mL [2,5,7]. TRUS-guided systematic biopsy was taken without knowledge of the results of the MPMRI followed by targeted biopsy cores in two studies [7,10], but it was taken with knowledge of the results of the MPMRI followed by targeted biopsy cores in five studies [2,5,8,11,12], and this information was unclear in three studies [1,3,15]. The modified Cochrane Collaboration tool [97] was used to assess the risk of bias in the Park 2011 RCT [2]

(Appendix III). Its quality was deemed to be 'low' because its randomization and allocation concealment methods were not described, and there were no sample size calculation and no intention-to-treat analysis.

Figure 1. Modified PRISMA flow diagram of studies considered in the systematic review.



Abbreviations: ASCO = American Society of Clinical Oncology, ASTRO = American Society for Radiation Oncology, AUA = American Urological Association, CUA = Canadian Urological Association, ESTRO = European Society of Radiotherapy & Oncology, RSNA = Radiological Society of North America, PCa = prostate cancer, MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI targeted biopsy, TRUS-SB = TRUS-guided systematic biopsy, Q1 = research question 1, Q2 = research question 2.

Table 1. Study design and patients' baseline characteristics

Study (sample size)		Design	Mean age ±SD[a] (years) (range)	Mean PSA±SD[a] (ng/mL) (range)	Median prior biopsy number (range)	Previous biopsy cores (range)
Q1 (1) MPMRI in biopsy-naïve patients						
Komai 2013 (324) [4]		Prosp	64 (40—79)	6.8 (2.8—20)	0	NA
Abd-Alazeez and Kirkham 2014 (129) [6]		Unclear	median 62 (41—82)	Median 5.8 (1.2—20)	0	NA
Q1 (2) Comparing MPMRI-TB with TRUS-SB in biopsy-naïve patients						
Haffner 2011 (555) [1]		Unclear	Median 64 (47—83)	Median 6.75 (0.18—100)	0	NA
Park 2011 (85) [2]		Prosp RCT	62 (37—92)[b]	5.9 (2.9—9.9)	0	NA
Delong champs 2013 [3]	**Group 1 (127)**	Prosp	63±7	8.1±3.7	0	NA
	Group 2 (131)		65±7	8.3±4.1	0	
	Group 3 (133)		65±8	9±3.9	0	
Wysock 2014 (67) [5]		Prosp	65 (56—70)	5.1 (3.4—6.9)	0	NA
Mozer 2014 (152) [7]		Retro	63 (50—76)	6 (4—10)	0	NA
Pokorny 2014 (223) [8]		Prosp	Median 63 (IQR 57—68)	Median 5.3 (IQR 4.1—6.6)	0	NA
Q2 (1) MPMRI in previous negative biopsy patients						
Hoeks 2012[c] (438) [9]		Retro	Median 66 (IQR 61—69)	Median 11.4 (IQR 8.6—18.3)	2 (IQR 2—3)	NR
Pepe 2013 (78) [13]		Prosp	Median 63 (49—72)	Median 11 (3.7—45)	1 (1—1)	Median 18
Abd-Alazeez and Ahmed 2014 (54) [14]		Unclear	Median 64 (39—75)	Median 10 (2—23)	1 (1—3)	At least 10—12
Q2 (2) Comparing MRI-TB with TRUS-SB in previous negative biopsy patients						
Vourganti 2012 (195) [10]		Retro	Median 62 (37—80)	Median 9.13 (0.3—103)	2 (1—9)	NR
Cornelis 2013 (178) [11]		Retro	62 (47-78)	10.7 (2.5—50)	1 (1—5)	NR
Costa 2013 (38) [12]		Retro	64 (48—77)	14.4 (1.8—33.1)	NR (2—5)	15 (6—24)
Sonn 2014 (105) [15]		Retro	Median 65 (IQR 59—70)	Median 7.5 (IQR 5.0—11.2)	2 (1—3)	94% of pts had ≥12 cores

Abbreviation: IQR = interquartile range, MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI targeted biopsy, NA = not applicable, NR = not reported, Prosp = prospective study, PSA = prostate-specific antigen, pts = patients, RCT = randomized controlled trial, Retro = retrospective study, SD = standard deviation, TRUS = transrectal ultrasound, TRUS-SB = TRUS-guided systematic biopsy.

[a]Different studies reported in different ways.

[b]This information came from 103 patients; 85 of them had final outcomes.

[c]The Hoeks 2012 study also reported the diagnostic outcomes for the index test of MRI targeted biopsy in previous negative TRUS-guided biopsy patients.

Outcomes

Meta-analyses of the study results were not feasible because patient characteristics, the definitions of positive MPMRI results and clinically significant prostate cancer, MPMRI

navigational system of biopsy, and MPMRI techniques among the eligible studies were different.

A summary of MPMRI techniques from the 15 included studies is shown in Appendix IV. Thirteen studies [2-11,13-15] used T2WI, DWI, and DCE together; and among them, two studies [10,13] added MRSI. However, comparison of diagnostic accuracy for T2WI, DWI, DCE, MRSI, and the combination of these four MRI sequences was performed in one study only for 78 patients with the prevalence of 18% for clinically significant prostate cancer in Table 2, showing similar diagnostic accuracy among the techniques [13].

Seven studies [1,3,4,6,7,11,14] used 1.5 Tesla magnet strength for most patients, and eight studies [2,5,8-11,13,15] used 3.0 Tesla. Three of 15 studies (20%) used endorectal coil [3,10,12].

Research Question 1: For biopsy-naïve patients with an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms): (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer, positively change patient management, or improve patient outcomes? (2) Is MPMRI followed by targeted biopsy better than TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and other outcomes mentioned in (1)?

Diagnostic accuracy outcomes

Two studies (n = 453) that met the preplanned study selection criteria reported diagnostic accuracy outcomes of MPMRI in biopsy-naïve patients with mean/median age of 62 to 64 years and PSA ≤ 20 ng/mL (Table 1). The Komai 2013 study [4] used a GS of ≥ 4+3 or the maximum core length ≥ 5 mm as the definition of clinically significant prostate cancer, and the prevalence of clinically significant prostate cancer among 324 patients was 24%. The sensitivity and specificity of MPMRI to detect clinically significant prostate cancer was 86% (95% confidence interval [CI], 78 to 94) and 72% (95% CI, 67 to 78), respectively, indicating that 14% of true clinically significant prostate cancer patients were missed and 28% of patients without clinically significant prostate cancer were falsely diagnosed. Among the MPMRI-positive patients, 50% of patients had clinically significant prostate cancer; among the MPMRI negative patients, 6% of patients were true clinically significant prostate cancer patients (Table 2).

In the Abd-Alazeez and Kirkham 2014 study [6], each half of the prostate for each patient was treated as one sample size when calculating diagnostic outcomes. When a threshold of ≥ 4 of 5 scores was used for positive MRI results compared with that of ≥ 3 of 5 scores, approximately 25% of true clinically significant prostate cancer patients were missed and the trade-off was that approximately 45% of non-clinically significant prostate cancer patients were not over-diagnosed, regardless of whether the definition of clinically significant prostate cancer was GS ≥ 7, or GS ≥ 7and/or the maximum core length ≥ 4 mm (Table 2).

Detection rate of clinically significant prostate cancer

Six studies (n = 1473) reported detection rates of clinically significant prostate cancer by MPMRI followed by targeted biopsy, TRUS-guided systematic biopsy, or both in Tables 3 and 4 [1-3,5,7,8]. The range of patients' mean/median age was 62 to 65 years and mean/median PSA was 5.1 ng/mL to 9.0 ng/mL. The median/mean biopsy cores per patient in patients who had MPMRI followed by targeted biopsy procedure were lower than those in patients who had TRUS-guided systematic biopsy procedure (two to four versus 10 to 12). MPMRI followed by targeted biopsy detected more clinically significant prostate cancer patients than TRUS-guided systematic biopsy in the Mozer et al study and the Pokorny et al

study [7,8], but the difference did not reach statistical significance. Additionally, in the Mozer et al study [7], only MPMRI-positive patients were recruited, which overestimated the detection rate of clinically significant prostate cancer from MPMRI followed by targeted biopsy because it was assumed that all MPMRI-negative patients were truly clinically significant prostate cancer free.

The Haffner et al and the Wysock et al studies [1,5] displayed the same detection rates of clinically significant prostate cancer for MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy, but the Wysock et al study only enrolled MPMRI-positive patients [5]. The Delongchamps et al study [3] reported that MPMRI followed by targeted biopsy, using two different software MPMRI-TRUS fusion methods, identified borderline statistically significantly ($p = 0.097$ for rigid system) or statistically significantly ($p < 0.01$ for elastic system) more clinically significant prostate cancer patients than TRUS-guided systematic biopsy and when the clinically significant prostate cancer definition was GS ≥ 7 or GS = 6 with maximum core length ≥ 5 mm, but no significant differences were found when the clinically significant prostate cancer definition of GS ≥ 7 was used. However, this study was not an RCT. Although the original authors stated that "patient characteristics were similar", the mean age and mean PSA among the three groups at baseline were borderline significantly different ($p = 0.06$ and $p = 0.05$, respectively).

The Park et al RCT [2] found that the clinically significant prostate cancer detection rate in the combination group of MPMRI followed by targeted biopsy plus TRUS-guided systematic biopsy was significantly higher than that in the TRUS-guided systematic biopsy alone group in 85 patients with PSA of 4.0 ng/mL to 9.9 ng/mL (11 of 44 = 25% versus two of 41 = 5%, $p = 0.01$) (Table 4), but among the 11 clinically significant prostate cancer patients who were detected in the combination group, 10 were identified by TRUS-guided systematic biopsy alone. However, patients in the combination group had MPMRI followed by targeted biopsy first and the radiologists who performed TRUS-guided systematic biopsy were not blinded to MPMRI results, which might overestimate the detection ability of TRUS-guided systematic biopsy.

Upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy

The Pokorny et al study [8] reported that among 75 clinically significant prostate cancer patients whose diagnoses were confirmed by radical prostatectomy, four patients (5%) were overgraded as clinically significant prostate cancer patients and 11 clinically significant prostate cancer patients (15%) were undergraded as non-clinically significant prostate cancer patients by MPMRI followed by targeted biopsy; four patients (5%) were overgraded and 18 (24%) were undergraded by TRUS-guided systematic biopsy.

Patient outcomes

Only the Pokorny 2014 study [8] reported side effects from biopsy. Among 223 patients who received TRUS-guided systematic biopsy first, two patients (0.9%) developed urosepsis and recovered, and one patient (0.4%) required admission for hematuria; among 143 patients under MPMRI followed by targeted biopsy, one patient (0.7%) experienced a vasovagal episode.

No other patient outcomes were reported.

Table 2. MPMRI or MPMRI-TB in the diagnosis of clinically significant prostate cancer

Study (prevalence of CSPCa)		Index test	Positive MRI	Reference standard	CSPCa definition	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Q1 (1) MPMRI in biopsy-naïve patients									
Komai 2013 (24%) [4]		T2WI+DWI+DCE for 270 pts; T2WI +DWI for 54 pts	≥3 of 5 scores[b]	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 and Kirkham 2014[a] [6]	**(30%)**	T2WI+ DWI+DCE (258 half prostates from 129 pts)	≥3 of 5 scores[b]	5mm template prostate mapping biopsy (≥20 cores)	GS ≥7 and/or CL ≥4mm	94% (88—99)	23% (17—29)	34% (28—41)	89% (81—98)
	(21%)		≥3 of 5 scores[b]		GS ≥7	93% (86—100)	21% (15—27)	24% (18—29)	91% (84—99)
	(30%)		≥4 of 5 scores[b]		GS ≥7 and/or CL ≥4mm	68% (57—78)	69% (62—75)	48% (38—57)	83% (77—89)
	(21%)		≥4 of 5 scores[b]		GS ≥7	70% (58—83)	65% (59—72)	35% (26—44)	89% (84—94)
Q2 (1) MPMRI in previous negative TRUS-SB patients									
Hoeks 2012[c] [9]	**(24% for MRI)**	T2WI+ DWI+DCE	NR	RP, f-up (mean 7 months, including repeated MRI-GB and TRUS-SB, etc.)	Difference between RP and non-RP pts[d]	92% (86—97)	41% (35—46)	33% (28—39)	94% (90—98)
	(38% for MRI-GB)	MRI-GB	NR	RP, f-up (mean 5 months, including repeated MRI-GB and TRUS-SB)	Difference between RP and non-RP pts[d]	93% (88—98)	91% (87—96)	87% (81—93)	96% (92—99)
Pepe 2013 (18%) [13]		T2WI	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)	56% (44—68)	33% (19—48)	100% (100—100)
		DWI				100% (100—100)	59% (47—71)	35% (20—50)	100% (100—100)
		DCE				100% (100—100)	59% (47—71)	35% (20—50)	100% (100—100)
		MRSI				100% (100—100)	63% (51—74)	37% (22—52)	100% (100—100)
		Combination				100% (100—100)	50% (38—62)	30% (17—44)	100% (100—100)
Abd-Alazeez and Ahmed 2014[a] [14]	**(31%)**	T2WI+ DWI+DCE (108 half prostates from 54 pts)	≥3 of 5 scores[b]	5mm template prostate mapping biopsy + MRI software MRI-US fusion (≥20 cores)	GS ≥7 and/or CL ≥4mm	76% (62—91)	42% (31—53)	38% (26—49)	79% (67—92)
	(21%)		≥3 of 5 scores[b]		GS ≥7	87% (73—100)	42% (32—53)	29% (18—40)	92% (84—100)
	(31%)		≥4 of 5 scores[b]		GS ≥7 and/or CL ≥4mm	68% (52—83)	85% (77—93)	68% (52—83)	85% (77—93)
	(21%)		≥4 of 5 scores[b]		GS ≥7	74% (56—92)	80% (71—89)	50% (33—67)	92% (86—98)

Abbreviations: CI = confidence interval, CL = maximum core length, CSPCa = clinically significant prostate cancer, DCE = dynamic contrast-enhanced MRI, DWI = diffusion weighted MRI, f-up = clinical follow-up, GB = guided biopsy, GS = Gleason score, MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI targeted biopsy, MRI = magnetic resonance imaging, MRSI = magnetic resonance spectroscopic imaging, NPV = negative predictive value, NR = not reported, PPV = positive predictive value, pts = patients, RP = radical prostatectomy, SD = standard deviation, T2WI = T2-weighted MRI, TRUS-SB = transrectal ultrasound-guided systematic biopsy, US = ultrasound.

[a]Diagnostic outcomes were also available for another four different definitions of clinically significant prostate cancer; the prevalence of clinical significant prostate cancer is half of prostate based.
[b]MRI was reported using a scale from 1 to 5: 1 = clinically significant disease is highly unlikely to be present, 2 = clinically significant disease is unlikely to be present, 3 = clinically significant disease is equivocal, 4 = clinically significant disease is likely to be present, 5 = clinically significant disease is highly likely to be present; for MPMRI, "≥ 3 of 5 scores" means that MRI was positive if any sequence had ≥ 3 scores; for MPMRI, "≥ 4 of 5 scores" means that MRI was positive if any sequence had ≥ 4 scores.
[c]Data provided in the text were inconsistent with those in Figure 3.
[d]The definition of clinically significant disease for patients with prostatectomy was: prostate cancer volume ≥ 0.5 mL, stage ≥ pT3, or Gleason grade (GG) ≥ 4; for patients without prostatectomy: prostate-specific antigen (PSA) > 10 ng/mL and PSA density > 0.15 ng/mL, stage ≥ T2b, GG≥ 4, or total cancer-core length ≥ 10mm.

Table 3. Comparing detection rates of transrectal MPMRI-TB and TRUS-SB for clinically significant prostate cancer

Study (sample size)		CSPCa definition		Transrectal MRI-TB				TRUS-SB			Comparing transrectal MRI-TB versus TRUS-SB			
				MRI navigational system (positive MRI definition)	Median / mean biopsy cores/ pt	CSPCa detection rate not from TRUS-SB (95% CI)		Median/ mean biopsy cores/ pt	CSPCa detection rate not from MRI-TB (95% CI)		CSPCa detection rate (95% CI)		P-value	
Q1 (2) Comparing transrectal MPMRI-TB with TRUS-SB in biopsy-naïve patients														
Haffner 2011 (n=555) [1]		GG >3 or CL ≥5 mm		Cognitive fusion (≥3 of 5 scores[a])	3.8	2% (1—4)[b]		10—12	2% (1—3)		43% (39—47) vs. 43% (39—47)		0.95	
Delong-champs 2013 [3]	Group 1 (n=127)	GS ≥7	GS ≥7 or GS = 6 with CL ≥5 mm	Cognitive fusion[c]	4	2% (0—4)	2% (0—5)	12	2% (0—4)	5% (1—8)	14% (8—20) vs. 14% (8—20)	31% (23—39) vs. 34% (26—42)	1.00	0.61
	Group 2 (n=131)			Software fusion (rigid system)[c]	4	5% (1—8)	11% (6—17)	12	0%	2% (0—4)	25% (18—33) vs. 20% (13—27)	44% (35—53) vs. 34% (26—42)	0.30	<0.10
	Group 3 (n=133)			Software MRI-TRUS fusion (elastic system)[c]	3	6% (2—10)	19% (12—25)	12	0%	2% (0—4)	20% (13—27) vs. 14% (9—20)	44% (36—52) vs. 26% (19—33)	0.20	<0.01
Wysock 2014[d] (n=67) [5]		GS ≥7		Cognitive or software fusion (≥2 of 5 scores[a])	4	4% (0—9)		12	4% (0—9)		33% (22—44) vs. 33% (22—44)		1.00	
Mozer 2014[d] (n=152) [7]		GS ≥7 or GS = 6 with CL ≥4 mm		Software fusion (≥2 of 5 scores[a])	2	9% (5—14)		12	3% (0—5)		43% (36—51) vs. 37% (29—44)		0.24	
Pokorny 2014 (n=223) [8]		GS ≥7 (4+3) or TTV >0.7mL		MRI-guided TB (≥3 of 5 scores[a])	2—3/ lesion	13% (9—17)		12	7% (3—10)		42% (35—48) vs. 35% (29—42)		0.17	
Q2 (2) Comparing transrectal MPMRI-TB with TRUS-SB in previous negative TRUS-guided biopsy patients														
Vourganti 2012[d,e] (n=195) [10]		GS ≥7		Software fusion (NR)	5	7% (4—11)		12	1% (0—2)		22% (16—28) vs. 16% (11—21)		0.12	
Cornelis 2013[d,f] (n=178) [11]		GS ≥7		Software fusion (NR)	2	2% (0—4)		12	0%		7% (4—11) vs. 5% (2—9)		0.51	
Costa 2013 (n=38) [12]		GS ≥7		Cognitive fusion (≥3 of 5 scores[a])	NR	21% (8—34)		NR	3% (0—8)		24% (10—37) vs. 5% (0—12)		0.02	
Sonn 2014[g] (n=105) [15]		GS ≥7 or GS = 6 with CL ≥4 mm		Software fusion (≥2 of 5 scores[a])	5	10% (5—16)		12	5% (1—9)		20% (12—28) vs. 14% (8—21)		0.27	

Abbreviations: CI = confidence interval, CL = maximum core length, CSPCa = clinically significant prostate cancer, GG = Gleason grade, GS = Gleason score, Mp = multiparametric, MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI targeted biopsy, MRI = magnetic resonance imaging, NR = not reported, pts = patients, TRUS-SB = transrectal ultrasound-guided systematic biopsy, TTV = total tumour volume.

[a]MRI was reported using a scale from 1 to 5: 1 = clinically significant disease is highly unlikely to be present, 2 = clinically significant disease is unlikely to be present, 3 = clinically significant disease is equivocal, 4 = clinically significant disease is likely to be present, 5 = clinically significant disease is highly likely to be present; for MPMRI, "≥3 of 5 scores" means that MRI was positive if any sequence had ≥3 scores; for MPMRI, "≥4 of 5 scores" means that MRI was positive if any sequence had ≥4 scores.

[b]The original authors stated that all cancers detected by MRI were clinically significant prostate cancer because MRI cannot identify a cancer <7 mm.

[c] T2-weighted MRI (T2WI), diffusion-weighted MRI (DWI), and each of the three parameters calculated from dynamic contrast-enhanced MRI (DCE MRI) were scaled as a 3-point score of 0—benign or probably benign, 1—intermediate or 2—malignant or probably malignant. A T2WI plus DWI score of 0 to 4 in the transition zone and a T2WI plus DWI plus DCE score of 0 to 10 in the peripheral zone.

[d]All patients were MRI-positive at the baseline.
[e] Data provided in Table 2 were inconsistent with those in Table 3. We used data in Table 2. Patients with more than one suspicion for prostate cancer from any MRI sequence were enrolled, but there was no definition for any suspicion from different MRI sequences.
[f]Data provided on pages 159 and 164 in the text were inconsistent with those in Table 4. We used data in Table 4.
[g]Among 105 patients, eight did not have MRI-targeted biopsy and another three did not have transrectal ultrasound systematic standard biopsy.

Table 4. Comparing Transrectal MPMRI-TB plus TRUS-SB with TRUS-SB in biopsy-naive patients in an RCT.

Study	CSD definition	Transrectal MPMRI-TB plus TRUS-SB					TRUS-SB			P-value
		MPMRI navigational system (positive definition)	Sample size	Biopsy cores/pt	Biopsy cores from MRI/pt	CSD detection rate (95% CI)	Sample size	Biopsy cores/pt	CSD detection rate (95% CI)	
Park 2011 [2]	GS ≥7	Cognitive fusion (NR)	44	10—12 plus 1 TB core/lesion	NR[b]	25% (12—38)	41	10—12	5% (0—11)	0.01

Abbreviations: CI = confidence interval, CSD = clinically significant prostate cancer, GS = Gleason score, MPMRI = multiparametric magnetic resonance imaging, MRI = magnetic resonance imaging, pt = patient, RCT = randomized controlled trial, TB = target biopsy, TRUS-SB = transrectal ultrasound-guided systematic biopsy.
[a]Positive magnetic resonance imaging (MRI) definitions: a hypointense region relative to the adjacent parenchyma for T2-weighted MRI; a region with a low apparent diffusion coefficient value relative to the adjacent parenchyma for diffusion-weighted MRI; a region with early wash-in and wash-out of contrast material relative to the adjacent parenchyma for dynamic contrast-enhanced MRI.
[b]Twenty-one of 44 patients with positive MPMRI results had MRI-TB.

Research Question 2: For patients who had a previous negative TRUS-guided systematic biopsy (at least eight cores) with an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms): (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer, positively change patient management, or improve patient outcomes? (2) Is MPMRI followed by targeted biopsy better than repeated TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and other above patient outcomes in (1)?

Diagnostic accuracy outcomes

Three studies (n = 570) reported diagnostic accuracy outcomes of MPMRI in patients who had a median of one to two previous negative TRUS-guided biopsies without PSA upper limitation [9,13,14] (Table 2). The overall sensitivity for MPMRI to identify clinically significant prostate cancer ranged from 68% to 100% and specificity ranged from 41% to 91%.

The Hoeks et al study [9] reported diagnostic outcomes for both MPMRI and MPMRI-guided targeted biopsy. The sensitivity and negative predictive value for MPMRI and MPMRI followed by targeted biopsy were similar and high (92% versus 93% and 94% versus 96%, respectively), indicating that 8% versus 7% of patients with clinically significant prostate cancer were missed; among MRI-negative patients or MPMRI followed by targeted biopsy-negative patients, 6% versus 4% of patients should have been patients with clinically significant prostate cancer. But the specificity and positive predictive value were different (41% versus 91%; 33% versus 87%, respectively), demonstrating the false-positive rate for MRI-positive patients was higher than that for MPMRI followed by targeted biopsy-positive patients (67% versus 13%).

In the Abd-Alazeez and Ahmed et al study [14], each half of the prostate for each patient was treated as one sample size when calculating diagnostic outcomes. When a threshold of ≥ 4 of 5 scores was compared with that of ≥ 3 of 5 scores for positive MRI results, approximately 10% of true clinically significant prostate cancer patients were missed and the trade-off was that approximately 40% of patients with non-clinically significant prostate cancer patients were not over-diagnosed, regardless of whether the definition of clinically significant prostate cancer was GS ≥ 7, or GS ≥ 7 and/or the maximum core length ≥ 4 mm.

Detection rate of clinically significant prostate cancer

Four studies (n = 516) reported the detection rates of clinically significant prostate cancer by MPMRI followed by targeted biopsy, TRUS-guided systematic biopsy, or both in patients who had median previous negative TRUS-guided biopsies of one to two in Table 3 [10-12,15]. Two studies only enrolled MPMRI-positive patients [10,11]. The overall detection rates of clinically significant prostate cancer by MPMRI followed by targeted biopsy but not by repeated TRUS-guided systematic biopsy ranged from 2% to 21%; the overall detection rates of clinically significant prostate cancer by repeated TRUS-guided systematic biopsy but not by MPMRI followed by targeted biopsy ranged from 0% to 5%. MPMRI followed by targeted biopsy detected more clinically significant prostate cancer patients than repeated TRUS-guided systematic biopsy in all four studies, but only one study with a small sample size found a statistically significant difference (n=38) [12].

Upgraded/downgraded results from MPMRI followed by targeted biopsy and repeated TRUS-guided systematic biopsy

The Vourganti et al study [10] reported that among 195 MPMRI-positive patients, 28 patients (14%) were upgraded by MPMRI followed by targeted biopsy from repeated TRUS-guided systematic biopsy including 25 patients with GS ≥ 7. However, it did not report how

many patients were upgraded by repeated TRUS-guided systematic biopsy from MPMRI followed by target biopsy. Also, this study did not report the further treatment information after biopsy, such as how many patients had radical prostatectomy; thus, it was unknown whether these upgraded information were true.

Patient outcomes

Two studies mentioned complications after biopsy. The Hoeks et al study [9] stated one patient (0.4%) had sepsis and four patients (1.5%) had a vasovagal reaction from MPMRI-guided target biopsy. No patients had significant complications that needed hospital admission from saturation biopsy in the Pepe et al study [13].

No other patient outcomes were reported.

Ongoing, Unpublished, or Incomplete Studies

The National Cancer Institute Clinical Trials Database (http://www.clinicaltrials.gov/) was searched on April 25, 2014 for potential trials meeting the selection criteria for this systematic review. There are 10 ongoing, unpublished, or incomplete trials that would be eligible for inclusion in the update of this guideline in the future (Appendix V).

DISCUSSION

With regard to the first research question, this systematic review showed that in biopsy-naïve patients with an elevated risk of clinically significant prostate cancer (prevalence of 21% to 30% for clinically significant prostate cancer), 6% to 32% of true patients with clinically significant prostate cancer were falsely diagnosed negative and 28% to 79% of patients with non-clinically significant prostate cancer were falsely diagnosed positive after MPMRI examination; in patients with MPMRI positive results, 50% to 76% were falsely diagnosed positive and in patients with MPMRI negative results, 6% to 17% were falsely diagnosed negative (Table 2). Two percent to 13% of patients were diagnosed as clinically significant prostate cancer by MPMRI followed by targeted biopsy alone but not by TRUS-guided systematic biopsy, and 0% to 7% were diagnosed as clinically significant prostate cancer by TRUS-guided systematic biopsy alone but not by MPMRI followed by targeted biopsy (Table 3). Based on the quality and results of the available studies, along with cost-effectiveness and resource issues, which are beyond the scope of this PEBC guideline, the Working Group does not recommend MPMRI followed by targeted biopsy as a standard of care in this population.

In patients with a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA) who had a previous negative TRUS-guided systematic biopsy (the second research question), MPMRI followed by targeted biopsy identified more patients with clinically significant prostate cancer consistently than repeated TRUS-guided systematic biopsy in all eligible studies, although most studies did not reach a statistically significant difference (Table 3). Also, MPMRI followed by targeted biopsy was less invasive because there were fewer biopsy cores obtained per patient than in repeated TRUS-guided systematic biopsy (Table 3). After MPMRI examination, 0% to 32% of true patients with clinically significant prostate cancer were falsely diagnosed negative and 9% to 59% of patients were falsely diagnosed positive; in patients with MPMRI-positive results, 13% to 71% were falsely diagnosed positive and in patients with MPMRI-negative results, 0% to 21% were falsely diagnosed negative (Table 2). Two percent to 21% of patients were diagnosed as clinically significant prostate cancer by MPMRI followed by targeted biopsy but not by repeated TRUS-guided systematic biopsy, and 0% to 5% were diagnosed as clinically significant prostate cancer by repeated TRUS-guided systematic biopsy but not by MPMRI followed by targeted biopsy (Table 3). Considering relatively fewer patients will need MPMRI followed by targeted biopsy than

those in the first research question, and based on the above evidence, the Working Group recommends that MPMRI followed by targeted biopsy may be considered to help in detecting more patients with clinically significant prostate cancer compared with repeated TRUS-guided systematic biopsy. It should be noted that this recommendation is not intended to be a reflexive examination after a negative biopsy, but rather only applicable to those who demonstrate a clinical suspicion of having clinically significant prostate cancer; e.g., a significantly rising PSA over time and/or abnormal digital rectal examination. The side effects after either biopsy were acceptable in the three studies that reported these outcomes [8,9,13].

Although this landscape is rapidly evolving, to date, there is insufficient evidence to support that the software MRI-TRUS fusion technique is more effective than the cognitive fusion method to guide MPMRI followed by targeted biopsy and there is insufficient evidence to suggest that the MRI-guided technique is more effective than the cognitive fusion or the software MRI-TRUS fusion techniques to guide targeted biopsy after MPMRI to identify clinically significant prostate cancer. Collected data from different studies have been obtained with different techniques (1.5 versus 3 Tesla scanners, endorectal coil versus no coil, different b-values on DWI, and different temporal resolution of DCE-MR etc.) in Appendix IV. It is impossible to do a subgroup analysis for each different technique because there were only 15 eligible studies for two research questions and two different patient populations. The Working Group, the MRI in Prostate Cancer Guideline Development Group, and the PEBC of Cancer Care Ontario believe that the current minimum requirements of MPMRI techniques that were summarized in Table 2 in the 2012 ESUR Guidelines [16] are reasonable to consider in Ontario. Before MRMRI is used in the clinical practice, diagnostic performance in each centre in Ontario should be assessed and physicians should be familiar with current international prostate MRI performing and reporting standards.

There are several main limitations in the existing literature regarding MPMRI in the diagnosis of clinically significant prostate cancer. First, the definitions of clinically significant prostate cancer were different in studies. Among the 15 included studies, seven studies [5,6,10-14] used GS ≥ 7, six studies [1,4,6,7,14,15] used GS = 6 plus maximum core length ≥ 4/5mm or GS ≥ 7, one study reported the outcomes by using both [3], and another study used different definition [9]. Compared with the definition of GS ≥ 7, the definition of GS = 6 with maximum core length ≥4/5 mm or GS ≥ 7 detected more clinically significant prostate cancer patients in the same population (Tables 2 and 3). Second, the definitions of MPMRI-positive results were various among clinical settings. Nine of 15 studies followed the prostate imaging-reporting and data (PI-RAD) system as described in the 2012 ESUR guideline [16]. Among them, six studies [1,4,6,8,12,14] used a score of ≥ 3 of 5, and three studies [5,7,15] used a score of ≥ 2 of 5 as the threshold respectively for their MPMRI positive definition from any MRI sequence. Four studies [2,9-11] did not state their definitions for MPMRI- positive patients, and two studies [3,13] used other definitions (Tables 2 and 3). A lower threshold of the PI-RAD score will result in a higher sensitivity and fewer true clinically significant prostate cancer patients will be missed, but the trade-off is that more non-clinically significant prostate cancer patients will have an unnecessary biopsy after MPMRI because of a lower specificity. Third, for the five studies that reported diagnostic accuracy outcomes, four of them used the template transperineal mapping biopsy/saturation biopsy (≥ 20 cores) as the reference standard that might upgrade or downgrade the final diagnosis for some patients [4,6,13,14]; additionally, the mean follow-up time for negative MPMRI/MPMRI followed by targeted biopsy patients was less than one year in the fifth study [9], which is not long enough to confirm the final diagnosis and potentially overestimates the diagnostic accuracy of MPMRI/MPMRI followed by targeted biopsy. Fourth, when comparing the detection rates of clinically significant prostate cancer between MPMRI followed by targeted biopsy and TRUS-

guided systematic biopsy/repeated TRUS-guided systematic biopsy in the 10 eligible studies [1-3,5,7,8,10-12,15], no preplanned 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 rates of false negatives and false positives from either biopsy. Fifth, no patient outcomes were reported regarding positively changing patient management or survival outcomes for the two research questions; patient outcomes are more important than diagnostic outcomes for the guideline Working Group to make recommendations.

A new updated 2014 NICE guideline of prostate cancer [98] was published after we searched for the existing guidelines. A careful examination of the studies included in the 2014 NICE guideline did ensure that no papers meeting our study selection criteria were missed in our current review. The part of the 2014 NICE guideline that was related to our research questions is shown in Appendix VI. The Working Group's recommendations in Section 1 are somewhat different with the 2014 NICE guideline. The possible reasons are as follows: first, our systematic review included one year more recent studies than the 2014 NICE guideline. Therefore, our systematic review has more evidence. Second, the NICE guideline used the Mowatt et al 2013 systematic review [24] (one of the 12 systematic reviews which the Working Group found from the literature) as a main base to make recommendation for the second research question. However, the Mowatt et al 2013 systematic review included many studies that regarded MPMRI followed by targeted biopsy, or MPMRI followed by targeted biopsy plus TRUS-guided systematic biopsy, as the reference standard to calculate diagnostic accuracy of MPMRI and then to conduct meta-analyses. The Working Group believed it was inappropriate because it would overestimate diagnostic accuracy of MPMRI, and that is why the Working Group had an exclusion criterion to avoid this limitation.

Itatani et al just published their full publication [99]; their previous published abstract was one of the 14 abstracts that needed to be followed up when this guideline is updated. This paper focused on biopsy-naïve patients who were suspected to have clinically significant prostate cancer and reported that the negative predictive value of MRI was 89.6%, which was at the middle between the two included studies in our systematic review in Table 2 (83% to 94%). The Working Group did not believe the results of the Itatani et al study would add additional important information to change the drafted recommendations. Therefore, the literature search was not updated at this moment.

Multicentre RCTs with patient outcomes are needed for these two important clinical research questions. Widening adoption of MPMRI in Europe and the United States may make this difficult due to loss of equipoise; however, such studies should be encouraged.

CONCLUSIONS

Based on the existing evidence and the Ontario context, the guideline Working Group does not recommend MPMRI followed by targeted biopsy as a standard care in biopsy-naïve patients with an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms). In patients who had a prior negative TRUS-guided systematic biopsy and demonstrate a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA), MPMRI followed by targeted biopsy may be helpful to detect more clinically significant prostate cancer cases as opposed to a repeat TRUS-guided systematic biopsy. Well-designed, well-powered, and good-quality RCTs or prospective comparative studies are needed to address these questions and to report patient outcomes.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found at the end of Section 3.

ACKNOWLEDGEMENTS AND AUTHORSHIP

The MRI in Prostate Cancer Guideline Development Group and the Working Group would like to thank the following individuals for their assistance in developing this report:

- Melissa Brouwers, Laurie Elit, Bill Evans, Sheila McNair, Hans Messersmith for providing feedback on draft versions.
- Waseem Hijazi for conducting a data audit.
- Sara Miller for copyediting.

A complete list of the members of the Working Group and the MRI in Prostate Cancer Guideline Development Group, with their affiliations and conflict of interest information, is provided in Section 3, Appendix I.

Appendix I. Literature search terms

Medline searching terms

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches
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="1997 -Current")
19	remove duplicates from 18

Embase searching terms

Database(s): **Embase** 1997 to 2014 Week 16

Search Strategy:

#	Searches
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="1997 -Current")

Appendix II. Assessment of study quality by QUADAS-2 tool

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Q1 (1) MPMRI in biopsy-naïve patients							
Komai 2013 [4]	?	☺	☹	☺	?	☺	☺
Abd-Alazeez and Kirkham 2014 [6]	?	☺	☹	☺	?	☺	☺
Q2 (1) MPMRI in previous negative TRUS-SB patients							
Hoeks 2012[a] [9]	?	?	☹	?	?	?	☺
Pepe 2013 [13]	☺	☺	☹	☺	☺	☺	☺
Abd-Alazeez and Ahmed 2014 [14]	☺	☺	☹	☺	☺	☺	☺
Q1 (2) Comparing MPMRI-TB with TRUS-SB in biopsy-naïve patients							
Haffner 2011 [1]	☺	?	☹	☺	☺	?	☺
Park 2011 [2]	☺	☹	☹	☺	☺	☺	☺
Delongchamps 2013 [3]	☺	?	☹	☺	☺	?	☺
Wysock 2014 [5]	☹	☹	☹	☺	☺	☹	☺
Mozer 2014 [7]	☹	☺	☹	☺	☺	☹	☺
Pokorny 2014 [8]	☺	☹	☹	☺	☺	☺	☺
Q2 (2) Comparing MPMRI-TB with TRUS-SB in previous negative TRUS-guided biopsy patients							
Vourganti 2012 [10]	☹	☺	☹	☺	☺	☺	☺
Cornelis 2013 [11]	☹	☹	☹	☺	☹	☹	☺
Costa 2013 [12]	☺	☹	☹	☺	☺	☹	☺
Sonn 2014 [15]	☺	?	☹	☺	☺	?	☺

☺Low Risk ☹High Risk ? Unclear Risk

Abbreviations: MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI followed by targeted biopsy, TRUS-SB = TRUS-guided systematic biopsy.

[a]Only 51 of 156 negative magnetic resonance imaging guided biopsy patients were followed to five months.

Appendix III. Quality assessment for RCT by modified Cochrane Collaboration Tool.

Study	Randomization method	Allocation concealment	Blinding (participants, personnel, outcome assessment)	Follow-up rate[a]	Expected Effect, Power, and Planned Sample Size	Intention-to-treat analysis	Selective reporting	Funding
Park 2011 [2]	Unclear	Unclear	Unblinded for participants; unclear for others	Yes (83%)	No	No	Unclear	Clinical Research Development Program grant CRS 108-13-1 from Samsung Medical Center

Abbreviations: RCT = randomized controlled trial.
[a]If the follow-up rate is ≥80%, we give it a "Yes" arbitrarily.

Appendix IV. Summary of MPMRI techniques from 15 included studies

Study	Magnet strength (Tesla)	Sequence: For DWI (b-values, s/mm^2); For DCE (temporal resolution, s/phase)	Imaging plane	Endo-rectal coil	Contrast agent	Matrix	Slices thickness (mm)	TR (ms)	TE (ms)
Q1 (1) MPMRI in biopsy-naïve patients									
Komai 2013 [4]	1.5T	T2WI; DWI (0/1000/2000); DCE (2.03)	NR	No	Gadopentetate dimeglumine 0.1 mmol/kg	304x304; 128x99; 176x176	0.8; 4; 4.4	1500; 5000; 4.1	152; 80; 2.0
Abd-Alazeez and Kirkham 2014 [6]	1.5T for 113 pts	T2WI; DWI (0/150/500/1000); DWI (1400); DCE (17)	Axial and coronal; Axial; Axial; Axial	No	20 mL Gadoteric acid 0.5 mmol/mL	256x256; 172x172; 172x172; 192x192	3; 5; 5; 3	5170; 2200; 2200; 5.61	92; <98; <98; 2.52
	3.0T for 15 pts	T2WI; DWI (0/100/300/800/1000); DWI (2000); DCE (15)	Axial and coronal; Axial; Axial; Axial			320x310; 126x81; 126x81; 256x256	3; 5; 5; 3	7340; 4300; 7500; 4.1	101; 80; 79; 1.5
Q1 (2) Comparing MPMRI-TB with TRUS-SB in biopsy-naïve patients									
Haffner 2011 [1]	1.5T	T2WI; T1W DCE	Axial; Axial	No	NR	272x231; 128x231	4; 4	3200; 6.4	110; 3.1
Park 2011 [2]	3.0T	T2WI; DWI; DCE	NR	No	NR	NR	NR	NR	NR
Delongchamps 2013 [3]	1.5T	T2WI; DWI (100/200/400/800); DCE (8.5)	NR	Yes	Gadolinium, 0.2mL/kg for DCE only	NR	1; 3.5; 3.5	1300; 5.11; 3700	120; 1.85; 104
Wysock 2013 [5]	3.0T	T2WI; DWI; DCE	NR	No	NR	NR	NR	NR	NR
Mozer 2014 [7]	1.5T	T2WI; DCE; DWI (0/200/1000 for Philips, 50/400/1000 for Siemens)	2 planes; NR; Axial	No	Gadoterate meglumine 20 mL	NR	NR	NR	NR
Pokorny 2014 [8]	3.0T	T2WI; DWI; DCE	NR	No	NR	NR	NR	NR	NR
Q2 (1) MPMRI in previous negative TRUS-SB patients									
Hoeks 2012[a] [9] **MPMRI for prostate exami-**	3.0T	T2WI; T2WI; DWI (0/50/500/800); DCE (NR); DCE (2.5)	Axial and coronal; Sagittal; SSEPI axial; axial; Spoiled axial	No	NR	320x320; 320x320; 128x128; 180x180; 128x128;	3; 3; 4; 4; 4	4480; 4950; 2500; 800; 32	103; 110; 64; 1.47; 1.47

	nation	3.0T	T2WI; T2WI; T2WI; DWI (0/50/500/1200); DCE (NR); DCE (3.5)	Axial; Coronal; Sagittal; SSEPI axial; axial; axial			320x320; 320x320; 320x320; 128x128; 128x128; 128x128;	3; 3; 3; 4; 3; 3	5180; 4320; 4000; 3000; 800; 36	101; 101; 101; 64; 1.53; 1.41
	MPMRI-guided targeted biopsy	3.0T	T2WI; DWI (0/100/400/800); Balanced SSFP	Axial; Axial; Axial and sagittal	No	NR	320x320; 160x120; 256x256	4; 3.6; 3	3620; 3300; 4.48	103; 60; 2.24
		3.0T	T2WI; DWI (50/100/1600); Balanced SSFP	Axial; Axial; Axial and sagittal			320x320; 160x120; 256x256	4[b]; 4; 3	3560; 3000; 4.56	104; 64; 2.28
Pepe 2013 [13]		3.0T	T2WI; DWI (NR); DCE (NR); MRSI	NR; Axial; Axial; Axial	No	Gadobutrol 0.1 mL/kg	NR	NR	NR	NR
Abd-Alazeez and Ahmed 2014 [14]		1.5T for 49 of 54 pts	T2WI; DWI (0/150/500/1000); DWI (1400); DCE (17)	Axial and coronal; Axial; Axial; Axial	No	Gadoterate meglumine 0.1 mmol/kg	256x256; 172x172; 172x172; 192x192	3; 5; 5; 3	5170; 2200; 2200; 5.61	92; <98; <98; 2.52
Q2 (2) Comparing MPMRI-TB with TRUS-SB in patients with previous negative TRUS-guided biopsies										
Vourganti 2012[c] [10]		3.0T	T2WI; T2WI; T2WI; DWI (0/188/375/563/750); MRSI; DCE	Sagittal; Axial; Coronal; Axial; Axial; Axial	Yes	NR	256x256; 256x256; 256x256; 112x108; 120x120; 256x256;	3; 3; 3; 3; 6; 5	2340; 8852; 2340; 4140; 980; 5.5	120; 120; 120; 57; 100; 2.1
Cornelis 2013 [11]		1.5T	T1WI; T2WI; DWI (NR); T1W-DCE (10)	Axial; Axial; Axial; Axial	No	Gadobenate dimeglumine	246x256; 246x256; 102x128; 128x160	3.5	646; 6450; 4500; 3.77	12; 116; 91; 1.46
Costa 2013 [12]		3.0T	T2WI; DCE	Transverse, coronal, axial; Axial	Yes	Gadopentetate dimeglumine, 0.1 mmol/kg	256x192; 256x224	2.0—2.8; 2.6—3.0	4500—7600; 7.1	165; 2.1
Sonn 2014[d] [15]		3.0T	T2WI; DWI (400/800/1000); DCE (NR)	NR	No	Gadopentetate dimeglumine, 0.1 mg/kg	256x205; 256x154; 320x225	1.5; 5; 1.5	3800—5040; 1600—2300; 2.7	101; 75—90; 1.1

Abbreviations: DCE = dynamic contrast-enhanced MRI, DWI = diffusion weighted MRI, MPMRI = multiparametric magnetic resonance imaging, MPMRI-TB = MPMRI followed by targeted biopsy, MRSI = magnetic resonance spectroscopic imaging, NR = not reported, s = second, SSEPI = steady-state echo planar imaging, SSFP = steady-state free procession, T2WI = T2-weighted MRI, TE = echo time, TR = repetition time, TRUS-SB = transrectal ultrasound-guided systematic biopsy.

[a]The Hoeks 2012 study also reported the diagnostic outcomes for the index test of MPMRI targeted biopsy in previous negative TRUS-guided biopsy patients.

[b]It was 120 in Table 1 in the original study, which did not make sense. We have contacted the corresponding author to confirm whether it should be 4, but there is no response.

[c]MRI parameter information was obtained from its references 11 and 12.

[d]MRI parameter information was obtained from its references 19.

Appendix V. Ongoing trials.

Investigator (country)	Title	Study design, sample size (age)	Protocol ID	Estimated study completion date
Yousef Mazaheri-Tehrani (United States)	Magnetic Resonance Spectroscopic Imaging of the Prostate at 3 Tesla	Non-RCT, 308 (≥21 years)	NCT00588679	August 2015
Mark Emberton (United Kingdom)	MRI in Diagnosing Prostate Cancer	Non-RCT, 714 (NR)	NCT01292291, MRC-PR11, EU-21104, UCL-11/009	April 2013
Markku Vaarala (Finland)	Evaluation of Diagnostic Value of 3-T Magnetic Resonance Imaging (MRI) in Suspected Prostate Cancer	RCT, 130 (40-72 years)	NCT01357512	December 2016
Erik Rud (Norway)	Biopsy Study Comparing MRI and Ultrasound Soft Image Fusion Guided Biopsies and Gold Standard Prostate Biopsies	Non-RCT, 200 (NR)	NCT01455792	September 2013
Michael Knopp (United States)	3-Tesla MRI in Finding Tumors in Patients with Known or Suspected Prostate Cancer	Non-RCT, 170 (≥20 years)	NCT01653093	March 2013
Nicolas Barry Delongchamps and Laurence Lecomte (France)	Study of Current Practice Which Compare the Rate of Prostate Cancer by Using 2 Kind of Transrectal Biopsies: 3 by IRM-echography Image Fusion and 12 Systematized Guided Echographies (MURIELLE)	Non-RCT, 90 (45-75 years)	NCT02050542	June 2014
Art Rastinehad (USA)[a]	MRI/TRUS Fusion Guided Prostate Biopsy - An Improved Way to Detect and Quantify Prostate Cancer	Non-RCT, 980 (≥18 years)	NCT01566045	April 2015
Lucy AM Simmons (UK)	Imaging for Significant Prostate Cancer Risk Evaluation	Non-RCT, 126 (≥20 years)	NCT01492270	July 2013
Christian Arsov (Germany)	A Prospective Study to Evaluate MRI Guided Biopsy Compared with Transrectal Ultrasound Guided Biopsy of the Prostate in Men with Increased PSA Values	RCT, 248 (>18 years)	NCT01553838	January 2014
Samr Taneja (USA)	Use of Multi-Parametric with Prostate Biopsy for Cancer Diagnosis	Non-RCT, 126 (40-75 years)	NCT01964638	March 2013

Abbreviations: MRI = magnetic resonance imaging, NR = not reported; PSA = prostate-specific antigen, RCT = randomized controlled trial, TRUS = transrectal ultrasound.
[a]They already published a paper with the first 105 patients that was included in our systematic review [59].

Appendix VI. Recommendations in the 2014 NICE guideline related to our guideline.

Clinical Research questions	Recommendations
Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer? ▫	No recommendations
In men with suspected prostate cancer whose initial TRUS biopsy is negative what should be the next investigation(s)?	1. Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound, 10—12 core biopsy to determine whether another biopsy is needed. 2. Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the following risk factors is present: • the biopsy showed high-grade prostatic intra-epithelial neoplasia • the biopsy showed atypical small acinar proliferation • abnormal digital rectal examination ▫

Abbreviations: MRI = magnetic resonance imaging, TRUS = transrectal ultrasound.

Guideline #27-2: Section 3

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

Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically significant Prostate Cancer: Guideline Development Methods and Review Process

M. Haider, X. Yao, D.A. Loblaw, A. Finelli, and the MRI in Prostate Cancer Guideline Development Group

Report Date: August 5, 2015

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [100]. 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 comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is produces evidence-based and evidence-informed guidelines, known as guideline reports, using the methods of the Practice Guidelines Development Cycle [100,101]. The guideline report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This guideline is comprised of the following sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base*. Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: Guideline Development Methods and Review Process*. Summarizes the guideline development process, the recommendations development process and the results of the formal external review of the draft version of the guideline.

FORMATION OF GUIDELINE DEVELOPMENT/WORKING GROUP

The CCO Clinical Imaging Program asked the PEBC to develop a guideline on multiparametric magnetic resonance imaging (MPMRI) in the diagnosis of prostate cancer. In consultation with the CCO Clinical Imaging Program, a GDG (Expert Panel) and a Working Group (the guideline authors) were formed; the group members with their conflict of interest declarations are listed in Appendix I. This Working Group consisted of one radiologist, one radiation oncologist, one urologist, and one methodologist. The GDG would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

OBJECTIVES AND RESEARCH QUESTIONS

This Working Group developed the following objectives for this guideline:

- To make recommendations with respect to the use of MPMRI in the diagnosis of clinically significant prostate cancer in patients with an elevated risk of clinically significant prostate cancer (according to prostate-specific antigen [PSA] level and/or nomograms) who are biopsy-naïve.
- To make recommendations with respect to the use of MPMRI in the diagnosis of clinically significant prostate cancer in patients with a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA) who had a negative transrectal ultrasound (TRUS)-guided systematic biopsy.

From the above objectives, the following research question was derived to direct the search for available evidence:

1. For biopsy-naïve patients with an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms):
   (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer (diagnostic accuracy outcomes including sensitivity, specificity, predictive value, and upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy), positively change patient management, or improve patient outcomes (including side effects and survival outcomes)?
   (2) Is MPMRI followed by targeted biopsy better than TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and the other above patient outcomes?
2. For patients who had a previous negative TRUS-guided systematic biopsy (at least eight cores) with a growing risk of having clinically significant prostate cancer (e.g., continued rise in PSA):
   (1) Does MPMRI or MPMRI followed by targeted biopsy add value in detecting clinically significant prostate cancer (diagnostic accuracy outcomes including sensitivity, specificity, predictive value, and upgraded/downgraded results from MPMRI followed by targeted biopsy and TRUS-guided systematic biopsy), positively change patient management, or improve patient outcomes (including side effects and survival outcomes)?
   (2) Is MPMRI followed by targeted biopsy better than repeated TRUS-guided systematic biopsy (at least eight cores) for detection rate of clinically significant prostate cancer, and the other above patient outcomes?

EVIDENTIARY BASE DEVELOPMENT

Using the research questions described above, a search for existing guidelines and systematic reviews, and a systematic review of the primary literature were conducted, as described in Section 2 of this guideline.

INTERNAL REVIEW

PEBC guidelines are reviewed by a panel of content experts—the MRI in Prostate Cancer Guideline Development Group and a methodology panel—Report Approval Panel (RAP). Both panels must approve the document. The Working Group was responsible for incorporating the feedback and required changes of both of these panels. The details of these reviews and actions taken are described below. Appendix I provides a list of members of the Working Group, RAP, and the MRI in Prostate Cancer GDG and summarizes conflict of interest declarations for all members. The PEBC conflict of interest policy is available on the website of CCO: https://archive.cancercare.on.ca/common/pages/UserFile.aspx?fileId=103568.

MRI in Prostate Cancer Guideline Development Group and Approval

The MRI in Prostate Cancer GDG acted as the Expert Panel for this document. For approval of the guideline document, 75% of the Cancer GDG membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, GDG members could suggest changes to the document, and make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

Of the 10 members of the MRI in Prostate Cancer GDG, nine members cast votes and one abstained in February 2015, for a total of 90% response. Of those that cast votes, nine approved the document (100%). The main comments from the Expert Panel and the Working Group's modifications/actions/responses taken in response are summarized in Table 1.

Table 1. Modifications/actions/responses regarding main comments from the Expert Panel.

Main comments	Modifications, actions, or responses
1. The narrative is very acronym heavy. I would recommend writing out uncommon acronyms like CSPCa, etc.	We have spelt out CSPCa, TB, and SB in the entire document.
2. Given the notable heterogeneity in results, it is likely that large differences are due to the MRI (equipment and protocol) and radiologist. I think we need to stress that diagnostic performance varies widely and should be assessed at each hospital before the test is used.	We have added a sentence to address this issue in Other considerations under Recommendation 2.
3. There is recent literature to support that effectiveness of MPMRI followed by targeted biopsy of the MRI-visible lesion to be a better alternative to systematic TRUS biopsy and therefore benefits the diagnosis of cancer. 1). Panebianco V, Barchetti F,	The literature search date for this guideline was on April 23, 2014. Thus, these three papers were published after this date. 1). The Panebianco et al study was an RCT, but its outcomes focused on patients with overall prostate cancer without subgroup analysis for patients with clinically significant prostate cancer. It reported that in TRUS-guided biopsy-naïve patients, none of

Sciarra A, Ciardi A, Indino EL, Papalia R, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: a randomized study. Urol Oncol. 2015;33:17.e1-7. 2). Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015;313:390-7. 3). Kaufmann S, Kruck S, Kramer U, Gatidis S, Stenzl A, Roethke M, et al. Direct Comparison of Targeted MRI-Guided Biopsy with Systematic Transrectal Ultrasound-Guided Biopsy in Patients with Previous Negative Prostate Biopsies. Urol Int. 2014 Sep 13. [Epub ahead of print]	130 men with negative MPMRI examination had a GS more than 6 after TRUS-guided saturation biopsy; in patients with negative TRUS-guided biopsy results and then negative MPMRI results, none of 147 men had a GS more than 6 after TRUS-guided saturation biopsy. That means in patients with MPMRI negative results, 0% was false negative, which is similar to the results from our included studies in Table 2 in Section 2. Also, since this RCT did not report the prevalence of clinically significant prostate cancer, it will not add too much information to change our recommendations. 2). The Siddiqui et al study mixed patient populations for research questions 1 and 2 together, thus it will be not analysed in the Tables even though we will update the literature search. Two previous papers from Siddiqui and his colleagues in the same clinical centre were included in our systematic review: Siddiqui 2013 (it was not analyzed in the Tables because it mixed patient populations for research questions 1 and 2 together) and Vourganti 2012 (it answered the second research question and was summarized in the Tables in Section 2) 3). The Kaufmann et al study only included 35 patients to compare MRI-guided biopsy with TRUS-guided biopsy in patients with previous negative prostate biopsies, which supports our second recommendation. Even though we update the literature search, the two recommendations will not be changed. Considering time and funding issues for this project, we have decided not to update the literature search at this moment.
4. A phrase was used several times in the document: “may be considered to help...” it may be better to say “is of value”.	Please see the second comment from Report Approval Panel review (Table 2 below). One member did not think that the evidence really supports even a “maybe” for the second recommendation. We have added more justifications in Section 1 and Section 2 to demonstrate why we think “maybe” is the appropriate term from the present evidence summarized in our systematic review. The recommendations might be changed when we update this guideline in the future if more strong evidence exists at that moment (Please see the PEBC Document Assessment and Review Protocol, available on the CCO website at: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf?redirect=true).

5. Rooij et al did a systematic review on the cost-effectiveness of prostate MRI and their results suggested comparable healthcare costs in MRI-guided biopsy and TRUS-guided biopsy but an improved quality of life in the imaging arm.	Since the cost-effectiveness issue is beyond the PEBC guideline scope and we are not sure whether the methods that Rooij et al used in their review were appropriate and fitted the Ontario context, we will not include this review in our document.

Report Approval Panel Review and Approval

This document was reviewed by three RAP members, the PEBC Director, and two research methodologists. The RAP approved the document for external review in December 2014. The summary of main comments from the RAP and the Working Group's modifications/actions/responses taken in response are showed in Table 2.

Table 2. Modifications/actions/responses regarding main comments from the Report Approval Panel.

Main comments	Modifications, actions, or responses
1. The objectives were somewhat difficult to understand without some greater detail on what MPMRI is and why it might be expected to be better than usual MRI or TRUS. The document never really explains what MPMRI is.	We have added more sentences to explain why we are interested in MPMRI in diagnosis of clinically significant prostate cancer in INTRODUCTION in Section 2 based on the reviewer's comments.
2. I am hesitant to support the second recommendation. I understand the rationale for wanting to say it may be of benefit but I do not think that the evidence really supports even a "maybe". The document would be more understandable if there was a better upfront description of the standard management of the at-risk men, the current standard of care, and the change in MRI technology that makes this guidance document necessary.	We have added more details about MPMRI in INTRODUCTION and more discussion why we made the second recommendation in Section 1 and in DISCUSSION in Section 2.
3. When I look at the summative evidence and the tables, it seems that the ranges of sensitivity, specificity, positive predictive values, and negative predictive values for biopsy naive vs. negative TRUS-guided systematic biopsy are similar. Is the reason why it is yes for one (negative TRUS-guided systematic biopsy) and not yes for the other (biopsy naive), like MRI availability?	We have added and revised some sentences under Justifications in Section 1 and under DISCUSSION in Section 2.
4. Only two options for diagnosing	We have added the discussion of template

	prostate cancer are discussed in INTRODUCTION: TRUS-guided biopsy and the MRI technique. Not clear if there are any others.	transperineal mapping biopsy or saturation biopsy in the first paragraph under INTRODUCTION in Section 2.
5.	The authors listed several limitations of this systematic review in DISCUSSION section, but they should indicate how each limitation would affect the outcomes.	We have added several sentences in DISCUSSION in Section 2 to indicate the influence from each limitation of this systematic review.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners. Refer to the PEBC Handbook (https://www.cancercareontario.ca/sites/ccocancercare/files/PEBCHandbook.pdf) for additional detail.

Targeted Peer Review

Six targeted peer reviewers from the world who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers and three responses were received. Their affiliations and conflict of interest declarations are in Appendix I. Key results of the feedback survey are summarized in Table 3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 4.

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

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. **Rate the guideline development methods.**	0	0	0	1	2
2. **Rate the guideline presentation.**	0	0	0	1	2
3. **Rate the guideline recommendations.**	0	0	0	1	2
4. Rate the completeness of reporting.	0	0	0	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	2	1
6. Rate the overall quality of the guideline report.	0	0	0	2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	0	2	1
8. I would recommend this guideline for use in practice.	0	0	0	0	3
9. What are the barriers or enablers to the implementation of this guideline report?	---I am not aware of similar robust guidelines in existence from other organizations (NICE in the UK				

	have a much less thorough assessment) and, as such, I think they will be of great interest to the prostate cancer community and may be endorsed by other groups (such as ASCO) in time. ---The recommendation on the first research question is very clear. However, the recommendation on the second question allows more judgement calls and individual decisions by the physicians. I think this is mostly due to limited evidence and can be addressed and improved in the future guidelines. ---Patient expectations could drive MRI examinations that are not recommended by these guidelines.

Table 4. Responses regarding main comments from targeted peer reviewers.

Main written comments	Modifications, actions, or responses
1. There is no focus comparing rates of diagnosis of low-risk or clinically insignificant prostate cancer (an accepted harm with current diagnostic pathways) between MPMRI and standard TRUS biopsies.	This systematic review and research questions focus on the use of MPMRI in the diagnosis of clinically significant prostate cancer in patients with an elevated risk of prostate cancer who are either biopsy-naïve or who have a previous negative TRUS-guided biopsy. Thus, we have added "clinically significant" into the guideline objectives to clarify this point.
2. I agree with comment 3 of the internal review (page 34) regarding the importance of 'Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. JAMA. 2015;313:390-7'. I appreciate the authors' response, there are mixed patient populations in this study BUT it is the best assessment to date regarding the role of MPMRI in prostate cancer diagnosis AND 807 (of 1003) patients had a previous standard biopsy (therefore addressing research question 2); this is a larger patient number than the other studies cited in the guideline combined. As such, I think this study should be discussed in the guideline as it adds support to the conclusions regarding research question 2.	Just like our response above: "the Siddiqui et al study mixed patient populations for research questions 1 and 2 together, thus it will be not analysed in Tables even though we will update the literature search." We need to follow the study selection criteria and keep consistent among all the literature evidence in this guideline.
3. I think two limitations on this topic could have been more clearly outlined. First issue is the problem with the standardization of MR image acquisition and interpretation. Collected data from different studies have been obtained with different techniques (1.5 vs 3T scanners, endorectal coil vs no coil, different b values on DWI, different temporal resolution of DCE-MR, etc.). MR images have also been interpreted by different radiologists completely based on subjective evaluation. These factors significantly limit the quality and reproducibility of the data. Second issue is the problem with targeting accuracy and standardization. The performance of MR targeted biopsies depend on targeting accuracy as much as the diagnostic performance of MRI.	We have added several sentences to reflect this reviewer's comments in DISCUSSION part under Section 2.
4. I'm not sure that the discussion of software MRI-	Although we do not have a research question

TRUS fusion technique belongs in the discussion section as this was not formally studied in this document.	about MRI technique, MRI technique is an important issue in MRI application. We even have added more discussion in that paragraph based on another reviewer's comments.
5. Terminology is a bit inconsistent for recommendation #2. Under the guideline objective, "patients with an elevated risk of prostate cancer" is listed. Under recommendations, patients are identified as those who "demonstrate a growing risk of having clinically significant prostate cancer (e.g., continued significant rise in PSA)." In the discussion, the patients are identified as having "a persistently elevated risk." What constitutes "a significant rise in PSA" should be better addressed? Terminology should be consistent throughout the document.	We have changed the terms to keep consistent throughout the document.
6. Is the recommendation #2 evidenced-based, or expert opinions based on the evidence that exists?	The recommendation #2 is mainly based on evidence: "all the eligible studies supported the notion that MPMRI followed by targeted biopsy detected a higher number of clinically significant prostate cancer when compared with repeated TRUS-guided systematic biopsy. However, most studies did not reach a statistical difference." However, any recommendation will involve considerations in Ontario context from guideline authors.

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 radiologists and radiation oncologists who showed their interest in prostate and urologist in the PEBC database, and Genitourinary Cancer Disease Site Group members were contacted by email to inform them of the survey. In total, 74 doctors were contacted: 54 who practice in Ontario versus 20 who practice outside Ontario. There were 22 (30%) responses, and among them, six 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 16 clinical practitioners are summarized in Table 5. The main comments from the consultation and the Working Group's responses are summarized in Table 6.

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

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	38	62
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	0	6	13	81
3. I would recommend this guideline for use in practice.	0	0	6	31	63
4. What are the barriers or enablers to the	---Variable access to MRI across Ontario for prostate				

implementation of this guideline report?	imaging; varying expertise across province in interpretation; it may be difficult to conduct the RCT recommended in the guideline due to increasing prevalence of MRI use. ---Changing established clinical practice especially in those who use MRI routinely to evaluate an elevated PSA level may be the barriers. ---There is a perception that this is a report written by "Toronto" physicians only. Additionally, the cost issue remains a challenge in any setting for getting access to appropriate imaging, new technologies, etc. Furthermore, there is inequitable access to prostate MRI in Ontario. Access is straightforward in Toronto and Ottawa for men with prior negative biopsies, but in other centres such as London, Hamilton, Barrie, Windsor, and Kingston, obtaining a 3-Tesla MRI scan is extremely difficult or impossible. ---Barriers: Possible lack of MRI availability. Enablers: This gives the average urologist another opportunity to make or discard the diagnosis of prostate cancer in those cases described in the guidelines presented.

Table 6. Responses regarding main comments from professional consultants.

Main written comments	Modifications, actions, or responses
1. I know how difficult it is, BUT, I wonder if should be emphasized that quality MRI is important (there are bad MRIs that even experienced radiologists cannot read).	We have added several sentences to reflect this reviewer's comments in DISCUSSION part under Section 2.
2. Data still limited for some issues, so this will need to be revisited in a few years.	All PEBC documents are maintained and updated through an annual assessment and subsequent review process. Please see detail under UPDATING heading on page 4.
3. The next guideline should address the Multiparametric MRI for the staging and surgical planning in prostate cancer.	The CCO PEBC has another ongoing guideline to address this concern (#27-3 Magnetic resonance imaging in staging for prostate cancer).
4. Was a subgroup analysis for patients with PSA <10 studied in Recommendation 1?	Eight studies focused on patients who were biopsy-naïve. There is no obvious different results between the studies including patients with PSA < 10 ng/mL and the studies including patients with various PSA levels. Thus, we did not conduct a subgroup for patients with PSA <10 studied in Recommendation 1.
5. I would consider rewording recommendation #2: MPMRI followed by targeted biopsy may be considered to help in detecting more clinically significant prostate cancer patients compared with repeated TRUS-guided systematic biopsy. I would suggest replacing "may be considered" with "should be considered".	To date, there is not sufficient evidence to support us to make a strong recommendation. Thus, we keep the original wording for recommendation #2.

Conclusion

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

Appendix I. Members of the Working Group, MRI in Prostate Cancer Guideline Development Group, and Report Approval Panel, and Targeted peer reviewers with their COI declaration.

1. Members of the Working Group

Name, Title	Affiliation	Declarations of interest
Masoom Haider, Radiologist	University of Toronto, Toronto, Ontario, Canada Sunnybrook Research Institute, Toronto, Ontario, Canada	Financial interests from professional income: Income drops >$10,000 if MRI not used to evaluation of prostate Professional Interests: Grants: Sentinelle – prostate coil evaluation; Principal investigator: ASIST trial, LINO trial on biopsy, MRI in active surveillance Other interests: Seeking grants and industry collaboration to validate the use of MRI for prostate cancer
Andrew Loblaw, Radiation Oncologist	University of Toronto, Toronto, Ontario, Canada Sunnybrook Research Institute, Toronto, Ontario, Canada	Financial interests: Receiving more than $5,000 totally in a single year to act in a consulting capacity from Amgen, AstraZeneca, Elekta, GE, Janssen, Paladin, Sanofi, Astellas, and Atlas; Receiving more than $5,000 other financial or material support in a single year from Janssen and Astellas. Professional Interests: Principal investigator: MRI-guided vs ultrasound guided prostate biopsy (ASIST) study, etc.; Grants: Sanofi and Paladin
Antonio Finelli, Urologist	Princess Margaret Hospital, Toronto, Ontario	None declared
Xiaomei Yao, Health Research Methodologist	Cancer Care Ontario, Toronto, Ontario, Canada	None declared

	McMaster University, Hamilton, Ontario, Canada	

2. Members of the MRI in Prostate Cancer Guideline Development Group

Name, Title	Affiliation	Declarations of interest
Glenn Bauman, Surgical Oncologist	Schulich School of Medicine & Dentistry, London, Ontario, Canada	Grant: CIHR, PCC, OICR examining the use of mpMRI for the diagnosis and staging of prostate cancer Principal investigator: 1. IGPC-2 Trial of Preprostatectomy Imaging in Localized Prostate Cancer 2. Prospective Study Using Hybrid PET/MRI to Evaluate Men with Suspected Recurrence Following Treatment for Prostate Cancer Published material: Bauman G, Haider M, Van der Heide UA, Menard C. 'Boosting imaging defined dominant prostatic tumors: a systematic review.' Radiother Oncol. 2013 Jun; 107(3):274-81
Rodney Breau, Surgical Oncologist	The Ottawa Hospital – General Campus, Ottawa, Ontario, Canada	None declared
Joseph Chin, Surgical Oncologist	Schulich School of Medicine & Dentistry London, Ontario, Canada	None declared
William Chu, Radiation Oncologist	Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada	Principal investigator: Integration of MRI for Prostate Radiotherapy – Motorcycle Ride for Dad: $35,000 grant during 2009-2010
Julian Dobranowski, Radiologist	St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada McMaster University Hamilton, Ontario, Canada	None declared

Sangeet Ghai, Radiologist	University of Toronto, Toronto, Ontario, Canada Princess Margaret Cancer Centre, Toronto, Ontario, Canada	Principal investigator: 1. Focal MR-Guided Focused Ultrasound Treatment f Localized Low-risk Prostate Cancer: Feasibility Study 2. Multi-center trial (5 sites) of high resolution transrectal ultrasound versus standard low resolution transrectal ultrasound for the identification of clinically significant prostate cancer Published material: 1. Murphy G, Haider MA, Ghai S, Sreeharsha B. 'The Expanding Role of Prostate MRI.' AJR Am J Roentgenol 2013 Dec; 201(6):1229-38. 2. Ghai S, Trachtenberg J. 'Prostate Cancer: A consensus of Trial Design for Focal Therapy.' Nat Rev Urol 2014 Apr; 11(4):190-2 3. Cepek J, Lindner U, Davidson SRH, Haider MA, Ghai S, Trachtenberg J, Fenster A. 'Treatment Planning for Prostate Focal Laser Ablation in the Face of Needle Placement Uncertainty.' Medical Physics 2014 Jan; 41(1):013301 Provided advice or guidance regarding objects of study: Speaker for "Prostate MRI" at 2014 Organ Imaging Review meeting

Kartik S. Jhaveri, Radiologist	Princess Margaret Cancer Centre, Toronto, Ontario, Canada	None declared
Laurence Klotz, Urologist	University of Toronto, Toronto, Ontario, Canada Sunnybrook Health Sciences Centre Toronto, Ontario, Canada	Principal investigator: ASIST Trial – OICR funded
Deanna Langer, Project Manager	Cancer Care Ontario, Toronto, Ontario, Canada	None declared
Bobby Shayegan, Urologist	St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada McMaster University Hamilton, Ontario, Canada	None declared

3. Members of the Report Approval Panel

Name, Title	Affiliation	Declarations of interest
Laurie Elit, Gynecologist	Juraviniski Cancer Center, Hamilton, Ontario, Canada	None declared
Melissa Brouwers, Director of PEBC	Cancer Care Ontario, Toronto, Ontario, Canada McMaster University, Hamilton, Ontario, Canada	None declared
Bill Evans, Medical Oncologist	Juraviniski Cancer Center, Hamilton, Ontario, Canada	None declared

4. Members of the Targeted Peer Reviewers

Name, Title	Affiliation	Declarations of interest
Suneil Jain, Radiation Oncologist	Queen's University, Belfast, Ireland	None declared
Aytek Oto, Radiologist	University of Chicago, Illinois, United States	Principal investigator (Philips Healthcare): 1. Optimization of prostate MR protocol 2. Prostate DW-MRI Principal investigator for phase II NIH funded clinical trial: MR-guided laser ablation for prostate cancer
Eric Remer, Radiologist	Cleveland Clinic Foundation,	None declared

References

1. Haffner J, Lemaitre L, Puech P, Haber GP, Leroy X, Jones JS, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU Int. 2011;108(8 B):E171-E8.
2. Park BK, Park JW, Park SY, Kim CK, Lee HM, Jeon SS, et al. Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy. AJR American Journal of Roentgenology. 2011;197(5):W876-81.
3. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. J Urol. 2013;189(2):493-9.
4. Komai Y, Numao N, Yoshida S, Matsuoka Y, Nakanishi Y, Ishii C, et al. High diagnostic ability of multiparametric magnetic resonance imaging to detect anterior prostate cancer missed by transrectal 12-core biopsy. J Urol. 2013;190(3):867-73.
5. Wysock JS, Rosenkrantz AB, Huang WC, Stifelman MD, Lepor H, Deng FM, et al. A prospective, blinded comparison of magnetic resonance (MR) imaging-ultrasound fusion and visual estimation in the performance of MR-targeted prostate biopsy: The PROFUS trial. Eur Urol. 2014;66(2):343-51.
6. Abd-Alazeez M, Kirkham A, Ahmed HU, Arya M, Anastasiadis E, Charman SC, et al. Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: A paired validating cohort study using template prostate mapping biopsies as the reference standard. Prostate Cancer and Prostatic Dis. 2014;17(1):40-6.
7. Mozer P, Roupret M, Le Cossec C, Granger B, Comperat E, de Gorski A, et al. First round of targeted biopsies with magnetic resonance imaging/ultrasound-fusion images compared to conventional ultrasound-guided trans-rectal biopsies for the diagnosis of localised prostate cancer. BJU Int. 2014 epub (after 2015, it has a full page citation: BJU Int 2015;115:50-7).
8. Pokorny MR, de Rooij M, Duncan E, Schroder FH, Parkinson R, Barentsz JO, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. Eur Urol. 2014;66(1):22-9.
9. Hoeks CMA, Schouten MG, Bomers JGR, Hoogendoorn SP, Hulsbergen-Van De Kaa CA, Hambrock T, et al. Three-tesla magnetic resonance-guided prostate biopsy in men with increased prostate-specific antigen and repeated, negative, random, systematic, transrectal ultrasound biopsies: detection of clinically significant prostate cancers. Eur Urol. 2012;62(5):902-9.
10. Vourganti S, Rastinehad A, Yerram NK, Nix J, Volkin D, Hoang A, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. J Urol. 2012;188(6):2152-7.
11. Cornelis F, Rigou G, Le Bras Y, Coutouly X, Hubrecht R, Yacoub M, et al. Real-time contrast-enhanced transrectal US-guided prostate biopsy: Diagnostic accuracy in men with previously negative biopsy results and positive MR imaging findings. Radiology. 2013;269(1):159-66.
12. Costa DN, Bloch BN, Yao DF, Sanda MG, Ngo L, Genega EM, et al. Diagnosis of relevant prostate cancer using supplementary cores from magnetic resonance imaging-prompted areas following multiple failed biopsies. Magn Reson Imaging. 2013;31(6):947-52.

13. Pepe P, Garufi A, Priolo G, Candiano G, Pietropaolo F, Pennisi M, et al. Prostate cancer detection at repeat biopsy: can pelvic phasedarray multiparametric MRI replace saturation biopsy? Anticancer Res. 2013;33(3):1195-200.
14. Abd-Alazeez M, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level--can it rule out clinically significant prostate cancer? Urol Oncol. 2014;32(1):45 e17-22.
15. Sonn GA, Chang E, Natarajan S, Margolis DJ, Macairan M, Lieu P, et al. Value of targeted prostate biopsy using magnetic resonance-ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol. 2014;65(4):809-15.
16. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22(4):746-57.
17. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014 [cited 2014 June 12]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=on#ixzz33sAjdNe4.
18. Barzell WE, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperineal 3-dimensional pathologic mapping of the prostate--a 4-year experience. Urology. 2007;70(6 Suppl):27-35.
19. Wang P, Guo YM, Liu M, Qiang YQ, Guo XJ, Zhang YL, et al. A meta-analysis of the accuracy of prostate cancer studies which use magnetic resonance spectroscopy as a diagnostic tool. Korean J Radiol. 2008;9(5):432-8.
20. Tan CH, Wei W, Johnson V, Kundra V. Diffusion-weighted MRI in the detection of prostate cancer: meta-analysis. AJR American Journal of Roentgenology. 2012;199(4):822-9.
21. Wu LM, Xu JR, Ye YQ, Lu Q, Hu JN. The clinical value of diffusion-weighted imaging in combination with T2-weighted imaging in diagnosing prostate carcinoma: a systematic review and meta-analysis. AJR American Journal of Roentgenology. 2012;199(1):103-10.
22. Haghighi M, Shah S, Taneja SS, Rosenkrantz AB. Prostate cancer: diffusion-weighted imaging versus dynamic-contrast enhanced imaging for tumor localization -a meta-analysis. J Comput Assist Tomogr. 2013;37(6):980-8.
23. Moore CM, Robertson NL, Arsanious N, Middleton T, Villers A, Klotz L, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol. 2013;63(1):125-40.
24. Mowatt G, Scotland G, Boachie C, Cruickshank M, Ford JA, Fraser C, et al. The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation. Health Technol Assess. 2013;17(20):vii-xix, 1-281.
25. Nelson AW, Harvey RC, Parker RA, Kastner C, Doble A, Gnanapragasam VJ. Repeat prostate biopsy strategies after initial negative biopsy: meta-regression comparing cancer detection of transperineal, transrectal saturation and MRI guided biopsy. PLoS ONE. 2013;8(2):e57480.
26. Overduin CG, Futterer JJ, Barentsz JO. MRI-guided biopsy for prostate cancer detection: a systematic review of current clinical results. Curr Urol Rep. 2013;14(3):209-13.
27. Pummer K, Rieken M, Augustin H, Gutschi T, Shariat SF. Innovations in diagnostic imaging of localized prostate cancer. World J Urol. 2014;32(4):881-90.
28. de Rooij M, Hamoen EH, Futterer JJ, Barentsz JO, Rovers MM. Accuracy of multiparametric MRI for prostate cancer detection: a meta-analysis. AJR Am J Roentgenol. 2014;202(2):343-51.

29. Polanec SH, Helbich TH, Margreiter M, Klingler HC, Kubin K, Susani M, et al. Magnetic resonance imaging-guided prostate biopsy: institutional analysis and systematic review. Rofo. 2014;186(5):501-7.
30. Zhang ZX, Yang J, Zhang CZ, Li KA, Quan QM, Wang XF, et al. The value of magnetic resonance imaging in the detection of prostate cancer in patients with previous negative biopsies and elevated prostate-specific antigen levels: a meta-analysis. Acad Radiol. 2014;21(5):578-89.
31. Ikonen S, Kivisaari L, Tervahartiala P, Vehmas T, Taari K, Rannikko S. Prostatic MR imaging. Accuracy in differentiating cancer from other prostatic disorders. Acta Radiol. 2001;42(4):348-54.
32. Prando A, Kurhanewicz J, Borges AP, Oliveira EM, Jr., Figueiredo E. Prostatic biopsy directed with endorectal MR spectroscopic imaging findings in patients with elevated prostate specific antigen levels and prior negative biopsy findings: early experience. Radiology. 2005;236(3):903-10.
33. Park BK, Lee HM, Kim CK, Choi HY, Park JW. Lesion localization in patients with a previous negative transrectal ultrasound biopsy and persistently elevated prostate specific antigen level using diffusion-weighted imaging at three Tesla before rebiopsy. Invest Radiol. 2008;43(11):789-93.
34. Vilanova JC, Comet J, Barcelo-Vidal C, Barcelo J, Lopez-Bonet E, Maroto A, et al. Peripheral zone prostate cancer in patients with elevated PSA levels and low free-to-total PSA ratio: detection with MR imaging and MR spectroscopy. Radiology. 2009;253(1):135-43.
35. Hambrock T, Somford DM, Hoeks C, Bouwense SA, Huisman H, Yakar D, et al. Magnetic resonance imaging guided prostate biopsy in men with repeat negative biopsies and increased prostate specific antigen. J Urol. 2010;183(2):520-7.
36. Kitajima K, Kaji Y, Fukabori Y, Yoshida KI, Suganuma N, Sugimura K. Prostate cancer detection with 3 T MRI: comparison of diffusion-weighted imaging and dynamic contrast-enhanced MRI in combination with T2-weighted imaging. J Magn Reson Imaging. 2010;31(3):625-31.
37. Labanaris AP, Engelhard K, Zugor V, Nutzel R, Kuhn R. Prostate cancer detection using an extended prostate biopsy schema in combination with additional targeted cores from suspicious images in conventional and functional endorectal magnetic resonance imaging of the prostate. Prostate Cancer Prostatic Dis. 2010;13(1):65-70.
38. Miyagawa T, Ishikawa S, Kimura T, Suetomi T, Tsutsumi M, Irie T, et al. Real-time virtual sonography for navigation during targeted prostate biopsy using magnetic resonance imaging data. Int J Urol. 2010;17(10):855-60.
39. Sciarra A, Panebianco V, Ciccariello M, Salciccia S, Cattarino S, Lisi D, et al. Value of magnetic resonance spectroscopy imaging and dynamic contrast-enhanced imaging for detecting prostate cancer foci in men with prior negative biopsy. Clin Cancer Res. 2010;16(6):1875-83.
40. Villeirs GM, Oosterlinck W, Vanherreweghe E, De Meerleer GO. A qualitative approach to combined magnetic resonance imaging and spectroscopy in the diagnosis of prostate cancer. Eur J Radiol. 2010;73(2):352-6.
41. Choi MS, Choi YS, Yoon BI, Kim SJ, Cho HJ, Hong SH, et al. The clinical value of performing an MRI before prostate biopsy. Korean J Urol. 2011;52(8):572-7.
42. Hadaschik BA, Kuru TH, Tulea C, Rieker P, Popeneciu IV, Simpfendorfer T, et al. A novel stereotactic prostate biopsy system integrating pre-interventional magnetic resonance imaging and live ultrasound fusion. J Urol. 2011;186(6):2214-20.
43. Natarajan S, Marks LS, Margolis DJA, Huang J, Macairan ML, Lieu P, et al. Clinical application of a 3D ultrasound-guided prostate biopsy system. Urol Oncol. 2011;29(3):334-42.

44. Pinto PA, Chung PH, Rastinehad AR, Baccala Jr AA, Kruecker J, Benjamin CJ, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancer detection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol. 2011;186(4):1281-5.
45. Rastinehad AR, Baccala Jr AA, Chung PH, Proano JM, Kruecker J, Xu S, et al. D'Amico risk stratification correlates with degree of suspicion of prostate cancer on multiparametric magnetic resonance imaging. J Urol. 2011;185(3):815-20.
46. Villeirs GM, De Meerleer GO, De Visschere PJ, Fonteyne VH, Verbaeys AC, Oosterlinck W. Combined magnetic resonance imaging and spectroscopy in the assessment of high grade prostate carcinoma in patients with elevated PSA: a single-institution experience of 356 patients. Eur J Radiol. 2011;77(2):340-5.
47. Arsov C, Quentin M, Rabenalt R, Antoch G, Albers P, Blondin D. Repeat transrectal ultrasound biopsies with additional targeted cores according to results of functional prostate MRI detects high-risk prostate cancer in patients with previous negative biopsy and increased PSA - A pilot study. Anticancer Res. 2012;32(3):1087-92.
48. Engehausen DG, Engelhard K, Schwab SA, Uder M, Wach S, Wullich B, et al. Magnetic resonance image-guided biopsies with a high detection rate of prostate cancer. The Scientific World Journal. 2012;2012:975971.
49. Lee SH, Chung MS, Kim JH, Oh YT, Rha KH, Chung BH. Magnetic resonance imaging targeted biopsy in men with previously negative prostate biopsy results. J Endourol. 2012;26(7):787-91.
50. Portalez D, Mozer P, Cornud F, Renard-Penna R, Misrai V, Thoulouzan M, et al. Validation of the European Society of Urogenital Radiology scoring system for prostate cancer diagnosis on multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. Eur Urol. 2012;62(6):986-96.
51. Roethke M, Anastasiadis AG, Lichy M, Werner M, Wagner P, Kruck S, et al. MRI-guided prostate biopsy detects clinically significant cancer: analysis of a cohort of 100 patients after previous negative TRUS biopsy. World J Urol. 2012;30(2):213-8.
52. Scheidler J, Weres I, Brinkschmidt C, Zeitler H, Panzer S, Scharf M, et al. Diagnosis of prostate cancer in patients with persistently elevated PSA and tumor-negative biopsy in ambulatory care: performance of MR imaging in a multi-reader environment. Rofo 2012;184(2):130-5.
53. Shigemura K, Motoyama S, Yamashita M. Do additional cores from MRI cancer-suspicious lesions to systematic 12-core transrectal prostate biopsy give better cancer detection? Urol Int. 2012;88(2):145-9.
54. Fiard G, Hohn N, Descotes JL, Rambeaud JJ, Troccaz J, Long JA. Targeted MRI-guided prostate biopsies for the detection of prostate cancer: initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion. Urology. 2013;81(6):1372-8.
55. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. J Urol. 2013;189(3):860-6.
56. Kuru TH, Roethke MC, Seidenader J, Simpfendorfer T, Boxler S, Alammar K, et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. J Urol. 2013;190(4):1380-6.
57. Numao N, Yoshida S, Komai Y, Ishii C, Kagawa M, Kijima T, et al. Usefulness of pre-biopsy multiparametric magnetic resonance imaging and clinical variables to reduce initial prostate biopsy in men with suspected clinically localized prostate cancer. J Urol. 2013;190(2):502-8.

58. Puech P, Rouviere O, Renard-Penna R, Villers A, Devos P, Colombel M, et al. Prostate cancer diagnosis: multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy--prospective multicenter study. Radiology. 2013;268(2):461-9.
59. Rastinehad AR, Turkbey B, Salami SS, Yaskiv O, George AK, Fakhoury M, et al. Improving detection of clinically significant prostate cancer: magnetic resonance imaging/transrectal ultrasound fusion guided prostate biopsy. J Urol. 2013;191(6):1749-54.
60. Siddiqui MM, Rais-Bahrami S, Truong H, Stamatakis L, Vourganti S, Nix J, et al. Magnetic resonance imaging/ultrasound-fusion biopsy significantly upgrades prostate cancer versus systematic 12-core transrectal ultrasound biopsy. Eur Urol. 2013;64(5):713-9.
61. Sonn GA, Natarajan S, Margolis DJA, MacAiran M, Lieu P, Huang J, et al. Targeted biopsy in the detection of prostate cancer using an office based magnetic resonance ultrasound fusion device. J Urol. 2013;189(1):86-91.
62. Hong CW, Walton-Diaz A, Rais-Bahrami S, Hoang AN, Turkbey B, Stamatakis L, et al. Imaging and pathology findings after an initial negative MRI-US fusion-guided and 12-core extended sextant prostate biopsy session. Diagn Interv Radiol. 2014;20(3):234-8.
63. Javali TD, Dwivedi DK, Kumar R, Jagannathan NR, Thulkar S, Dinda AK. Magnetic resonance spectroscopy imaging-directed transrectal ultrasound biopsy increases prostate cancer detection in men with prostate-specific antigen between 4-10ng/mL and normal digital rectal examination. Int J Urol. 2014;21(3):257-62.
64. Lawrence EM, Tang SY, Barrett T, Koo B, Goldman DA, Warren AY, et al. Prostate cancer: performance characteristics of combined TW and DW-MRI scoring in the setting of template transperineal re-biopsy using MR-TRUS fusion. Eur Radiol. 2014;24(7):1497-505.
65. Thompson JE, Moses D, Shnier R, Brenner P, Delprado W, Ponsky L, et al. Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: a prospective study. J Urol. 2014;192(1):67-74.
66. Volkin D, Turkbey B, Hoang AN, Rais-Bahrami S, Yerram N, Walton-Diaz A, et al. Multiparametric MRI and subsequent MR/ultrasound fusion-guided biopsy increase the detection of anteriorly located prostate cancers. BJU Int. 2014;114(6b):E43-9.
67. Zhang J, Xiu J, Dong Y, Wang M, Han X, Qin Y, et al. Magnetic resonance imagingdirected biopsy improves the prediction of prostate cancer aggressiveness compared with a 12core transrectal ultrasoundguided prostate biopsy. Molecular medicine reports. 2014;9(5):1989-97.
68. Arumainayagam N, Ahmed H, Moore C, Freeman A, Sohaib A, Kirkham A, et al. A negative multi-parametric MRI can rule out up to 97% of clinically significant prostate cancer. J Urol. 2011;185(4):e927-8.
69. Komai Y, Numao N, Yoshida S, Kawakami S, Ishii C, Sakura M, et al. Multi-parametric magnetic resonance imaging can detect prostate cancers missed by transrectal 12-core biopsy with high accuracy. J Urol. 2011;1):e848-9.
70. Lee SH, Yeom CD, Park KK, Chung MS, Chung BH, Rha KH. Hard to detect prostate cancer diagnosed by targeted biopsy using combined T2 weighted and diffusion weighted magnetic resonance imaging. J Urol. 2011;1):e849-e50.
71. Pasticier G, Rigou G, Deminiere C, Bernhard J, Riviere J, Robert G, et al. Contrast-enhanced U.S.-guided biopsies following MRI in men with elevated PSA and previous negative biopsy. J Clin Oncol. 2011 (suppl; abstr e15130).
72. Abd-Alazeez M, Ahmed H, Moore C, Freeman A, Allen C, Kirkham A, et al. The role of multiparmetric MRI in men with negative biopsy and elevated PSA - can it rule out clinically significant disease? J Urol. 2012;187(4):e585.

73. Ahmed H, Arumainayagam N, Kirkham A, Allen C, Sohaib S, Freeman A, et al. What burden of prostate cancer can radiologists rule-out on multi-parametric MRI? An analysis based on template prostate mapping biopsies as the reference standard. J Urol. 2012;187(4):e586.
74. Kasivisvanathan V, Dufour R, Moore C, Ahmed H, Freeman A, Charman S, et al. Magnetic resonance image-guided prostate biopsy versus transperineal template prostate biopsy in the diagnosis of clinically significant prostate cancer. J Urol. 2012;187(4):e826-7.
75. Robertson N, Moore C, Villers A, Klotz L, Emberton M. The ability of MRI guided biopsy to detect clinically significant prostate cancer: a systematic review. J Urol. 2012;1:e491-e2.
76. Sonn GA, Natarajan S, Margolis D, Macairan M, Lieu P, Huang J, et al. Value of targeted biopsy in detecting prostate cancer using an office-based MR-US fusion device. J Urol. 2012;1:e829.
77. Siddiqui MM, Rais-Bahrami S, Stamatakis L, Vourganti S, Hoang A, Nix J, et al. Gleason score upgrading on MRI/ultrasound fusion guided prostate biopsy versus systematic 12-core trus biopsy. J Urol. 2013;1:e910.
78. Sonn G, Natarajan S, Margolis D, Chang E, Macairan M, Lieu P, et al. Prospective evaluation of MRI-ultrasound fusion biopsy to diagnose prostate cancer in men with prior negative biopsies. J Urol. 2013;1:e604.
79. Sonn G, Natarajan S, Margolis D, Chang E, Macairan M, Lieu P, et al. Targeted biopsy with MRI-ultrasound fusion. J Urol. 2013;1):e519.
80. Thompson J, Stricker P, Brenner P, Moses D, Shnier R, Delprado W, et al. Magnetic resonance imaging detects significant prostate cancer and could be used to reduce unnecessary biopsies: Initial results from a prospective trial. J Urol. 2013;1):e910-e1.
81. Mozer P, Roupret M, Le Cossec C, Granger B, Comperat E, de Gorski A, et al. First round of trans-rectal targeted biopsies with magnetic resonance imaging/ultrasound-fusion images versus conventional ultrasound-guided biopsies for the diagnosis of localised prostate cancer. J Urol. 2014;191(4):e750.
82. Cool DW, Romagnoli C, Izawa JI, Chin J, Gardi L, Ward AD, et al. Enhanced tumour sampling and gleason grading through fusion of mri to 3d transrectal ultrasound (TRUS) biopsy. J Urol. 2012;1):e819-e20.
83. Leslie S, Goh A, Lewandowsk PM, Huang EYH, De Castro Abreu AL, Berger AK, et al. Contemporary image-guided targeted prostate biopsy better characterizes cancer volume, gleason grade and its 3d location compared to systematic biopsy. J Urol. 2012;1:e827.
84. Margolis D, Kumar D, Macairan ML, Narayanan R, Natarajan S, Gandhi N, et al. Prostate MRI/ultrasound fusion and biopsy yield. J Clin Oncol. 2012;suppl 5: abstr 206.
85. Numao N, Ito M, Fukushima H, Takeshita H, Yoshida S, Matsuoka Y, et al. Magnetic resonance imaging guided prostate biopsy versus systematic 14-core prostate biopsy including anterior samplings in detecting significant cancer and assessing cancer aggressiveness. J Urol. 2013;1):e603-e4.
86. Ukimura O, Marien A, Palmer S, De Castro Abreu AL, Leslie S, Shoji S, et al. Magnetic resonance imaging targeted prostate biopsy with 3-dimensional ultrasound tracking system in comparative analysis to systematic random biopsy on 131 consecutive patients with prebiopsy magnetic resonance imaging. J Urol. 2013;1):e896.
87. Itatani R, Namimoto T, Atsuji S, Katahira K, Morishita S, Kitani K, et al. Negative predictive value of multiparametric MRI for prostate cancer detection: outcomes of 5-year follow up for men with negative findings on initial MRI. Radiological Society of North America. 2013 annual meeting abstract:VSGU31-11.
88. Bjurlin M, Wysock J, Sakar S, Venkataraman R, Valley G, Rosenkrantz A, et al. Risk of cancer on MRI-targeted and systematic prostate biopsy. J Urol. 2014;191(4):e416-7.

89. Boesen L, Nørgaard N, Chabanova E, Løgager V, Balslev I, Mikines K, et al. Multiparametric MRI can improve the detection rate of prostate cacer and updated the gleason score at repeated biopsy. J Urol. 2014;191(4):e749-50.
90. Borkowetz A, Zastrow S, Huber J, Froehner M, Wirth M. MRI-targeted TRUS-guided transperineal fusion biopsy is significantly superior to systematic transrectal TRUS-biopsy. J Urol. 2014;191(4):e748.
91. Eldred-Evans D, Sturch P, Meiers I, Polson A, Rottenberg G, Popert R. MRI-ultrasound fusion targeted prostate biopsy: the importance of biopsying outside the MRI lesion. J Urol. 2014;191(4):e756.
92. Le J LP, Natarajan S, Dorey F, Margolis D, Huang J, Marks L. Targeted prostate biopsy: are systematic biopsies still necessary? J Urol. 2014;191(4):e749.
93. Rubin R, Siddiqui M, George A, Walton-Diaz A, Rais-Bahrami S, Su D, et al. The efficiency of MRI/US fusion targeted prostate biopsies in finding clinically significant prostate cancer compared to standard template biopsy. J Urol. 2014;191(4):e589.
94. Shakir N GA, Rothwax J, Siddiqui M, Rais-Bahrami S,Stamatakis L, et al. Multiparametric MRI characteristics of patients upgraded by MRI/ultrasound fusion guided biopsy across PSA-based cutoffs. J Urol. 2014;191(4):e71.
95. Simmons L, Kanthbalan A, Ahmed H, Moore C, Punwani S, Freeman A, et al. Prostate imaging (Multi-parametric MRI and prostate histoscanning) compared to transperineal ultrasound guided biopsy for significant prostate cancer risk evaluation - the PICTURE study. J Urol. 2014;191(4):e753.
96. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36.
97. Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions. Version 5.1.0.. The Collaboration, 2011 [updated March 2011]. Available from: www.cochrane-handbook.org.
98. National Institute for Health and Care Excellence. Prostate Cancer: diagnosis and treatment. 2014. Available from: http://www.nice.org.uk/guidance/cg175. Accessed on April 20, 2015.
99. Itatani R, Namimoto T, Atsuji S, Katahira K, Morishita S, Kitani K, et al. Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies. Eur J Radiol. 2014;83(10):1740-5.
100. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
101. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.