

Multi-parametric MRI scans prior to biopsy for improving diagnosis of prostate cancer

Introduction

Prostate cancer is the most common cancer among men in the UK, with around 47,000 new cases diagnosed in 2013 alone. Around 150,000 men a year have transrectal ultrasound (TRUS) guided biopsies in the UK, to try to diagnose prostate cancer, but there are several problems with the use of TRUS biopsies for prostate cancer diagnosis. This briefing paper explores issues around how prostate cancer is diagnosed, and discusses a diagnostic pathway that helps

to address these problems, based on the results of the PROMIS study.

Problems with the current approach to diagnosing prostate cancer

The current way of diagnosing prostate cancer (Figure 1) is not ideal. PSA alone is not enough to diagnose prostate cancer, as it is non-specific. TRUS biopsies are also not a very good diagnostic tool. They can miss clinically significant tumours; PROMIS found

Key points

- Transrectal ultrasound (TRUS) guided biopsies are not a very good diagnostic tool for prostate cancer. While they may identify some tumours that will never be significant, they miss around half of clinically significant tumours, and are associated with significant side-effects, including sepsis.
- A multi-parametric MRI scan prior to biopsy can identify at least one quarter of men presenting with an elevated PSA who might safely avoid prostate biopsies (around 40,000 men a year in the UK).
- Multi-parametric MRI scans followed by a biopsy which is guided by the MRI findings may reduce the over-diagnosis of clinically insignificant prostate cancer.
- Multi-parametric MRI scans followed by a biopsy which is guided by the MRI findings can also improve the detection of clinically significant prostate cancers, and reduce the need for repeat biopsies.
- For this approach to be implemented in the NHS, work needs to be done to train radiologists to use MP-MRI scans for prostate cancer diagnosis; and to ensure that hospitals have sufficient capacity to perform highly accurate MP-MRI scans.
- Training for biopsies that are based on using the MRI information to help deploy the biopsy needles better will also be required.

The PROMIS study

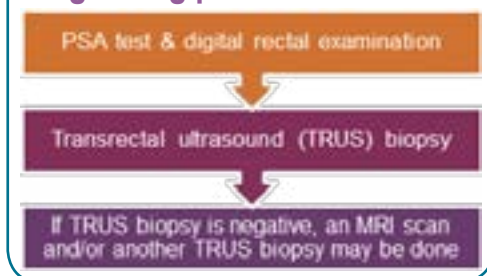
The 'Prostate MRI Imaging Study' (PROMIS) tested whether the use of a multi-parametric MRI (MP-MRI) scan before a first prostate biopsy could identify men who might safely avoid a biopsy. PROMIS was also trying to find out how accurate MP-MRI was at detecting clinically significant cancers, in comparison to TRUS biopsies.

PROMIS was a 'Paired-Validating Cohort Study'. It compared the accuracy of two diagnostic tests, MP-MRI and TRUS biopsy, both given to all subjects. Each test was also compared against Template Prostate Mapping (TPM) biopsy (using a 5mm sampling frame), in terms of sensitivity, specificity and positive and negative predictive values. TPM biopsy was used as the 'gold standard' to compare the other tests to, as it gives a complete, systematic overview of the prostate, and is very accurate in diagnosing prostate cancer. It is a test that can be applied as a reference test to men at risk, so those with and without cancer were subjected to the same gold standard comparison.

Men taking part in the study had all three tests, with blinding of the test results between the tests, allowing the results to be compared with one another in a paired fashion. This design provides the highest level of evidence for assessing diagnostic accuracy.

Men were eligible to take part in the PROMIS study if their doctor had a clinical suspicion that they may have prostate cancer (raised PSA [up to ≤ 15 ng/ml], ethnicity or a previous family history of prostate cancer in a first degree relative) and they had never had a prostate biopsy before. 576 men from 11 hospitals in England had all three tests.

Figure 1: The usual way of diagnosing prostate cancer



TRUS biopsies missed 52% of clinically significant cancers. TRUS biopsies can also have side-effects, including infections (some life-threatening), pain, urinary problems and bleeding.

Following a 'negative' TRUS biopsy, many men will go on to have additional tests (repeated TRUS biopsies, MP-MRI scans or template biopsies) to confirm whether or not they really have prostate cancer. On the other hand, if one of the needles happens to take a sample from a clinically insignificant tumour, it can lead to unnecessary anxiety and over-treatment (with associated side effects, including incontinence and impotence). Unnecessary treatments are also costly for healthcare services especially as they offer no benefit in terms of longer survival for men with clinically insignificant tumours.

While TPM biopsies are very accurate, they are not the standard practice as a first line test because they usually require general anaesthetic (which has risks), and they are more resource intensive and time-consuming than TRUS biopsies. It is not feasible to use template biopsies for all men who currently have prostate biopsies.

Some hospitals already use MP-MRI to help diagnose prostate cancer, but it is not yet standard practice, as, until the PROMIS study, there was not enough evidence

to show that MRI results are good at identifying or ruling out clinically significant prostate cancer.

How accurate is MP-MRI at diagnosing prostate cancer?

Sensitivity of MP-MRI

MP-MRI had very good sensitivity and was able to correctly detect important cancer in almost all (93%) of men with significant prostate cancers. MP-MRI only missed a small number (7%) of significant cancers.

Specificity of MP-MRI

MP-MRI was not very good at excluding all the men who did not have significant cancers. The MP-MRI only predicted a diagnosis of no significant cancer in less than half (41%) of men who in fact turned out not

The MP-MRI scans used in PROMIS

- 1.5 Tesla, no endorectal coil
- Independent Quality Assurance and Quality Control of scans
- Compliant with international guidance (T2W, Diffusion (ADC + b=1500), Dynamic gadolinium contrast) through a process of site set-up in which scans were evaluated centrally prior to the study until high quality multi-parametric sequences were obtained
- Radiologists used the LIKERT scoring on a range of 1 to 5 to assess the likelihood of the prostate harbouring significant cancer (1=highly unlikely to harbour significant cancer, 2=unlikely to harbour significant cancer, 3=uncertain/equivocal, 4=likely to harbour significant cancer, 5=highly likely to harbour significant cancer)
- The mp-MRI scan was considered positive if it was scored as ≥ 3

Assessing diagnostic accuracy

Studies looking at how accurate diagnostic approaches are look at how the tests perform on four measures:

Sensitivity: sensitivity means the proportion of 'true positives' (in this case, clinically significant tumours) the test identifies. The higher the sensitivity, the less likely the test is to miss a clinically significant tumour. If the sensitivity is low, the test is likely to miss some clinically significant tumours.

Specificity: specificity means the proportion of 'true negatives' the test correctly identifies. If the specificity is low, it means the test is likely to pick up a high number of 'false positives', leading to overdiagnosis.

Positive predictive value:

Positive predictive value is the proportion of people who truly do have the disease among those who have a positive result from the test.

Negative predictive value:

Negative predictive value is the proportion of people who do not truly have the disease among those who have a negative result from the test.

Histological definition of clinically significant cancer

PROMIS used the following histological definition of clinically significant cancer to draw its primary outcomes:

- Gleason $\geq 4+3$ and/or
- Cancer core length ≥ 6 mm

PROMIS also investigated whether using other definitions of clinically significant cancer changed the conclusions. These were secondary analyses. The other definitions tested were:

- Any Gleason pattern $\geq 3+4$ AND/OR cancer core length ≥ 4 mm
- Any Gleason score 7 ($\geq 3+4$)

to have significant cancer. For the remaining 59% of men who had no clinically significant cancer in their TPM biopsies, MP-MRI tended to err on the side of caution and report a positive result when in fact the man did not have significant cancer. This result would not be regarded as a final diagnosis as the man would require a confirmatory biopsy.

Positive predictive value of MP-MRI

The positive predictive value for MP-MRI was 51%. This means that if MP-MRI says there is significant cancer, in 51% of cases this is correct - and the man does have a significant cancer.

Negative predictive value

The negative predictive value for MP-MRI was 89%. This means that if MP-MRI says there is no significant cancer, in 89% of cases this is correct - and the man does not have significant cancer.

How does this compare to the accuracy of TRUS biopsies?

As Table 1 shows, MP-MRI had much better sensitivity than TRUS-biopsy, while TRUS-biopsy had much better specificity than MP-MRI. The strengths and weaknesses of the two tests are complementary, which allows them to be combined in a way that improves our overall strategy for diagnosing prostate cancer.

Table 1: Diagnostic accuracy of TRUS-biopsy and MP-MRI in the detection of clinically significant prostate cancer

| TPM-biopsy definition of clinical significance | Prevalence of disease on TPM-biopsy, N (%) [95% CI] | Test attribute | MP-MRI % | TRUS-biopsy % | p-value |
|--|---|----------------|----------|---------------|----------|
| Primary Definition (Gleason \geq 4+3 and/or cancer core length \geq 6mm) | 230 (40% [36-44]) | Sensitivity | 93 | 48 | p<0.0001 |
| | | Specificity | 41 | 96 | p<0.0001 |
| | | PPV | 51 | 90 | p<0.0001 |
| | | NPV | 89 | 74 | p<0.0001 |
| Secondary Definition (Gleason \geq 3+4 and/or cancer core length \geq 4mm) | 331 (57% [53-62]) | Sensitivity | 87 | 60 | p<0.0001 |
| | | Specificity | 47 | 98 | p<0.0001 |
| | | PPV | 69 | 98 | p<0.0001 |
| | | NPV | 72 | 65 | 0.025 |
| Any Gleason score 7 (\geq3+4) | 308 (53% [49-58]) | Sensitivity | 88 | 48 | p<0.0001 |
| | | Specificity | 45 | 99 | p<0.0001 |
| | | PPV | 65 | 99 | p<0.0001 |
| | | NPV | 76 | 63 | p<0.0001 |

Did using different definitions of clinically significant disease affect the findings?

There are differing views amongst clinicians about how to define disease that is likely to represent a clinically significant risk. Changing how 'clinically significant' was defined (using the definitions in box 4) changed how many men were categorised as having clinically significant prostate cancer. Using other definitions, MP-MRI continued to have significantly better sensitivity and negative predictive value than TRUS biopsies, and worse specificity and positive predictive value (see Table 1), indicating that biopsies were still required after a suspicious MP-MRI.

Which cancers get missed?

A very small number of men with important cancer would be missed if MP-MRI was used as a test to decide who needs a TRUS biopsy. In PROMIS, of the 230 men who had significant cancers, MP-MRI only missed 17 of these (7%). The remaining 203 men with important

cancers would all have been recommended to have a biopsy.

Table 3 shows the histological characteristics of the cases missed by MP-MRI or TRUS-biopsy, according to the different definitions of 'clinically significant'. The cases missed by MP-MRI were towards the lower end of the risk spectrum for significant disease (either Gleason 3+4 with core lengths of 1-12mm, or Gleason 3+3 with core lengths of 4-8mm). Data from the recently-published ProtecT trial, which included men with Gleason scores of 6 or 7, showed 10 year prostate cancer specific survival of at least 98.8%. ProtecT found no significant difference between men randomised to active surveillance or radical treatment. This suggests that cases missed by MP-MRI scans are likely to have a low risk of harm.

Table 2: Histological characteristics on TPM-biopsy of cases missed by MP-MRI and TRUS-biopsy using the 3 definitions of clinically significant prostate cancer

| Definition of significant | MP-MRI missed cases | TRUS-Biopsy missed cases |
|---|---|--|
| Primary Definition (Gleason $\geq 3+3$ and/or cancer core length $\geq 6\text{mm}$) n=230 | Total = 17 1 x 3+3 with core length 8mm 16 x 3+4 with core lengths 6-12mm | Total = 119 7 x 3+3 with core lengths 6-11mm 99 x 3+4 with core lengths 6-14mm 13 x 4+3 with core lengths 3-16mm |
| Secondary Definition (Gleason $\geq 3+4$ and/or cancer core length $\geq 4\text{mm}$) n=331 | Total = 44 6 x 3+3 with core lengths 4-8mm 38 x 3+4 with core lengths 1-12mm | Total = 132 18 x 3+3 with core lengths 4-11mm 104 x 3+4 with core lengths 1-14mm 10 x 4+3 with core lengths 3-16mm |
| Any Gleason score 7 ($\geq 3+4$) n=308 | Total = 38 38 x 3+4 with core lengths 1-12mm | Total = 159 146 x 3+4 with core lengths 1-14mm 13 x 4+3 with core lengths 3-16mm |

Using MP-MRI as triage prior to TRUS biopsies

Combining the two tests, using MP-MRI as a triage to decide who requires a TRUS biopsy, has the potential to exploit the relative strengths of both tests. It could **reduce the number of men having a biopsy by around a quarter; almost double the proportion of significant cancers correctly detected; and reduce the number of men over-diagnosed by around a third.**

Carrying out the MP-MRI scan prior to the biopsy may improve diagnostic accuracy through enabling the TRUS biopsy to focus on the areas with the highest risk, as seen on the scan. This was not done as part of PROMIS (the biopsies were performed blind to the results of the MRI scan to avoid bias), but may improve outcomes further in real life.

An additional advantage of carrying out an MP-MRI first is that the volume of the prostate can be measured accurately with the MRI scan. This allows calculation of the PSAD (PSA density) which may help to plan any subsequent biopsy and/or management decisions.

The literature also shows that local staging is improved with a pre-biopsy MP-MRI, as there is no artefact from bleeding and inflammation causing areas of the prostate to look worse than they are. PROMIS was unable to evaluate this specific issue as all men underwent MRI prior to biopsy.

Implementing MP-MRI as triage before biopsy

The PROMIS researchers are recommending that the diagnostic pathway should be changed so that patients have an MP-MRI scan as a 'triage' test to decide who needs to have a TRUS biopsy. Patients with a positive MP-MRI should be advised to have a biopsy. Patients whose MP-MRI scan indicates no evidence of important cancer might then be advised to not have a TRUS biopsy, although clinicians may consider other factors before making this recommendation. PROMIS did not evaluate what follow-up men should have if they are advised to not have a biopsy: this should be decided in conjunction with the patient and his GP by the urological team. One approach, until further

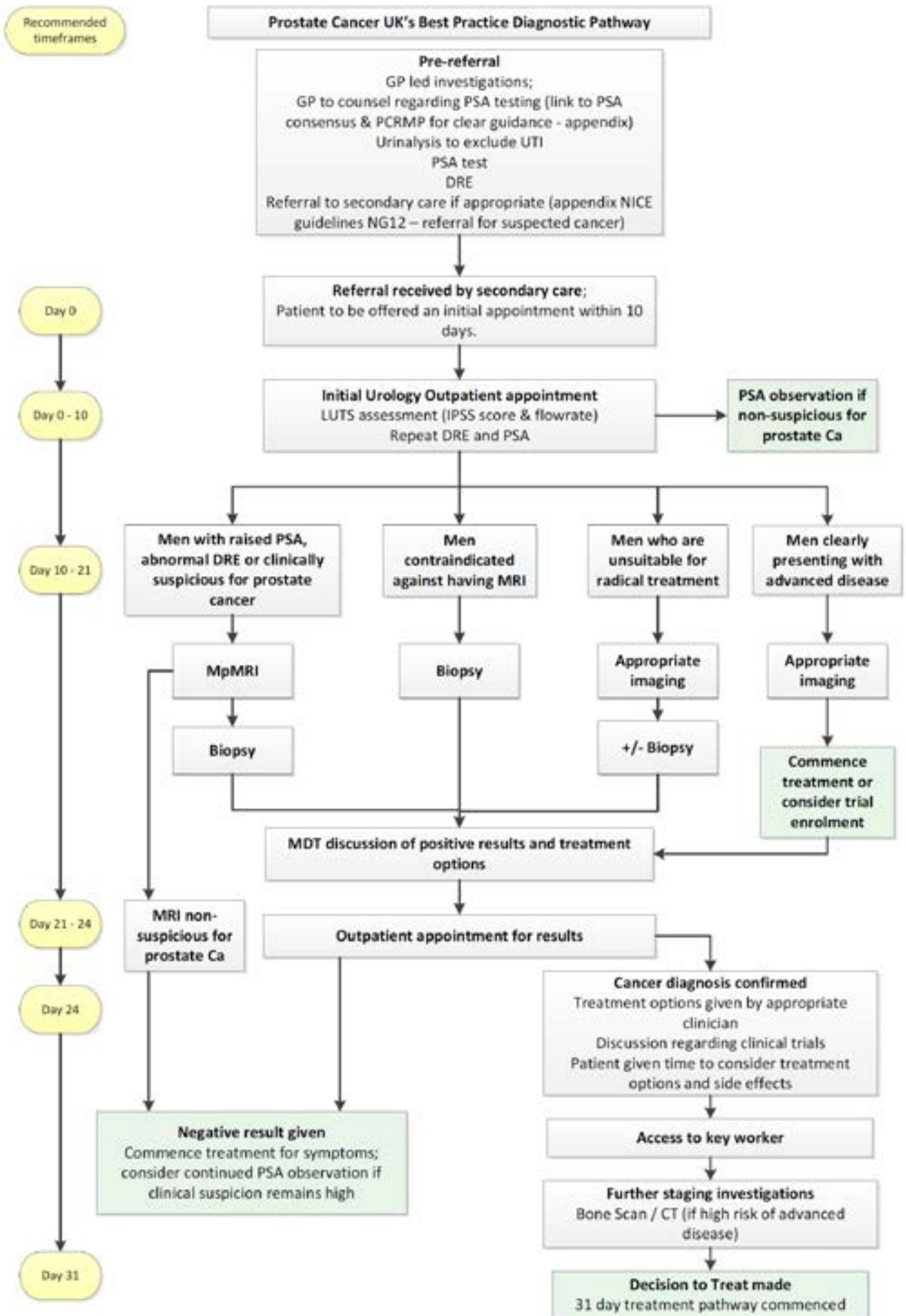
evidence is available, would be to offer a one-year urology clinical review with PSA, and to consider a repeat MRI scan.

Prostate Cancer UK have worked with radiologists and urologists to develop a Best Practice Diagnostic Pathway (Figure 2), taking into account the PROMIS findings.

Can radiologists correctly identify who needs a biopsy based on MP-MRI scans?

In PROMIS, two radiologists each reported separately the MP-MRI scans for 132 men, blind to what the other radiologist reported. They agreed with each other's scoring for 106 of the scans (80% agreement). For the remaining 26 (20%) scans, there was disagreement between the radiologists as to whether the man had significant disease or not. If MP-MRI became part of standard care, national training programmes for reporting these scans would be required for radiologists. The Royal College of Radiologists is planning a webinar on this topic in the next few months, and a face-to-face training day in October 2017.

Figure 2: Prostate Cancer UK Best Practice Diagnostic Pathway



Can urologists use the MP-MRI results to target their biopsies?

As well as having appropriately trained radiologists to interpret MP-MRI scan results, urologists will also need to have appropriate training and experience of prostate ultrasound and biopsy, and of using MRI scans to target TRUS-biopsies. This may help to improve the sensitivity of TRUS biopsies, and reduce the need for repeat biopsies.

Requirements for implementing MP-MRI scans prior to biopsy

Prostate Cancer UK are working with urologists and radiologists to develop a checklist for clinical commissioning groups in England that are considering commissioning MP-MRI prior to TRUS biopsy. The checklist sets out important criteria that CCGs should aim to have in place for MP-MRI before biopsy to deliver effective results:

- Appropriate equipment in place, with capacity to enable prostate MRI for men with a PSA above the upper limit of age-specific normal range
- Adherence to the clinical consensus for MP-MRI before biopsy on practice standards, so that consistency of practice is achieved
- Training undertaken by radiologists, with expectation for expert radiologist pairing
- Training undertaken by radiographers
- Radiologists and radiographers audited through quality assurance mechanism
- Effective multidisciplinary team in place

Conclusions

The current approach to diagnosing prostate cancer - using TRUS-biopsies for all men identified as being at risk of prostate cancer - means tens of thousands of men are having unnecessary biopsies in the UK each year. Adding an MP-MRI scan as triage, to decide who needs a biopsy and help target the biopsy to the area at risk, could reduce the number of men needing biopsies, improve detection of clinically significant cancer, and potentially reduce overdiagnosis. In order for this change to take place safely, work needs to be done to make sure the quality of the MP-MRI scans is high enough, and that radiologists reading those scans have the skills to safely distinguish between men who require a biopsy and those who do not.

Recommendations

1. Trusts with the necessary scanner and radiologist capacity should consider introducing MP-MRI as triage to decide who requires a biopsy.
2. Patients with MP-MRI scans that do not show signs of clinically significant prostate cancer might be advised against TRUS-biopsies.
3. Further analysis of the PROMIS data set should be carried out to develop an improved algorithm for identifying which men are most at risk of clinically significant prostate cancer.

Further information

Ahmed et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet* (2017). DOI: [http://dx.doi.org/10.1016/S0140-6736\(16\)32401-1](http://dx.doi.org/10.1016/S0140-6736(16)32401-1).

To sign-up to receive the PCUK checklist for clinical commissioning groups in England visit <http://prostatecanceruk.org/checklist>. The checklist will be sent when it is ready.

Credits

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