PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Prostate Cancer Diagnostic Pathway: Is a One-Stop Cognitive Magnetic Resonance Imaging Targeted Biopsy Service A Realistic Goal in Everyday Practice? A pilot cohort in a Tertiary Referral Centre in the United Kingdom.
AUTHORS	Bass, Edward James; Freeman, Alex; Jameson, Charles; Punwani, Shonit; Moore, Caroline M; Arya, Manit; Emberton, Mark; Ahmed, Hashim Uddin

VERSION 1 – REVIEW

REVIEWER	Leslie C Thompson Urologist Australia
REVIEW RETURNED	14-Jan-2018

GENERAL COMMENTS	This is a very nice concise prospective study which corroborates previous imaging and target Bx papers done circa 2012/2013 (your references 6 and 33) and should be published with a few minor additions if authors are agreeable. Comments: 1. The authors use transperineal targeting for the biopsies which is excellent bacteriologically, but it should be noted that this requires a much higher skill level than TRUS and this is usually obtained from extensive work using brachytherapy apparatus which is not available in community Urology settings. 2. Also, to be successful, there must be a high level of specialist skill in acquisition and interpretation of images and some quality control measures in place which I know there is at the authors place. Without this expertise and QC, the problem is overcalling of PIRADS 3 and 4, (not under calling). This should be noted because expertise and QC is the key to success. 3. One good index of QC is the number of PIRADS (or Likert) 3's in a series, and it is thought this should be around 20% . In this series it was 23% (per man), but 44% per lesion. This suggests that after the radiologist has called the main lesion, he is not really paying enough attention to subsequent lesions ("Satisfaction of Search Bias"). This could be mentioned because the average Urologist does not know any of the standard radiological biases. With regard to second and third lesions: It is uncomfortable and time consuming (and somewhat frustrating because of bleeding from the

	first biopsy) to biopsy second and third lesions, especially under LA.. Is there any opportunity to drill down on the data you have and find out if biopsy of these second and third lesions changed the management of the cases? Would be clinically useful information. 4. I'm not familiar the UCL criteria for its Likert scoring. My only comment, is for international communication, PIRADS V 2 seems to be the most used in the literature, and accepted by ESUR and ACR. Thus, if the authors particular system is pretty close to the weighted PIRADS V 2, it would be good to mention this in terms of communication. 5. Similarly, these sort of papers require a specific definition of grade and core length and +ve core numbers, tailored for targeted biopsies (as opposed to high volume biopsies). In your reference 33 supplementary tables, these authors had a go at this to the best of their ability (attached file), and did include high volume 3+3, so again I wasn't too sure of the interpretation of your UCL 1 or 2 criteria, but I take it that you are classifying all 3+3 and low volume 3+4 as low risk, and anything above 6mm 3+4 as intermediate/high risk. Could you make this clearer please? maybe a table? 6. I see the number of needle passes per lesion on average was 4, but per patient was 9. It would be good to know how well the patients tolerated the TP approach under LA and whether you had them fidgeting with the grid in place or not, and roughly how long it took to do – just a practical comment would be good. 7. Finally, while the concept of an image based diagnostic pathway (MRI followed by a quick MRI guided targeted biopsy) may be "novel" in UK, this pathway has been practised since 2011 in some pioneering research centres internationally (Netherlands, Australia, and USA.), albeit not TP. Good to acknowledge. Good work.

REVIEWER	Pepe Pietro Italy Prostate cancer
REVIEW RETURNED	15-Jan-2018

GENERAL COMMENTS	The paper refer about the accuracy of mpMRI and cognitive fusion transperineal targeted biopsy in the diagnosis of prostate cancer (PCa) and conclude that this approach reduces the time to diagnosis and treatment. The paper is interesting but some points should be improved and explained. 1) Clinical data of patients should be added (i.e., digital rectal examination). 2) Why the study was stopped in 03 2016? A greater number of patients should be evaluated. 3) Men with mpMRI PI-RADS 3 have been considered suspected for PCa and suitable for prostate biopsy; conversely, literature data recommend prostate biopsy in men with PI-RADS > 4. The authors should explain their choice of inclusion criteria for mpMRI targeted biopsy (PI-RADS 3). 4) Only 57/87 (65%) men with PI-RADS > 3 underwent targeted biopsy; the absence of histological specimen in 30/87 (35%) reduce significantly the accuracy of the protocol considering that only 112 men were evaluated. 5) The advantages of transperineal approach should be reported in the discussion, but in this series a comparison with transrectal

	approach was not performed (second declared objective of the study). Reference that compare transrectal vs transperineal approach in the same population should be added (a). 6) The reported detection rate for PCa in the presence of PI-RADS 3 is equal to 18% resulting superimposable with literature data; on the contrary, the detection rate of PCa for PI-RADS 4 (24/49: 49%) and 5 (23/42: 55%) is significantly lower than that showed in others papers. The Authors should explain their data. 7) It is unknown if a rapid diagnosis (4 weeks less) of prostate cancer improves life expectancy of the patient! 8) The false negative rate of mpMRI for clinically significant PCa (15-20% of the cases) should be clearly reported in the discussion (b). In addition EAU guideline recommendations regarding the use of mpMRI in case of initial biopsy should be cited. 9) The Authors have not reported the false negative rate of mpMRI because standard biopsy was not performed; these data should be added in the discussion. 10) Which was the clinical follow up for the 55/112 (49%) men (22 of them with negative mpMRI) who were not submitted to prostate biopsy? A standard prostate biopsy was suggested as second diagnostic step to rule out the presence of PCa missed by mpMRI? 11) Reference 32 refers to an Abstract presented at AUA in 2016 and not to a published paper. a) Pepe P, Garufi A, Priolo G, Pennisi M: Transperineal Versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer. Clin Genitourin Cancer. 2017 Feb;15(1):e33-e36. doi: 10.1016/j.clgc.2016.07.007. Epub 2016 Jul 21. b) Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, Reiter RE, and Marks LS: Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer 2016; 122: 884-892.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a very nice concise prospective study which corroborates previous imaging and target Bx papers done circa 2012/2013 (your references 6 and 33) and should be published with a few minor additions if authors are agreeable.

Comments:

The authors thank the reviewer for their kind points. We shall respond to each in order below.

1. The authors use transperineal targeting for the biopsies which is excellent bacteriologically, but it should be noted that this requires a much higher skill level than TRUS and this is usually obtained from extensive work using brachytherapy apparatus which is not available in community Urology settings.

Thank you for the relevant points. In regard to the skill level required, the authors believe that this may be overstated. Whilst good knowledge of prostate anatomy is essential for such cognitive approaches to targeted biopsy, we do not believe that these should be out of the

scope of already specialist providers of biopsy services, namely radiologists and urologists, even if there is a demonstrable learning curve. Furthermore, whilst demonstrated with TRUS, authors such as Cool DW [AJR Am J Roentgenol 2015] have found no difference in cancer detection rate in regardless of the level of experience of the operator. Finally, cancer detection rates for the cognitive approach to targeted biopsy remain on a par with image guided (USS/MRI and in-bore) [Wegelin et al 2017 Eur Urol]. We have now passed comment on this in the discussion section on page 11.

2. Also, to be successful, there must be a high level of specialist skill in acquisition and interpretation of images and some quality control measures in place which I know there is at the authors place. Without this expertise and QC, the problem is overcalling of PIRADS 3 and 4, (not under calling). This should be noted because expertise and QC is the key to success.

This is a pertinent point. We agree that in less experienced centres, it is overcall of lesions as PIRADS 3/4 that is of most concern, as 4/5 lesions are far more likely to harbour significant disease. Further, it would of course be true that if avoiding biopsies were of interest, a significant overcall of PIRADS 3 lesions would lessen the benefit of an mpMRI led pathway in this regard. Having said this, the increasingly widespread uptake of PIRADS v2 over v1, with its ability to define PIRADS 4 lesions over 3 lesions with the second parameter (DCE / DWI), alongside its more easily understood and applicable design should reduce this overcall effect going forward. Furthermore, we should stress that this is a pilot study of a pathway going forward and one that may be aspired to, rather than one that is ready to be adopted nationwide immediately, before any interested centre is ready. We have addressed this point on page 11.

3. One good index of QC is the number of PIRADS (or Likert) 3's in a series, and it is thought this should be around 20%. In this series it was 23% (per man), but 44% per lesion. This suggests that after the radiologist has called the main lesion, he is not really paying enough attention to subsequent lesions ("Satisfaction of Search Bias"). This could be mentioned because the average Urologist does not know any of the standard radiological biases.

With regard to second and third lesions: It is uncomfortable and time consuming (and somewhat frustrating because of bleeding from the first biopsy) to biopsy second and third lesions, especially under LA. Is there any opportunity to drill down on the data you have and find out if biopsy of these second and third lesions changed the management of the cases? Would be clinically useful information.

This is an interesting point and a cognitive bias that we were unaware of. Certainly this shall be added to the discussion section on page 12. In regard to whether the second or third lesions histology would change management the answer is yes, at least in this centre. For example, a second lesion on the contralateral side to the first, which is positive for significant disease, would make focal therapy a less efficacious approach to treatment. However, in the bulk of centres where this is not practiced then there would likely be little change in approach

to the curative therapy, save for planning for RARP in the case of potential nerve sparing procedures. In this series, of the 20 men who had >1 lesion on mpMRI, the non-primary lesions harboured a higher-grade disease and/or higher volume. However, in only one of these men was the secondary lesion a lower likert score. Regardless, both of these men went on to have robotic assisted radical prostatectomies. This information has been added to the results section on page 9 and discussed on page 12.

4. I'm not familiar the UCL criteria for its Likert scoring. My only comment, is for international communication, PIRADS V 2 seems to be the most used in the literature, and accepted by ESUR and ACR. Thus, if the authors particular system is pretty close to the weighted PIRADS V 2, it would be good to mention this in terms of communication.

Thank you for your constructive criticism. In regard to the choice of radiological score, the Likert score uses a five-point scale much like the PI-RADs score whilst allowing for the radiologist's overall impression to characterize the level of suspicion for prostate cancer on the images. Our choice was based on the outcomes of the 2011 European consensus meeting [Dickinson et al Eur Urol. 2011] which met prior to the Prostate Imaging and Data Reporting System (PIRADS) MP-MRI reporting consensus meeting [Barentsz et al. European Radiology. 2012]. Whilst we acknowledge the widespread use of the PI-RADs scoring system and its standardized nature, the Likert score has demonstrated equivalency [Rosenkrantz et al. AJR Am J Roentgenol. 2013]. This has been clarified in the Patients and Methods section on page 7.

5. Similarly, these sort of papers require a specific definition of grade and core length and +ve core numbers, tailored for targeted biopsies (as opposed to high volume biopsies).

In your reference 33 supplementary tables, these authors had a go at this to the best of their ability (attached file), and did include high volume 3+3, so again I wasn't too sure of the interpretation of your UCL 1 or 2 criteria, but I take it that you are classifying all 3+3 and low volume 3+4 as low risk, and anything above 6mm 3+4 as intermediate/high risk. Could you make this clearer please? Maybe a table?

Thank you for shedding light on this; we have added a 'traffic light like' figure to explain this in better detail. This can be found as figure 3. We acknowledge that the definitions used for radiological and histological prostate cancer risk stratification lack standardization as whole. However, the UCL definition has been used in all of our groups previously published papers and is shared by others including the UCLA, Heidelberg, Southend and Cambridge study groups. Whilst we acknowledge other commonly used histological stratification systems such as the Epstein criteria exist, they are based from TRUS biopsy and not validated for a transperineal approach. By comparison the UCL definition have been validated for this purpose.

6. I see the number of needle passes per lesion on average was 4, but per patient was 9. It

would be good to know how well the patients tolerated the TP approach under LA and whether you had them fidgeting with the grid in place or not, and roughly how long it took to do – just a practical comment would be good.

Once again an important question. In a previous paper [Bass EJ et al, Prostate Cancer Prostatic Dis 2017] we reported the length of the first 20 procedures as a mean of 27 minutes and a median of 30 minutes. Furthermore, the VAS scores were reported as a median of 1.0 with a single procedural abandonment. We have added this information to the discussion section on page 7.

7. Finally, while the concept of an image based diagnostic pathway (MRI followed by a quick MRI guided targeted biopsy) may be "novel" in UK, this pathway has been practised since 2011 in some pioneering research centres internationally (Netherlands, Australia, and USA.), albeit not TP. Good to acknowledge.

Good work.

Thank you for highlighting this, we agree this would be a worthwhile addition to the introduction section on page 6.

Reviewer: 2

The paper refer about the accuracy of mpMRI and cognitive fusion transperineal targeted biopsy in the diagnosis of prostate cancer (PCa) and conclude that this approach reduces the time to diagnosis and treatment.

The paper is interesting but some points should be improved and explained.

Once again the authors thank the reviewer for their constructive criticism. We shall respond to each in order below.

1) Clinical data of patients should be added (i.e., digital rectal examination).

An interesting point and in most cases one that would be entirely agreeable. However, in this case the authors do not believe this to be a necessity for the following reasons. The mpMRI was performed prior to the patient meeting with a urologist. In the majority of cases – we admit – a digital rectal examination was performed by a primary care physician. However, the positive predictive value of digital rectal examination in these circumstances is as low as 5% (Hoogendam A et al, Fam Pract, 1999). Naturally, this rises in more experienced hands to around 30% (Hoogendam A et al, Fam Pract, 1999), however in the case of a patient having a suspicious DRE, in the absence of a concordant target on mpMRI, full templates under general anaesthetic were performed in place of targeted biopsies.

2) Why the study was stopped in 03 2016? A greater number of patients should be evaluated.

The authors agree, however, we openly admit that this work is a pilot study to assess the

feasibility of such a diagnostic pathway from both service and diagnostic standard of care parameters.

3) Men with mpMRI PI-RADS 3 have been considered suspected for PCa and suitable for prostate biopsy; conversely, literature data recommend prostate biopsy in men with PI-RADS > 4. The authors should explain their choice of inclusion criteria for mpMRI targeted biopsy (PI-RADS 3).

Thank you for pointing out our lack of clarity here. As part of the pathway protocol, men with lesions rated as >4 were advised to have a biopsy, those with 3 were given a choice and most (18 men) did not undergo biopsy. Our reasoning for this was threefold. First, the PICTURE and PROMIS trials used a PIRADS score of >/=3 as suspicious. Second, whilst the positive predictive value of a rating of >4 is undoubtedly exceptional and higher than lesions rated as 3, studies have regardless demonstrated PPVs of almost 50% (Grey A et al BJUI 2015). Certainly, biopsies have been proposed on the basis of digital rectal examination, which even in combination with PSA has not demonstrated as strong a PPV. Third, from this centre's own data, we know that around 20% of men with such a lesion will harbour significant disease which rises to almost 40% if they are black or have a first degree relative with prostate cancer. In this particular series, 15% of Likert 3 lesions harboured such disease in keeping with this. Whilst perhaps mandating a biopsy in such patients is too strong, we believe offering it is appropriate as it minimizes the false negative rate of mpMRI.

4) Only 57/87 (65%) men with PI-RADS > 3 underwent targeted biopsy; the absence of histological specimen in 30/87 (35%) reduce significantly the accuracy of the protocol considering that only 112 men were evaluated.

The authors thank the reviewer for there observation. Again, we stress that this study reports on a pilot rapid diagnostic protocol for prostate cancer in terms of service feasibility. The biopsy technique in terms of cancer detection as its primary outcome measure has previously been described (Bass EJ et al Prostate Cancer Prostatic Dis 2016). This demonstrated the significant cancer detection rate as 71% and any cancer detected as 78%.

5) The advantages of transperineal approach should be reported in the discussion, but in this series a comparison with transrectal approach was not performed (second declared objective of the study). Reference that compare transrectal vs transperineal approach in the same population should be added (a).

The authors agree that such advantages are important and we have amended the discussion on page 10 to comment on this. A direct comparative study was not performed as the PRECISION trial was currently recruiting during the pilot period. PRECISION will directly compare these two biopsy methods, thus repeating the work was not deemed necessary especially in the context of recent work demonstrating exceptionally low post biopsy sepsis rates in targeted transperineal biopsy (Grummet J et al World J Urol 2017)

6) The reported detection rate for PCa in the presence of PI-RADS 3 is equal to 18% resulting

superimposable with literature data; on the contrary, the detection rate of PCa for PI-RADS 4 (24/49: 49%) and 5 (23/42: 55%) is significantly lower than that showed in others papers. The Authors should explain their data.

The authors again apologise for any lack of clarity here, the denominators and numerators are incorrect in the applicable table and as such have been corrected in table 1.

7) It is unknown if a rapid diagnosis (4 weeks less) of prostate cancer improves life expectancy of the patient!

The authors agree, in fact, much evidence suggests there may be little difference in survival at all (Redaniel MT et al BMC Cancer 2013). However, the literature also suggests that the psychological impact of a potential diagnosis of prostate – or indeed any cancer – is not to be understated (Brocken P et al Psychooncology 2012). We believe that this alone is reason enough to enact a pathway with the ability to answer the questions that run through a patient's head when addressing such a life event. The introduction section has been amended to explicitly state this on page 4.

8) The false negative rate of mpMRI for clinically significant PCa (15-20% of the cases) should be clearly reported in the discussion (b). In addition EAU guideline recommendations regarding the use of mpMRI in case of initial biopsy should be cited.

The authors agree that the negative predictive value of mpMRI is of utmost importance to such a pathway. The findings of PROMIS are discussed at length in the discussion section as well as the findings of Fütterer's systematic review, which investigated this rate using either template biopsy or whole mount prostatectomy specimens as the reference standard. However, we have commented upon the EAU and NICE guidance in regard to mpMRI in the discussion section on page 11.

9) The Authors have not reported the false negative rate of mpMRI because standard biopsy was not performed; these data should be added in the discussion.

We thank the reviewer for their comments. We agree that whilst and calculable false negative rate would be an agreeable addition to the findings of this pilot study, this question has been strongly answered by PROMIS and realistically do not add a significant amount of value here. A false negative rate of targeted biopsy is also an interesting question, and one that would require a dedicated trial to calculate in a robust manner.

10) Which was the clinical follow up for the 55/112 (49%) men (22 of them with negative mpMRI) who were not submitted to prostate biopsy? A standard prostate biopsy was suggested as second diagnostic step to rule out the presence of PCa missed by mpMRI?

An important question in the context of this study. We have added to our results section on pages 9 and 10 to address this. Nine were discharged for PSA surveillance in the community, 10 were kept on PSA surveillance in secondary care, 4 underwent lower urinary tract symptom

investigation and treatment and one underwent template biopsies under general anaesthetic.

11) Reference 32 refers to an Abstract presented at AUA in 2016 and not to a published paper.

We thank the reviewer for bringing this to our attention. A more appropriate reference has been chosen to illustrate this point in the manuscript.

a) Pepe P, Garufi A, Priolo G, Pennisi M: Transperineal Versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer. Clin Genitourin Cancer. 2017 Feb;15(1):e33-e36. doi: 10.1016/j.clgc.2016.07.007. Epub 2016 Jul 21.

b) Filson CP, Natarajan S, Margolis DJ, Huang J, Lieu P, Dorey FJ, Reiter RE, and Marks LS: Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: The role of systematic and targeted biopsies. Cancer 2016; 122: 884-892.

VERSION 2 – REVIEW

REVIEWER	LES THOMPSON UROLOGIST BRISBANE AUSTRALIA
REVIEW RETURNED	02-Apr-2018

GENERAL COMMENTS	Good revision performed. No further comments.

REVIEWER	Pietro Pepe Urology Unit - Cannizzaro Hospital - Catania (ITALY)
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	The paper is interesting but the majority of the comments mailed in the first revision were not discussed and/or explained by the Authors. It is not possible to make clinical conclusions performing only 57 cognitive transperineal targeted prostate biopsies; in addition, the EAU guidelines published in 2018 recommended the necessity to perform standard biopsy in addition to targeted cores in naive men. On the contrary, the Authors have well explained the literature data, but their preliminary data (the study stopped in 2016/03) are insufficient to make conclusions.

VERSION 2 – AUTHOR RESPONSE

At initial submission, there was concern noted that the work does not constitute a pilot study as it aims to investigate the superiority of mpMRI over systematic TRUS biopsy. We must stress that this was not our intention as larger studies, properly and specifically designed for this purpose have been performed already. Firstly the PROMIS trial (Lancet 2017) demonstrated for the first time that mpMRI had a high enough negative predictive value to ‘rule out’ with a high degree of certainty a diagnosis of clinically significant prostate cancer and further that around a quarter of men could avoid a needless biopsy. Further, the PRECISION trial (NEJM 2018) demonstrated the superiority of mpMRI-targeted biopsy over standard systematic TRUS biopsy in both higher clinically significant detection rates and lower insignificant cancer detection rates. Once again, this showed that men could avoid a biopsy in cases and further, that men who would ordinarily be diagnosed with a cancer that would have little to no effect on their life expectancy would avoid said diagnosis.

It is regrettable that we were not clearer, the purpose of this study was to elucidate whether or not such a change from the status quo namely TRUS biopsy, to the evidence based novel pathway in the manuscript was feasible from a service provision perspective. This was the reason for the reporting of 'times to diagnosis and treatment'. Whilst these parameters were crucial to determine whether such a transformation was possible, the reporting of cancer detection rates is equally so. It goes without saying that without a high degree of diagnostic certainty, a diagnostic pathway is not fit for purpose. If by speeding up the pathway our cancer detection rates fell below the standard set by the formally mentioned validating studies then they should not be adopted in their current form. Thankfully, that has not been the case.

Further, in consideration of the reviewers thoughts and criticisms. Once again we must stress that this is not a validating study for mpMRI or targeted biopsy, that work has already been performed and reported widely. It is indeed true that international guidelines, whether they be from the Europeans, British or Americans states the need to perform systematic biopsies in addition to targeted biopsy. We must state that our own NICE guidance has yet to be updated to recommend mpMRI prior to biopsy at all despite multiple works demonstrating it to be appropriate from both a diagnostic as well as a healthcare economic perspective. We did not set out to validate existing guidelines in this study, we aimed to demonstrate that a change to clinical practice in view of recent findings of the aforementioned clinical trials was feasible. If we do not work in this way then little moves forward without consideration of possible findings then we as a community have lost equipoise – not an insignificant or unknown phenomenon in surgical oncology.

VERSION 3 – REVIEW

REVIEWER	Les Thompson Australia
REVIEW RETURNED	21-Jul-2018

GENERAL COMMENTS	Comments on Revised manuscript 024941 The authors make a compelling argument for using the image-based diagnostic pathway for intermediate and high risk PC. They suggest it should be as time-efficient, and cost-efficient as possible and give good evidence from current literature The wording in the manuscript is anachronistic because mpMRI has generally found acceptance as the first line investigation (It is now July 2018 vs the start of the series in February 2015). Also the use of "real-world" suggests other series were not from the real world. I am not convinced (from the trial design) that the authors have proven that T/P Cognitive biopsy under LA is accurate enough. However, I appreciate it is a pilot trial. Nevertheless, there is no visual record of the location of the deployed biopsy needle in 2 planes (as there is in MRGB). I still maintain that this technique needs a lot of experience to perfect and this experience generally comes with repetitive use of the brachytherapy jig. The sample size is small. From work with previous trial design for comparative studies, I understand from statisticians that you need about 220 patients – but the author's response that this is simply a "pilot" is reasonable. The place of PIRADS 3 in the image-guided pathway is evolving and needs some contemporary comment, probably as an editorial. 1. In any test, when dealing with equivocal "calls", the general advice is to default to the lower (negative) call, because the specificity

	should be weighted over the sensitivity to maintain the integrity of the test. 2. One of the quality control parameters in mpMRI is the number of PIRADS 3 calls in any given series, and it is thought this should be less than 20% 3. There is good argument therefore in not doing a biopsy on PIRADS 3 unless there are other indications of high risk (for example, a positive FH, a low F/T ratio, a high PSA density, using the volume calculated on the MRI) 4. Furthermore, if a biopsy is indicated on a high risk/PIRADS 3, the lesion is almost always a very poor target, thus these PIRADS 3/high risk patients should logically have trans-perineal grid biopsies under GA, not just a target biopsy under LA. 5. I don't like the idea of just asking PIRADS 3 patients whether they wanted a biopsy or not as you suggested you did in the response to reviewer 2 on p 35 "As part of the pathway protocol, men with lesions rated as >4 were advised to have a biopsy, those with 3 were given a choice and most (18 men) did not undergo biopsy." I commend the authors on their efforts to pilot a very efficient and cost effective diagnostic pathway. The manuscript is what it says it is, a report of a "pilot" study done 3 years ago. I think it should be published as it is, but with an editorial encapsulating the comments I've made above.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

The authors make a compelling argument for using the image-based diagnostic pathway for intermediate and high risk PC. They suggest it should be as time-efficient, and cost-efficient as possible and give good evidence from current literature

The authors thank the reviewer for their kind comments.

The wording in the manuscript is anachronistic because mpMRI has generally found acceptance as the first line investigation (It is now July 2018 vs the start of the series in February 2015). Also the use of "real-world" suggests other series were not from the real world.

We agree that if talking solely about the use of mpMRI prior to biopsy, then this is somewhat of an anachronism. However, whilst apologizing for a lack of clarity here we would add that we are referring to the use of an MRI-targeted biopsy led pathway. Indeed, pre biopsy MRI is not yet ubiquitous in the United Kingdom and when used outside of early adopting centres, images are often not reported prior to systematic biopsy. To clarify, changes have been made in the 'Introduction' section of the manuscript.

I am not convinced (from the trial design) that the authors have proven that T/P Cognitive biopsy under LA is accurate enough. However, I appreciate it is a pilot trial.

We agree, this would need a larger trial.

Nevertheless, there is no visual record of the location of the deployed biopsy needle in 2 planes (as there is in MRGB).

Fusion systems allowing for this do have a possible advantage here. However, a properly powered trial is required to determine whether or not there is a clinical difference made by any difference in accuracy between the two techniques. Unfortunately this is beyond the scope of this study but getting an answer to this question is certainly anticipated.

I still maintain that this technique needs a lot of experience to perfect and this experience generally comes with repetitive use of the brachytherapy jig.

We agree that experience is required to perfect the technique. Indeed, it may be easy for centres who have pioneered targeted and transperineal to expect all to pick up the technique with ease. But of course, in reality these developments have been years in the making. We would advocate that developing such services are done in a controlled manner with quality control measures worked in using data gained by original studies from pioneer reporters. We have added to the 'discussion' section in regard to this.

The sample size is small. From work with previous trial design for comparative studies, I understand from statisticians that you need about 220 patients – but the author's response that this is simply a "pilot" is reasonable.

Thank you for being understanding. We agree the purpose of this study was to pilot a new pathway design as opposed to compare MRI-targeted biopsy to the standard TRUS.

The place of PIRADS 3 in the image-guided pathway is evolving and needs some contemporary comment, probably as an editorial.

We agree, an excellent suggestion, this would be very interesting.

1. In any test, when dealing with equivocal “calls”, the general advice is to default to the lower (negative) call, because the specificity should be weighted over the sensitivity to maintain the integrity of the test.

The authors agree entirely.

2. One of the quality control parameters in mpMRI is the number of PIRADS 3 calls in any given series, and it is thought this should be less than 20%

This is interesting and a wonderfully simple way to quality control mpMRI reporting.

3. There is good argument therefore in not doing a biopsy on PIRADS 3 unless there are other indications of high risk (for example, a positive FH, a low F/T ratio, a high PSA density, using the volume calculated on the MRI)

We agree. Our clarity was lacking in regard to this point in our ‘methods’ section, as thus it has been amended.

4. Furthermore, if a biopsy is indicated on a high risk/PIRADS 3, the lesion is almost always a very poor target, thus these PIRADS 3/high risk patients should logically have trans-perineal grid biopsies under GA, not just a target biopsy under LA.

Likewise, our ‘methods’ section has been amended.

5. I don’t like the idea of just asking PIRADS 3 patients whether they wanted a biopsy or not as you suggested you did in the response to reviewer 2 on p 35
   “As part of the pathway protocol, men with lesions rated as >4 were advised to have a biopsy, those with 3 were given a choice and most (18 men) did not undergo biopsy.”

Again, we have expanded out ‘methods’ section to clarify our practice here.

I commend the authors on their efforts to pilot a very efficient and cost effective diagnostic pathway. The manuscript is what it says it is, a report of a “pilot” study done 3 years ago.

Once again, we thank the reviewer for their kind comments.

VERSION 4 – REVIEW

REVIEWER	Dr Les Thompson Brisbane Australia Retired Urologist
REVIEW RETURNED	05-Sep-2018

GENERAL COMMENTS	Thank you for asking me to review this paper again. The authors have rewritten much of it and it is now clear, concise, and useful. The sentence beginning line 40 is good because it acknowledges that this is a special skill that needs to be learned in a quality controlled environment. I would recommend publication.