Author’s response to reviews

Title: Clinical utility of a non-invasive urine test for risk assessing patients with no obvious benign cause of hematuria: A urologist-patient real world data analysis

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Responses to reviewer’s comments BURO-D-17-00218

Lough et al. Clinical utility of a non-invasive urine test for risk assessment of patients with no obvious benign cause of hematuria

Reviewer #1 (Chang Wook Jeong)

Comment #1:

I can't find the name of authority (IRB) who review and approved the study. I can't also find the trial registration number.

Authors’ response #1:

No institutional review board authority or clinical trial registration number has been included in this manuscript because they are not relevant to a theoretical study of this nature.

Specifically, this study was not a clinical trial, but rather a theoretical exercise where urologists were questioned about their expected diagnostic algorithm under set circumstances defined by a series of case studies.
However, institutional review board consent was obtained when performing the clinical trials from which the case studies were derived. Details are provided in the methods sections of Kavalieris et al. (Reference #26) and O’Sullivan et al. (Reference #27).

Comment #2:

Study objective is not clear. In abstract/background section they described that "The aim of the present study was to demonstrate the clinical utility of communicating objective information about the likelihood of UC on the diagnostic behavior of physicians towards individual patients with AMH.” But, I think real aim was to evaluate clinical usefulness of Cxbladder test. Please, clearly state the aim of the study, and keep focusing it through entire manuscript.

Authors’ response #2:

This terminology was chosen for consistency with the terminology used by the relevant regulatory authorities and reimbursement agencies (e.g. the Centers for Medicare and Medicaid) in the US, the primary market in which Cxbladder is available to urologists.

In addition, the Authors believe “clinical utility’ to be largely synonymous with ‘clinical usefulness’.

However, in light of the Reviewer’s comment, the Authors have amended the final two sentences in the Introduction in the Abstract to read:

A high-resolution risk-assessment tool would offer clinical utility in prioritizing patients for appropriate work-up without compromising the standard of care or resulting in harm. The aim of this study was to demonstrate the enhanced clinical utility of communicating objective information on physicians’ diagnostic decisions for patients with AMH and the impact on potential harm.

The aim stated on page 6 in the final paragraph of the Introduction has also amended to read:

The aim of the present study was to demonstrate the enhanced clinical utility of communicating objective information on the physicians’ diagnostic decisions for patients with AMH.

Comment #3:

What is the major difference from your previous article 'Adv Ther. 2017;3:1087-96'? Primary end-point looks same with same study population.

Authors’ response #3:

The Reviewer is correct in noting that the primary endpoint is the same as Darling et al. (Reference #12).
Darling et al. was the primary publication for this study and focused on the population-level impact of information being made available from Cxbladder. This manuscript focuses on the changes made by urologists at an individual interaction level, providing additional granularity and permitting statistical analysis. For example, population-level changes presented in Darling et al. do not show how individual urologists may have chosen to either increase or decrease the number of tests and procedures for individual patients and the reader did not have the possibility of judging changes in the context of individual patient details relating to gender, age and level of hematuria.

Comment #4:

Do you have any data after changing decision and procedures? What is gold standard for cancer diagnosis in the study? Don't you have any possibility of missing bladder cancer?

Authors’ response #4:

The Authors note that this is a theoretical, rather than a clinical, study that examined whether or not urologists would alter their choice of diagnostics on the basis of being provided data from Cxbladder. No clinical outcomes were assessed or followed up.

As noted in the Discussion, the Authors considered this study design to be the most pragmatic method of assessing the impact of Cxbladder on clinical decision making, due to concerns relating to:

a) The impact and feasibility of interfering with real-life clinical diagnostic processes; and

b) The inherent variation contributed by both the cases and decision-making of participating urologists.

The design was intended to minimize patient case-based variation and provide for an analysis of participating urologist decision-making. Therefore, no follow-up was performed to provide data beyond the change in requested tests and procedures.

As noted in the Introduction, the gold standard for performing a diagnosis of urothelial carcinoma (UC), as defined by the American Urological Association and European Association of Urology, involves invasive procedures, such as cystoscopy and computed tomography (CT) scans.

The Authors also note the Reviewer’s comment about the possibility of missing bladder cancer. Of course, no test is 100% accurate and the sensitivity (probability of a patient with UC being accurately identified) of Cxbladder Triage and Cxbladder Detect have been noted in the Introduction and are presented in Kavalieris et al. (Reference #26) and O'Sullivan et al. (Reference #27). The negative predictive value of Cxbladder Triage (i.e., the probability of negative result being true) is also presented here and in Kavalieris et al.
However, to jointly address the Reviewer’s comments about the gold standard for detection of UC and the possibility of UC being missed, results presented in Darling et al., and discussed here, led to 100% of patients with UC being referred to the gold standard for diagnosing urothelial carcinoma versus only 2/3 of patients in the absence of data from Cxbladder.

Comment #4:

Introduction is too long. Please shorten it to have concise background and objective of the study.

Authors’ response #4:

The Authors have deleted several sentences from the Introduction that may be considered to be superfluous to shorten its length.

However, the Authors believe that it is important to provide a reasonable discussion of currently unmet needs in the management of individual patients presenting with hematuria and how this is negatively impacting their quality of care, resulting in significant harm to patients from both unnecessary procedures and delayed diagnoses of urothelial carcinoma, especially given that some of the cases presented here directly address undertreated groups, such as young people and women.

Therefore, the Authors have also amended paragraphs 2, 4 and 6 of the Introduction on pages 4–6 as indicated below:

The current American Urological Association (AUA) guidelines recommend a full urological work-up to diagnose or rule out UC in patients with AMH within 180 days [3, 4], however several barriers to referral for a full urological work-up exist. For example, clinical diagnostic algorithms for patients with hematuria are complicated, difficult to follow and enable a degree of latitude in their interpretation [1]. Many physicians are also conscious of the burden of invasive procedures and the potential for harm and lack of compliance by patients when confronted with the prospect of many and varied invasive procedures. Invasive procedures, such as cystoscopy and contrast computed tomography (CT) scans, have the potential to impact their patients in terms of adverse events, financial cost and emotional…

….. Treatment for UC is more likely to be delayed for women than men, and although the incidence of UC is higher for men [18-23], women are less likely to undergo procedures after being referred and have a higher risk of presenting with UC at an advanced stage and have poorer survival outcomes [21,24]. Therefore, a simple, rigorous and accurate segregation of patients using a non-invasive risk-assessment tool may reduce barriers to referral…..

… Cxbladder has previously demonstrated clinical utility in reducing the net number of diagnostic tests, particularly invasive procedures, requested by urologists assessing a real-world sample population of patients with AMH [12] and led to all patients ultimately diagnosed with UC receiving a cystoscopy and/or CT scan as part of a diagnostic work-up, in line with the AUA
guidelines, compared with 16/24 patients presenting with standard referral data [4,12]. There is therefore potential for an increased risk of harm from the one-third of UC-positive cases potentially missed using non-invasive procedures in the baseline case.

Reviewer #2 (John Gebhart)

The clinical study by Lotan et al performed a multi-center clinical trial to compare several non-invasive urine tests including the newly developed Cxbladder monitor test for recurrent urothelial carcinoma in 803 UC patients. The results showed that Cxbladder monitor outperformed urine cytology and other FDA-approved assay in terms of sensitivity and negative predictive value. The results are interesting but the authors need to further clarify a few issues:

Comment #1 (abstract):

Much of the conclusion section provides new results on the testing patterns, these should be removed from the conclusion and added to the results section.

Authors’ response #1:

The Authors have moved two key sentences from the Conclusions section of the Abstract to the Results section on page 3 to address this comment.

Comment #2:

The definition of an "invasive" test skews results in favor of Cxbladder. For instance, why is a non-contrast CT scan considered "invasive"? Likewise, the statement that "all" providers changed management is misleading as some of these were forgoing other noninvasive measures (urine cytology, UroVysion FISH).

Authors’ response #2:

The definitions of “invasive” and “non-invasive” were made on the basis of potential harm to a patient undergoing a diagnostic procedure, both physical and emotional. While a non-contrast computed tomography (CT) scan may be considered to be less invasive than a contrast CT scan or cystoscopy, patients are still exposed to potentially harmful radiation, unlike urine tests or ultrasound.

However, the Authors have remained cognizant of the degree of harm/invasiveness associated with individual tests and are continuing to explore the concept of relative harm associated with each diagnostic test and procedure. Accordingly, the Authors intend to draft a separate manuscript covering this topic given the need for peer review of any methodology associated with assessing relative harm in the diagnosis of urothelial carcinoma before applying any harm score or index to this data set.
Furthermore, the Authors do not believe that the word “all” is misleading. The research question posed by the Authors included a binary (yes/no) outcome of whether or not a change in clinical management strategy occurred as a result of disclosing Cxbladder data. Indeed, this additional Cxbladder data did change urologist behavior: we interpret the decision to forego urine cytology and/or UroVysion fluorescence in situ hybridization as a demonstration of a level of confidence in Cxbladder results. As these Cxbladder results translate to an actionable clinical impact for clinicians, patients and payers, the Authors do not believe this can be alternatively described as “no change”, as would be required to address the Reviewer’s comment.

Comment #3:

A more compelling use of the available data would be to compare management decisions between the various noninvasive tests available (UroVysion, urine cytology, etc.), and then the reader could compare options. Essentially, the data provided argue that more information allows for better patient specific decision-making, but doesn't give any data to why this specific test should be preferred above the other available options.

Authors’ response #3:

The Authors note the Reviewer’s comment, but wish to point out the primary goal of the study was to evaluate the provision of Cxbladder data, rather than a comparison between Cxbladder and other non-invasive data, on urologist decision making behaviour. Additionally, we suggest that the following points are considered:

• The lack of clinical utility of non-invasive urine tests (with the exception of Cxbladder) beyond acting as an adjunct to cystoscopy is already well-established in the literature, as noted in the Introduction. The data presented here also indicates that urologists are not requesting a single urine test, but often both urine cytology and UroVysion fluorescence in situ hybridization. Therefore, any demonstration of utility for a non-invasive urine test of urothelial carcinoma is of high clinical relevance.

• This study was designed to consider changes in urologist behavior in response to a single variable – the presence or absence of data from Cxbladder Triage, and subsequently Cxbladder Detect. To compare outcomes between all available non-invasive urine tests would not be feasible because of the number of permutations required to be examined.

• Cxbladder is provided to patients prior to attending a urological consultation and can be performed at home. Therefore, this experiment represents a fair representation of a true clinical context within which a urologist is making diagnostic decisions. On that basis, the decision for the urologist is whether or not urine cytology and UroVysion FISH are necessary, not whether or not the same choices may occur if one of three options for urine tests is selected at the time of a consultation.

Comment #4:
In Line 38-40 it needs to specifically state that the sensitivity and negative predictive value are in a population of patients with macrohematuria, not asymptomatic microhematuria as in this study. The prevalence of the underlying conditions can greatly impact these results.

Authors’ response #4:

The Cxbladder Triage settings, as described by Kavalieris et al. (reference #26), specifically account for presentation with macro- versus microhematuria when determining the test outcome.

Therefore, the Authors consider the sensitivity and negative predictive value presented in this manuscript to be a fair and accurate representation of the performance characteristics of the test.

Comment #5:

A cost analysis should be added comparing the cost of obtaining the Cxbladder test(s) in all patients to the number of decreased procedures.

Authors’ response #5:

The reviewer correctly points out that an implication of this work is a net reduction in procedure utilization, and as a result, a net reduction in cost to payers may be expected.

The financial implications of access and use of Cxbladder are currently being addressed in a separate study and the results will be submitted to an international peer-reviewed journal for consideration for publication as soon as possible.

However, the Authors note the need for additional clarity regarding appropriate resource allocation with Cxbladder and have amended paragraphs 2 and 3 of the Discussion on page 12 to read:

Accordingly, Cxbladder has the potential to become a fundamental component of the standard of care for the management and diagnostic workup of patients with hematuria that will provide benefits to the patient and the healthcare system from the appropriate de-escalation in the total number and invasiveness of procedures used.

The clinical utility of Cxbladder in reducing the overall diagnostic burden of patients with hematuria from a population-level perspective has previously been demonstrated by reducing overall and total invasive procedures by 25% and 31%, respectively [12]. The present analysis extends that previous study outcome by providing resolution at an individual interaction level, showing that all participant physicians modified their chosen diagnostic work-ups to reflect the risk assessment provided by Cxbladder, i.e. escalation or de-escalation of invasiveness to reflect probability of UC. Notably, this was often observed as a change in nature of the procedures requested, not only the total number. In particular, the prevalence of UC was a 2.75-fold higher in the subset of patients referred to a physician-directed protocol by Cxbladder Triage, providing
evidence that the escalation of procedures is appropriate for this subset of patients, while no patients with a negative result had UC, justifying a de-escalation.

Comment #6:

Was there significant variations in the degree of reduced procedures among the 12 physicians? What was the agreement among the physicians for the clinical scenarios.

Authors’ response #6:

Data demonstrating the wide inter-urologist variation at baseline, variation at baseline versus guideline-recommendations and increased agreement with the availability of Cxbladder results is presented in Darling et al. (reference #12) and has not been presented here to avoid overlap.

Furthermore, the Authors believe that inspection of the baseline data summaries provides a consistent indication of decision-making variation exhibited by the participating urologists.

Comment #7:

How were the 33 cases selected? The original publication simply says "systematically selected", thorough further description is needed, including selection criteria. Were these randomly chosen, or chosen by a physician blinded to the outcome of the evaluation/pathology identified? Selectively choosing the cases may greatly impact the findings and utility of Cxbladder testing.

Authors’ response #7:

Patient cases for use in this study were systematically selected from existing clinical trial datasets using criteria including availability of all required clinical data, the Cxbladder tests results and availability of subsequent clinical truth, as detailed in the Methods section of Darling et al. (reference #12). Collectively these cases were intended to represent a cohort of asymptomatic hematuria patients presenting to a physician.

Comment #8:

The final diagnosis in any positive cases should be presented, among the 33 how may had a cancer dx, and were they low grade urothelial ca in the ureter or a high grade bladder UC, or a Renal cell ca? This may impact the utility of the Cxbladder test and the potential for missed diagnoses. Likewise, you should comment on any "missed diagnoses" that would have resulted from decreasing testing.

Authors’ response #8:
The Authors wish to refer the Reviewer to Table 1 of Darling et al. (reference #12) where the patient disposition and final diagnosis has been presented previously, including the details of the type and grade of any urothelial carcinoma (UC) discovered. This has not been included in this manuscript to avoid overlap.

Also, as discussed in response to Reviewer #1 and in this manuscript, Darling et al. reported that 100% of patients with UC were referred to guideline-recommended tests and procedures for diagnosing UC (i.e. invasive tests, such as cystoscopy) compared with only 2/3 of patients in the absence of data from Cxbladder.

It is not possible to speculate whether or not any patients with UC would be missed after being referred to a physician-directed protocol, although a case study has been published noting persistent positive results for Cxbladder being associated with upper urinary tract urothelial carcinoma that was not detected by computed tomography or magnetic resonance imaging scans. The tumor was only discovered following ureteroscopy that was driven by Cxbladder reporting. (Tan et al. J Endourol Case Rep 2016;2:235–237).

Comment #9:

What was the length of follow-up in the study to evaluate missed diagnoses on the initial evaluation? This is not stated in either the current study or the original publication (ref 12).

Authors’ response #9:

The Authors wish to refer the Reviewer to the original clinical studies from which these case studies were drawn, Kavalieris et al. (Reference #26) and O’Sullivan et al. (Reference #27). Cystoscopy was performed contemporaneously with Cxbladder for all patients to assess its performance characteristics.

Importantly, as noted in Darling et al. (reference #12), patients who were ultimately diagnosed with urothelial carcinoma had an increased chance of being referred to receive the most sensitive and specific guideline-recommended procedures.

Furthermore, given the high negative predictive value of Cxbladder Triage (98%; i.e. 98% of negative results are true), the Authors did not consider it necessary to include a rare instance of examining outcomes of a patient with a false-negative result for Cxbladder Triage.

Comment #10:

The original publication notes that all 12 participating physicians were given honoraria, this needs to be explicitly stated in this manuscript as well. Would also recommend providing the monetary value offered.

Authors’ response #10:
The following statement has been added to the Methods section, Participant and patient case details subsection on page 6:

Participating physicians were offered honoraria as compensation for the time spent participating in the study.

Pacific Edge Ltd., the study sponsor, aims to adhere to all international ethical standards regarding clinical research and good publication practices and expects that the individual participating urologists will declare the exact monetary value of the honoraria, as required, by any local or regulatory framework or register. However, due to individual privacy, and participants being resident across the USA, Singapore, Australia and New Zealand, which have differing market rates for urologist’s time, for the sake of clarity the Authors believe that this is the best possible method of expressing that the study sponsor has applied international best practice in compensating the participants for their time.

General amendments

A data sharing statement has been added to the Declarations section.

The Authors have renumbered Blackwell et al as reference 11 and renumbered the references, as required, throughout.

The Authors have also noted that Blackwell has now been published in Eur Urol Focus and have updated this reference accordingly, including the full publication details.

References for the sensitivity and specificity of Cxbladder Triage and Detect have been added in the Introduction.

Various edits have been made throughout the manuscript for increased clarity and have been marked up accordingly, e.g. ‘interactions’ has been replaced with ‘clinical decisions’ throughout and abbreviations added to the List of Abbreviations.

The authors' response letter has been included as a supplementary file.