Reviewer's report

Title: A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma

Version: 1
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Reviewer: see-tong pang

Reviewer's report:

1. The present study aimed to find out those patients with hematuria who need not full urologic examination. The model was developed based on patients with macrohematuria, and applied to patients with microscopic hematuria. However, though this model gave high NPV, since there was no UC found in the microscopic hematuria group, how do you determine the false negative rate? Is it safe to let it go if the patient with hematuria is triaged out according to G+P INDEX without a definite diagnosis?

Can this method differentiate urothelial carcinoma and renal cell carcinoma?

2. Patients with UTI or urolithiasis were excluded from the study group. It implicated that patients with hematuria have already received some kinds of examination before you could choose those who fit the inclusion criteria. This made it difficult to define full urologic examination. Only for those patients whose hematuria etiology could not be found would receive further invasive examinations. So what role would G+P INDEX play? A screening tool or part of the full urologic examination? And at what timing would it be used?

3. In the Background you mentioned that the Cxbladder Detect consisted with four markers that are overexpressed in UC alongside a fifth marker (CXCR2) that is elevated in non-malignant inflammatory conditions (Page 6, Line 21-24). However, it the Results (Page 11, Line 8), the G INDEX = -6.22 + 0.77 x IGFBP5 -1.11 x HOXA13 + 1.56 x MDK + 1.24 x CDK1 – 0.43 x CXCR2, means that HOXA13 gives negative effect to UC. Could you please explain the role of HOXA13 in UC patients? Additionally, two of the markers used in G+P INDEX, CDC and IL8R replaced CDK1 and CXCR2 in G INDEX (Page 11, Line 14), please explain why.

4. There are several noninvasive type of detection methods to improve the diagnosis of bladder tumor such as UroVysion, BTA, NMP22 and cytology. What is the advantage of CxBladder Detect as compare to these methods?

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
'I declare that I have no competing interests' below.