The Development and Clinical Validation of a High Sensitivity Urine biomarker test for the Determination of Recurrence in Urothelial Carcinoma Patients

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Introduction and Objectives
To develop a high sensitivity, urine based, gene expression test for the determination of recurrence of Urothelial Carcinoma (UC) and to assess the performance of this test for the segregation of patients with a low probability of recurrence from those requiring further investigation.

Methods
1093 samples were collected from 803 patients prospectively recruited at 11 community and tertiary centres the United States. Voided urine samples were collected pre-cystoscopy for urine dipstick, NMP22 Bladderchek, NMP22 ELISA, urine cytology and Cxbladder. Local cytology and FISH were also collected where available. Patients were partitioned into either a training or validation set based on demographic and risk factors. The training set (n=354 patients) was used to develop a novel algorithm (Cxbladder Monitor) encompassing gene expression data and previous tumor occurrence information. Cxbladder Monitor was validated using an independent validation set (n=449 patients). Final model parameters were derived on all data and bootstrap methods used to estimate 95% CIs and performance characteristics.

Results
Incidence of confirmed UC within the recruited population was 11%. Confirmed tumor stage was as follows : 64% Ta, 14% T1, 22% Tis. Grade was confirmed as 50% low grade and PUMLMP and 50% high grade disease. Final model Cxbladder Monitor exhibited a sensitivity of 93% (95% CI 82, 97), outperforming all direct comparator tests and locally obtained FISH results, across all stages and grades of tumor; see table 1. Cxbladder Monitor demonstrated an NPV of 97% (95% CI: 93, 98).

Conclusions
Cxbladder Monitor has been developed in response to the limitations of current urine based tests, and the unmet clinical need for a high sensitivity, high NPV test to enhance the clinical investigation of recurrent UC. Cxbladder Monitor demonstrated potential to rule out those patients with a low risk of having recurrent disease and therefore to reduce cystoscopy burden on patients undergoing routine investigation. Use of Cxbladder Monitor could reduce the number of invasive procedures required for the evaluation of recurrent UC.

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