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MiR663a and VIM promoter methylation: a multiplex test for discriminating bladder cancer from inflammatory disease

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Introduction & Objectives: Bladder Cancer (BlCa) is one of the most incident cancers, occupying the seventh place in the worldwide cancer prevalence ranking. Haematuria is the most common clinical sign of BlCa, although this symptom is shared with other benign pathologies such as bladder inflammatory disease, constituting a challenge for cancer identification. Thus, early, accurate and non-invasive BlCa detection is determinant to improve both patient's and hospital financial management. VIM and miR663a were previously identified as epigenetic biomarkers for BlCa detection in 2 independent studies. The purpose of this work was to combine the 2 gene's methylation in a multiplex test to assess its usefulness as a urine-based biomarker test.

Results: A multiplex panel was designed to simultaneously assess the gene's methylation levels (by quantitative methylation specific PCR, and using ACTB as reference gene) in tissue of a cohort 93 patients and 19 normal bladder mucosae. This panel was able to identify BlCa with a 96.3% sensitivity and 88.2%specificity. ROC curve analysis was also a good indicator of biomarker performance for both genes (VIM AUC= 98% and miR663a AUC= 90%, p< 0.0001). In a testing cohort (BlCa N= 27) compared with healthy donor (HD) controls (N= 24), the methylation panel also performed well, with 92.6% sensitivity and 75% specificity.
Moreover, in an independent validation cohort (BlCa N= 100 and HD N= 57), 87% sensitivity and 86% specificity were achieved. Remarkably, this same panel showed a similar performance in discriminating cancer patients from bladder inflammatory conditions (IC, N= 174). Indeed, the methylation panel maintained a high cancer detection accuracy (77%), with 80% sensitivity and, more importantly, 86.8% negative predictive value. Furthermore, comparing with available urine cytology reports, the multiplex panel could correctly identify 87% of the analyzed cases, whereas cytology only identified malignancy in 41%.

Conclusions: In conclusion, this multiplex methylation panel could discriminate BlCa from both healthy individuals and inflammatory symptomatic patients, whom better represent the population group to which a urine-based test would be offered. This test could help better predict and early detection of BlCa, minimizing the use of invasive techniques and its related economic effort.