Urinary Protein Biomarker Panel for the Detection of Recurrent Bladder Cancer

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Running title: Biomarkers to detect recurrent bladder cancer

Keywords: bladder cancer, disease recurrence, biomarker, urinary proteins, non-invasive detection

Financial support: This work was supported by Florida Department of Health James and Esther King Team Science Award 10KT-01 (C Rosser).

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Conflicts of interest: CJ Rosser and Steve Goodison are officers for Nonagen BioScience Corp.
Word count: 2,334
Total number of figures and tables: 3
ABSTRACT

Background: Up to 70% of patients with non-muscle invasive bladder cancer (NMIBC) experience disease recurrence, making it one of the most prevalent cancers in the US. The purpose of this study was to test the performance of a multiplex urinary biomarker assay for the monitoring of voided urine for recurrent bladder cancer (BCa).

Methods: This retrospective, multicenter study included a total of 125 subjects with a history of BCa. Voided urine specimens were collected prior to procedure from these subjects (53 with confirmed tumor recurrence and 72 with confirmed non-tumor recurrence) for analysis. A prediction rule consistent of single parameter's results sum of 10 urine-based biomarkers (IL8, MMP9, MMP10, SERPINA1, VEGFA, ANG, CA9, APOE, SERPINE1, SDC1) was measured using enzyme-linked immunosorbent assays. The diagnostic performance of the biomarker panel was assessed using receiver operator curves (ROC) and descriptive statistical values (e.g., sensitivity and specificity).

Results: The combination of all 10 biomarkers outperformed any single biomarker with a calculated AUROC for the diagnostic panel of 0.904 [95% CI: 0.853 - 0.956]. The multiplex assay achieved an overall sensitivity of 79% and specificity of 88% for recurrent BCa, and significantly outperformed the Urovysion cytogenetic assay (sensitivity 42%, specificity 94%) and voided urinary cytology (sensitivity 33%, specificity 90%).

Conclusions: A diagnostic panel of 10 urinary biomarkers that accurately detects primary BCa also performs well for the detection of recurrent BCa.

Impact: The identification of a reliable urine-based surveillance and detection assay would be of benefit to both patients and the healthcare system.
INTRODUCTION

Seventy to eighty percent of newly diagnosed bladder cancers (BCa) are non-muscle invasive bladder cancer (NMIBC). Although NMIBC is rarely fatal initially, there is a high rate of disease recurrence (50-70%) and disease progression to MIBC over time (30%) [1]. Because of the high rate of tumor recurrence, it is estimated that 500,000 Americans suffer from BCa at any one time, making it the second most prevalent cancer in the US [2]. Due to the described risks of recurrence, guidelines recommend that patients should be monitored after initial diagnosis and treatment using a regimen that prescribes surveillance every 3-6 months for 3 years, and at least annually beyond that. Current surveillance relies on the gold standard methods of cystoscopy and voided urine cytology (VUC), plus imaging and biopsy. There are no reliable standalone urinary biomarkers for the detection of BCa recurrence currently available in the clinic. The development of an accurate, non-invasive urine-based assay would be of tremendous benefit to both patients and the healthcare system.

We have previously coupled high throughput, discovery-based technologies (i.e., genomics and proteomics) with bioinformatics in order to derive diagnostic signatures that show promise for the accurate detection of primary BCa in voided urine samples [3-5]. Analysis of candidate protein biomarker panels in an independent patient cohorts confirmed that a panel of 10 biomarkers (IL8, MMP9, MMP10, SERPINA1, VEGFA, ANG, CA9, APOE, SERPINE1 and SDC1) was optimal for the non-invasive detection of BCa [6,7]. We have subsequently reported the validation of the 10-biomarker diagnostic panel in a large cohort of patients (n = 308), which included controls with diverse urologic conditions (e.g., urolithiasis, moderate-severe voiding symptoms, urinary tract infection and hematuria) [8], and through analysis of samples obtained from multiple sites in the US and in Europe (n = 320) [9] in an external laboratory. In the current study, we set out to evaluate the performance of the 10 urinary biomarkers in our primary
BCa detection panel to detect recurrent BCa in a multicenter cohort comprised of patients with a history of BCa undergoing routine surveillance.

**MATERIALS AND METHODS**

*Specimen and Data Collection*

The study was approved by the Institutional Review Boards at MD Anderson Cancer Center-Orlando (Orlando, FL) and the Hospital Clinic of Barcelona (Barcelona, Spain). Banked urine samples were collected from patients presenting to the outpatient Urology clinics at the two institutes. From each subject just prior to cystoscopy, approximately 50 milliliters of voided urine was collected and assigned a unique identifying number before laboratory processing as previously described [4-10] and stored at -80°C prior to analysis. Patients with self-reported renal disease or documented renal insufficiency (GFR < 60 mL/min/1.73 m²) were not selected for inclusion in the current study. The two tissue banks were queried for suitable specimens for analysis (*i.e.*, samples from subjects with a history of BCa who presented to clinic for routine BCa surveillance), which included 147 samples. Due to inadequate volume for analysis (*e.g.*, < 3 mL), urinary protein levels > 700 μg/mL, urinary creatinine levels < 35 mg/dL or the absence of critical clinical data, 22 samples were excluded thus leaving us with 125 subjects, which comprised the current study cohort. Data are reported using the REMARK criteria [11]. All subjects underwent cystoscopy (patients with high-grade disease underwent cystoscopy every 3 months for 2 years then every 6 months for 2 years then annually, while patients with low-grade disease underwent cystoscopy every 6 months for 2 years then annually). The majority of subjects had voided urine specimen sent to clinical laboratory for both voided urinary cytology (VUC) (92%) and Urovysion cytogenetic test (74%). Urovysion cytogenetic test is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via fluorescence in situ
hybridization. The combined 10 urinary biomarker assay was compared to VUC and UroVysion cytogenetic test. Approximately 5% of VUC and Urovysion assays could not be interpreted because of poor quality or insufficient material. In patients with an abnormally appearing cystoscopy, abnormal VUC and/or an abnormal UroVysion cytogenetic test, histological examination of urothelia was performed. When cancer was confirmed histologically, tumor grade and stage was recorded. Median follow-up of the entire cohort was 18 months (range 1-65 months).

**Urinary Enzyme-Linked Immunosorbent Assays (ELISA)**

Levels of human Interleukin 8 (IL8, Cat # ab46032 Abcam, Cambridge, MA, USA), Matrix Metalloproteinase 9 (MMP9, Cat # DMP900 R&D Systems Inc., Minneapolis, MN, USA), Plasminogen Activator Inhibitor 1 (SERPINA1, Cat # EA-0207 Signosis Inc., Sunnyvale, CA, USA), Vascular Endothelial Growth Factor A (VEGFA, Cat # 100663 Abcam, Cambridge, MA, USA), Angiogenin (ANG, Cat # CK400 CellSciences, Canton, MA, USA), Carbonic Anhydrase 9 (CA9, Cat # DCA900 R&D Systems Inc., Minneapolis, MN, USA), Matrix Metalloproteinase 10 (MMP10, Cat # DMP1000 R&D Systems Inc., Minneapolis, MN, USA), human Apolipoprotein E (APOE, Cat # KA 1031 Abnova, Walnut, CA, USA), human A1AT (SERPINE1, Cat # ab108799, Abcam) and human Syndecan 1 (SDC1, Cat# ab46507 Abcam, Cambridge, MA, USA) were monitored in urine samples using commercial enzyme-linked immunosorbent assays (ELISA) as listed above using the BioTek FLx800™multi-well plate reader (BioTek US, Winooski, VT) with the Gen5 Data Analysis Software package (BioTek US). Frozen supernatants were thawed and the ELISA’s were conducted according to the manufacturer’s instructions. Calibration curves were prepared using purified standards for each protein assessed. Curve fitting was accomplished by either linear or four-parameter logistic regression following the manufacturer’s instructions. Due to the unavoidable variability of
voided urine with respect to total volume and time within the bladder, biomarkers were normalized to urinary creatinine for comparison [6-9,12]. Laboratory personnel were blinded to final diagnosis.

**Data Analysis**

We investigated the diagnostic performance of each of the 10 urinary biomarkers for the detection of recurrent BCa. We used the Wilcoxon rank sum test to determine the association between each individual biomarker and the presence of recurrent BCa (yes vs. no). Each biomarkers was normalized to creatinine and cubic-root transformed. Next a prediction rule was generated = 0.223(IL-8) - 1.871(MMP9) + 2.239(SERPINA1) + 0.356(ANG) - 0.216(VEGFA) 0.330(CA9) + 0.689(MMP10) + 6.889(APOE) - 0.408(SERPINE1) + 1.021(SDC1) - 0.141 to determine the nonparametric receiver operating characteristic (ROC) curves [13] for the combination of the 10 biomarkers by plotting the values of sensitivity against the false-positive rates (1-specificity) at varying cutoff thresholds. The sensitivity, specificity, positive predictive value (PPV), and the negative predictive value (NPV) were calculated from ROC data. Statistical significance in this study was set at $p < 0.05$ and all reported $p$ values were 2-sided. All analyses were performed using SAS software version 9.3.

**RESULTS**

Pertinent information on demographics and clinicopathologic presentation of the cohort of 125 patients are presented in Table 1. Of the 125 patients with a history of BCa, 53 were found to have recurrence in follow-up. Median size of recurrent tumor was 2 cm. The ability of each of the test biomarker, whether elevated or reduced, to predict the presence of recurrent BCa was analyzed using nonparametric ROC analyses, according to National Cancer Institute guidelines [14]. Table 2 provides AUROC and corresponding sensitivity, specificity, PPV and NPV values.
for all biomarkers tested. Urinary SERPINA1 was the most accurate single biomarker with an AUROC of 0.864 (95% CI: 0.799 - 0.929), a sensitivity of 87%, specificity of 72%, PPV of 70% and NPV of 88%. Urinary MMP10 was the second most accurate single biomarker with an AUROC of 0.837 (95% CI: 0.758 - 0.917), sensitivity of 77%, specificity of 82%, PPV of 76% and NPV of 83%, and third most accurate was SDC1 with an AUROC of 0.818 (95% CI: 0.741 - 0.895), sensitivity of 60%, specificity of 93%, PPV of 86% and NPV of 76%. The combination assay (all 10 biomarkers in the diagnostic panel) resulted in an AUROC of 0.904 [95% CI: 0.853 - 0.956], outperforming any single biomarker. The multiplex assay achieved an overall sensitivity of 79%, specificity of 88%, PPV of 82% and NPV of 85% for BCa. Table 3 compares the overall sensitivity and specificity achieved using the combined 10 urinary biomarker assays, the commercial UroVysion cytogenetic test, and VUC. Values are further segregated according to tumor grade at the time of documented BCa recurrence. Overall sensitivity was highest for the 10-biomarker assay (79%), relative to the UroVysion cytogenetic test (42%) and VUC (33%). Importantly, sensitivity for the detection of low-grade tumors was markedly improved with the 10-biomarker assay (90% sensitivity) compared to UroVysion (14%) and VUC (17%). VUC and the UroVysion cytogenetic test had only slightly better overall specificity compared to the 10-biomarker assay (90%, 94% and 88%, respectively).

**DISCUSSION**

The probability of BCa recurrence after initial diagnosis is associated with tumor size, stage, grade and multifocality [15]. As with primary BCa, when recurrent BCa is identified as NMIBC rather MIBC or metastatic disease, the 5-year survival rate can be quite favorable, thus timely diagnosis and intervention can dramatically affect outcomes [16]. Consequently, for patients with a history of BCa, rigorous surveillance is well advised. The gold standard for the diagnosis of recurrent BCa remains cystoscopy. While cystoscopy has good sensitivity (~75%) for the
detection of bladder tumors [17], the procedure itself is invasive, uncomfortable and costly [18-20]. Complicating matters further, cystoscopy has been associated with significant patient anxiety [21] and can impact patient compliance with a strict follow-up regimen set forth by current guidelines [22]. VUC (the microscopic evaluation of shed cancer cells in voided urine) is routinely used as a non-invasive adjunct test to cystoscopy, but has low sensitivity particularly for the detection of low-grade tumors (~20-40%) [23, 24]. Coupled with the fact that VUC is also prone to considerable inter-observer variation [25], it is understandable that this method has not emerged as a standalone test for the detection of BCa. The limitations of cystoscopy and VUC underscore the continuing need to explore and validate less invasive BCa detection methods that can achieve clinically acceptable levels of sensitivity and specificity.

For a urinary biomarker test to be valid for the evaluation of subjects with a history of BCa it needs to achieve high sensitivity for the early detection of BCa. Acceptable sensitivity would reduce the number of unnecessary invasive cystoscopies by stratifying patients at clinical work-up. Only those patients with a positive urinary test would be deemed to be at high-risk for BCa and would undergo cystoscopy to confirm or refute the presence of a cancer. With a reported sensitivity of 79% in our cohort, the combined 10-biomarker assay significantly outperformed VUC (33%) and the Urovysion assay (42%), and, if validated, approaches the level of sensitivity required for incorporation into the surveillance regimen of patients with BCa.

It might be expected that a molecular assay derived to detect primary BCa would not perform as well for the detection of recurrent BCa. Our molecular profiling discovery studies were performed on distinct cohorts comprised of patients that had confirmed BCa or no disease. Those with BCa had predominantly high-grade and high-stage disease, a scenario that can lead to highly sensitive assays initially, but the performance decreases as more complex cohorts with more low-grade and low-stage cases are included. Patients under surveillance for recurrent BCa are more likely to present with low stage BCa. Our program of refining our candidate panels of
biomarkers in a series of validation cohorts may have avoided this issue [7-9]. Continued bladder tumor recurrence after an initial diagnosis may be explained by the field-cancerization theory [26]. As has also been proposed in squamous cell carcinomas of the head and neck [27], the theory suggests that secondary cancer events occur as a consequence of widespread molecular changes in previously uninvolved bladder mucosa initiated by external cancer-causing influences. This phenomenon could create latent disease, or predispose the mucosa to malignant events on subsequent insult. If such widespread molecular changes were representative of established tumors, then a test that performed well for primary BCa may be compromised for surveillance and detection of recurrent disease. However, in this study, this does not appear to be the situation. All of the individual biomarkers tested performed well in this surveillance cohort, and results obtained for the combined 10-biomarker urinary protein assay were similar for recurrent disease as for primary diagnosis. It may be that the analytes in the 10-biomarker assay are not impacted substantially at the expression level by the intermediate pre-recurrence field-effect. The fact that a single test can detect both primary and recurrent BCa is encouraging from the point of view of efficiency and standardization in a clinical setting.

Clinically, accurate non-invasive bladder cancer assays would have a clear impact on the clinical management of BCa patients. The ultimate goal is to be able to detect BCa in a timely manner such that the patient can expect an improved survival as well as improved quality of life, and compliance with the recommended surveillance program is paramount. Less onerous investigation protocols would surely improve compliance, and the resulting early detection would benefit both the patient and the healthcare system. We recognize that our study has some limitations. First, the sample size (n = 125) is relatively small and findings must be confirmed in a larger cohort, preferably with longer follow-up data. We are currently compiling samples from multiple centers for the next study based on these encouraging results. In addition, this small sample size may account for the low sensitivity (52%-65%) in detecting high-grade cancers with...
10-biomarker assay, VUC or Urovysion assay. The reported sensitivities of VUC and UroVysion assay are somewhat low compared to other studies [28, 29], but this may be due to the fact that these tumors are recurrent not primary tumors. Furthermore, as there is only a small number of cases, the results for VUC and Urovysion assay, especially for low-grade tumors, may be of limited value. Second, as part of a phased methodical approach to biomarker discovery and confirmation, processed urines were retrieved from tissue banks for analysis in this study. To address this, we are investigating the performance of the selected biomarkers in urines processed via a number of different protocols, including the testing of unprocessed freshly voided urines.

For clinical implementation, a molecular test needs to be cost-effective, as well as accurate, especially if that test is to be used over a long period of follow-up as in the case for BCa. The detection of urinary proteins through multiplexed analyses has the potential to be relatively simple to perform and interpret, and affordable. The 10-biomarker assay described here performs favorably in detecting recurrent BCa, supporting the idea that a non-invasive urine test can be valuable for the surveillance of patients with a history of BCa.

In this study, we were able to confirm that a diagnostic panel of 10 urinary biomarkers that accurately detects primary BCa also performs well for the detection of recurrent BCa. If these findings are confirmed in larger, multicenter studies, then it is conceivable that such a relatively simple, non-invasive urinary molecular assay could also be incorporated into the surveillance regimen for patients with a history of BCa.

ACKNOWLEDGMENTS

This work was supported by Florida Department of Health James and Esther King Team Science Award 10KT-01 (CJR).
REFERENCES


Table 1. Demographic and clinicopathologic characteristics of 125 subject study cohort.

<table>
<thead>
<tr>
<th>Variable(s)</th>
<th>Recurrence</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 53)</td>
<td>No (n = 72)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>71 ± 10</td>
</tr>
<tr>
<td></td>
<td>Median [min, Max]</td>
<td>73 [48, 87]</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>11 (20.8%)</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>42 (79.2%)</td>
</tr>
<tr>
<td>Race</td>
<td>Other</td>
<td>2 (3.8%)</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>51 (96.2%)</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>No</td>
<td>18 (36.0%)</td>
</tr>
<tr>
<td></td>
<td>Quit</td>
<td>11 (22.0%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>21 (42.0%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>3 (5.7%)</td>
</tr>
<tr>
<td>Urinary Protein (μg/ml)</td>
<td>Mean ± SD</td>
<td>91.0 ± 206.6</td>
</tr>
<tr>
<td></td>
<td>Median [min, Max]</td>
<td>29.5 [0, 1077.8]</td>
</tr>
<tr>
<td>Urinary Creatinine (mg/dL)</td>
<td>Mean ± SD</td>
<td>57.2 ± 31.3</td>
</tr>
<tr>
<td></td>
<td>Median [min, Max]</td>
<td>51.1 [10.7, 134.5]</td>
</tr>
<tr>
<td>Initial Stage</td>
<td>Non-muscle invasive (Ta = 34, T1 = 11, Tis = 4)</td>
<td>49 (92.5%)</td>
</tr>
<tr>
<td></td>
<td>Muscle invasive (all T2)</td>
<td>4 (7.5%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0</td>
</tr>
<tr>
<td>Initial Grade</td>
<td>Low-grade</td>
<td>30 (56.6%)</td>
</tr>
<tr>
<td></td>
<td>High-grade</td>
<td>23 (43.4%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>0</td>
</tr>
</tbody>
</table>

* p < 0.05 indicates significant imbalance between patients with recurrence and patients without recurrence

^, 16 subjects treated with chemotherapy and radiation therapy and 2 subjects treated with aggressive transurethral bladder tumor resection
Table 2.  Protein biomarker performance data for the detection of recurrent bladder cancer

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>AUC</th>
<th>AUC 95% CI</th>
<th>Nº of Correctly Predicted Events</th>
<th>Nº of Correctly Predicted Nonevents</th>
<th>Nº of Events Predicted as Events</th>
<th>Nº of Events Predicted as Nonevents</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL8</td>
<td>0.774</td>
<td>0.685</td>
<td>0.862</td>
<td>29</td>
<td>69</td>
<td>3</td>
<td>24</td>
<td>55</td>
<td>96</td>
<td>91</td>
</tr>
<tr>
<td>MMP9</td>
<td>0.771</td>
<td>0.683</td>
<td>0.859</td>
<td>29</td>
<td>68</td>
<td>4</td>
<td>24</td>
<td>55</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>SERPINA1</td>
<td>0.864</td>
<td>0.799</td>
<td>0.929</td>
<td>46</td>
<td>52</td>
<td>20</td>
<td>7</td>
<td>87</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>ANG</td>
<td>0.804</td>
<td>0.726</td>
<td>0.882</td>
<td>29</td>
<td>68</td>
<td>4</td>
<td>24</td>
<td>55</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>VEGFA</td>
<td>0.757</td>
<td>0.667</td>
<td>0.847</td>
<td>30</td>
<td>68</td>
<td>4</td>
<td>23</td>
<td>57</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>CA9</td>
<td>0.814</td>
<td>0.737</td>
<td>0.891</td>
<td>32</td>
<td>68</td>
<td>4</td>
<td>21</td>
<td>60</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>MMP10</td>
<td>0.837</td>
<td>0.750</td>
<td>0.917</td>
<td>41</td>
<td>59</td>
<td>13</td>
<td>12</td>
<td>77</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>APOE</td>
<td>0.775</td>
<td>0.685</td>
<td>0.865</td>
<td>39</td>
<td>60</td>
<td>12</td>
<td>14</td>
<td>74</td>
<td>83</td>
<td>76</td>
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<tr>
<td>SERPINE1</td>
<td>0.778</td>
<td>0.693</td>
<td>0.863</td>
<td>29</td>
<td>68</td>
<td>4</td>
<td>24</td>
<td>55</td>
<td>94</td>
<td>88</td>
</tr>
<tr>
<td>SDC1</td>
<td>0.818</td>
<td>0.741</td>
<td>0.895</td>
<td>32</td>
<td>67</td>
<td>5</td>
<td>21</td>
<td>60</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>All 10 Biomarkers</td>
<td>0.904</td>
<td>0.853</td>
<td>0.956</td>
<td>42</td>
<td>63</td>
<td>9</td>
<td>11</td>
<td>79</td>
<td>88</td>
<td>82</td>
</tr>
</tbody>
</table>

AUC, Area under the curve

CI, confidence interval

PPV, positive predictive value

NPV, negative predictive value
Table 3. Diagnostic Performance of the 10-biomarker assay, Urovysion and voided urine cytology in a cohort of patients with a history of bladder cancer

<table>
<thead>
<tr>
<th>Tumor Grade at Recurrence</th>
<th>Combined 10-biomarker assay (n = 53)</th>
<th>Urovysion cytogenetic assay (n = 24)</th>
<th>Voided urine cytology (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nº Detected / Total Cancers</td>
<td>Nº Detected / Total Cancers</td>
<td>Nº Detected / Total Cancers</td>
</tr>
<tr>
<td></td>
<td>Low 25/29 15/23 42/53</td>
<td>High 1/7 9/17 10/24</td>
<td>Low 4/24 11/20 15/45</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>90 [0.786, 1]</td>
<td>14 [0, 0.402]</td>
<td>17 [0.018, 0.316]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td>[0.458, 0.847]</td>
<td>[0.332, 0.768]</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>0.88 [0.799, 0.951]</td>
<td>0.938 [0.878, 0.997]</td>
<td>0.90 [0.834, 0.971]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td>[0.799, 0.951]</td>
<td>[0.834, 0.971]</td>
</tr>
</tbody>
</table>
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Cancer Epidemiol Biomarkers Prev Published OnlineFirst April 8, 2014.

Updated version: Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-14-0035

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