Evaluation of the MiCheck® MIA test performance in differentiating aggressive from non-aggressive prostate cancer – the MiCheck-01 prospective trial

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Introduction
A diagnostic test which can better inform both clinicians and patients regarding a decision to proceed with a prostate biopsy and/or mp-MRI while still utilizing traditional parameters of Prostate Specific Antigen (PSA) kinetics and/or the digital rectal examination (DRE) is still an unmet need. The MiCheck® test is designed as a triage test to assist clinicians in the decision to proceed to either an MRI scan or prostate biopsy. The MiCheck® test is a simple blood test that measures the levels of the Glypican-3 protein and related signalling molecules.

The MiCheck-01 prospective trial builds on the successful results of two previous pilot trials (1, 2). The first trial examined the ability of the MiCheck® test to distinguish between normal subjects (Arm 1) or patients with benign disease (Arm 2) or Gleason 7 and above prostate cancer (Arm 3). Each arm had 100 patients. The MiCheck® test showed sensitivity of 80% and specificity of 100% in distinguishing between subjects with Gleason ≥7 (Arm 2) and normal or BPH patients (Arms 1 and 2). A similar multivariate approach was used to differentiate between aggressive prostate cancer (defined as GS ≥4+3) and non-aggressive prostate cancer (GS <3+3). A set of 27 non-aggressive prostate cancer samples and 47 aggressive prostate cancer samples ranging from GS 3+4 to GS 5+5 were obtained from two independent commercial sources. The MiCheck® test could differentiate aggressive from non-aggressive prostate cancer with a sensitivity of 80% and specificity of 90%.

Specific Aims
The specific aims of the MiCheck-01 prospective trial were to:
1. Confirm the ability of the MiCheck® test to differentiate between prostate cancer subjects and non-cancerous subjects.
2. Confirm the ability of the MiCheck® test to differentiate between non-aggressive (Gleason 3+3) and clinically significant (defined as Gleason ≥4+3) prostate cancer.

Methods
The trial consisted of two arms: Arm 1 (normal patients, n=62) and Arm 2 (prostate biopsies patients, n=132).

Inclusion criteria: Arm 1: Age ≥50, Low PSA (performed at most 12 months prior) with low PSA (defined as PSA ≤ 1.5 ng/mL between ages 50 and 69 and PSA ≤ 2 ng/mL above age 60).

Arm 2: Age ≥45, all subjects who were referred for prostate biopsy for high PSA, High PSA was defined as PSA ≥ 6 ng/mL between ages 40 and 60, PSA ≥ 10 ng/mL between ages 60 and 60 and PSA ≥ 3 ng/mL for age 60 and above age 60.

Exclusion criteria: Prior history of cancer, patients taking ADT, DRE or other prostate manipulations within 72 hrs, subjects taking 5-40s.

The trial was conducted in 12 urological trial centers under the coordination of the CUSP Clinical Research Consortium. Serum and plasma samples were collected. Samples underwent a central PSA measurement, and a centralized review of biopsy.

A panel of soluble proteins were analyzed using multianalyte index assay (MIA) technology. Assays were evaluated for collinearity and interactions, and analyses excluded 11 statistically significant interactions were observed, however none were found. Algorithms are being developed for non-cancer vs cancer patients and aggressive vs non-aggressive cancer patients. Central pathology classification was used for algorithm development.

Results

Table 1. Patient characteristics by Arm and status

<table>
<thead>
<tr>
<th>Arm</th>
<th>No cancer</th>
<th>No cancer</th>
<th>No cancer</th>
<th>No cancer</th>
<th>No cancer</th>
<th>No cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>Median (Range)</td>
<td>10.0 (2.0)</td>
<td>18.0 (15.0)</td>
<td>5.0 (2.0)</td>
<td>1.0 (2.0)</td>
<td>2.0 (2.0)</td>
</tr>
<tr>
<td>Age</td>
<td>Median (Range)</td>
<td>70 (26)</td>
<td>70 (26)</td>
<td>65 (26)</td>
<td>65 (26)</td>
<td>65 (26)</td>
</tr>
<tr>
<td>Race</td>
<td>N (%): White</td>
<td>33 (50%)</td>
<td>42 (64%)</td>
<td>15 (22%)</td>
<td>5 (8%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td></td>
<td>Other/Unknown</td>
<td>5 (7%)</td>
<td>7 (11%)</td>
<td>4 (6%)</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Figure 1. ROC curves and performance of the MiCheck® test. ROC curves are shown for [A] Cancer vs no cancer and [B] Aggressive vs non-aggressive prostate cancer. Sensitivity, specificity and AUC values are shown for MiCheck® and PSA at the optimal cut-off level. Also shown is performance of MiCheck® test compared to commercially available tests.

Discussion and Conclusions
Algorithm development was performed using Arm 2 patients (i.e. all patients proceeding to biopsy on the basis of elevated PSA).

Initial results indicate that the MiCheck® test can distinguish Arm 2 cancer vs non-cancer patients with superior performance to existing tests such as PSA, PHI or Opikron. Similarly, the MiCheck® test shows superior performance for the detection of aggressive vs non-aggressive prostate cancer.

The centralized Gleason review results correlated well with those obtained from local site pathology with a trend to upgrading to higher Gleason score. Centralised PSA showed a high correlation with results obtained from the medical record.

Further analysis and algorithm development is ongoing. Additionally, we are currently using the prospective trial samples to analyse performance on the PHI test as a head-to-head comparison.

References and Acknowledgements


3. Sandelin et al. Comparison Between the Four-knowledge Panel and Prostate Health Index for Predicting Prostate Cancer. Eur. Urol. 68 (1) [2015]; 119

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Dr Robert Bortolanci and Philip Prall are retained by Mimonic as independent consultant statisticians.

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