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 mpMRI 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-1 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 60% and specificity of 96% in distinguishing between subjects with Gleason ≥7 (Arm 3) and normal or BPH patients (Arms 1+2. A similar multi-analyte approach was used to differentiate between aggressive prostate cancer (defined as GS ≥3+4) 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 85% 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-significant (Gleason 3+3) and clinically significant (defined as Gleason ≥ 3+4) prostate cancers.

Methods

The trial consists of two arms: Arm 1 (normal patients, n=52) and Arm 2 (prostate biopsy patients, n = 332).

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 60 and PSA < 3 ng/mL above age 60.

Arm 2: Age ≥40, all subjects who were referred for prostate biopsy for high PSA. High PSA was defined as PSA ≥ 1 ng/ml between ages 40 and 49, PSA ≥2 ng/mL between ages 50 and 60 and PSA ≥ 3 ng/mL for age 60 and above age 60.

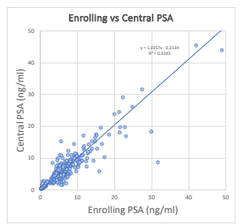
Exclusion criteria: Prior history of cancer, patients taking ADT, DRE or other prostate manipulation within 72 hrs, subjects taking 5 ARIs. The trial was conducted in 12 urological trials centers under the co-ordination of the CUSP Clinical Research Consortium. Serum and plasma samples were collected. Samples underwent a central PSA measurement, and a centralized review of biopsy.

A panel of soluble proteins were analyzed using multi-analyte index assay (MIA) technology. Assays were evaluated for colinearity and interaction, and analytes excluded if 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

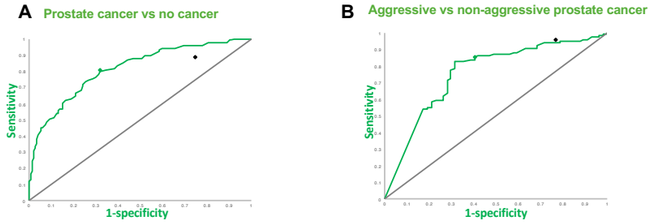
Table 1. Patient characteristics by Arm and status

Overall patient summary	All patients	Arm 1 Non-CaP	Arm 2 Non CaP	Arm 2 CaP	Arm 2 Non-aggr CaP	Arm 2 Aggr CaP
Total	384	52	148	184	64	120
Age						
Mean (SD)	64 (8.0)	59 (6.1)	64 (7.7)	65 (8.2)	62 (7.5)	66 (8.2)
Median (Range)	64 (40-85)	58 (50-74)	65 (40-82)	65 (45-85)	62 (45-79)	66 (48-85)
>50 years, N (%)	372 (97%)	52 (100%)	141 (95%)	179 (97%)	61 (95%)	118 (98%)
BMI						
Mean (SD)	30 (5.9)	31 (6.0)	29 (4.8)	30 (6.6)	30 (6.7)	29 (6.4)
Median (Range)	29 (18-73)	29 (22-50)	29 (20-44)	28 (18-72)	29 (21-60)	28 (18-73)
Prostate Volume (cc)						
Mean (SD)	52 (30)	-	64 (35)	42 (19)	46 (18)	40 (20)
Median (Range)	43 (13-189)	-	52 (15-189)	38 (13-121)	40 (18-95)	37 (13-121)
Central PSA (ng/ml)						
Mean (SD)	7.4 (14)	1.1 (0.7)	5.8 (3.0)	10.4 (20)	5.8 (3)	12.8 (24)
Median (Range)	5.5 (0.2-237)	0.8 (0.2-2.7)	5.0 (1.2-18)	6.7 (1.5-237)	5.6 (1.5-17.3)	7.5 (2.4-237)
<2 ng/ml, N (%)	46 (12%)	42 (81%)	3 (2%)	1 (1%)	1 (2%)	0 (0%)
2-10 ng/ml, N (%)	287 (75%)	10 (19%)	135 (91%)	142 (77%)	58 (1%)	84 (70%)
4-10 ng/ml, N (%)	221 (58%)	0 (0%)	100 (68%)	121 (66%)	42 (66%)	79 (66%)
3-15 ng/ml, N (%)	281 (73%)	0 (0%)	127 (86%)	154 (84%)	54 (84%)	100 (83%)
10-20 ng/ml, N (%)	42 (11%)	0 (0%)	11 (7%)	31 (17%)	5 (8%)	26 (22%)
>20 ng/ml, N (%)	10 (3%)	0 (0%)	0 (0%)	10 (5%)	0 (0%)	10 (8%)
>50 yr + PSA 4-10, N (%)	213 (55%)	-	97 (66%)	116 (63%)	39 (61%)	77 (64%)
>50 yr + PSA 4-10 + Normal DRE, N (%)	154 (44%)	-	77 (52%)	77 (42%)	33 (52%)	44 (37%)
Race, N (%)						
White	335 (87%)	44 (85%)	129 (87%)	162 (88%)	54 (84%)	108 (90%)
Black	45 (12%)	7 (13%)	17 (11%)	21 (11%)	10 (16%)	11 (9%)
Other/Unknown	4 (1%)	1 (19%)	2 (1%)	1 (1%)	0 (0%)	1 (1%)
Hispanic Ethnicity, N (%)						
Yes	31 (8%)	2 (4%)	15 (10%)	14 (8%)	5 (8%)	9 (8%)
No	348 (91%)	49 (94%)	132 (89%)	167 (91%)	58 (91%)	109 (91%)
Unknown	5 (1%)	1 (2%)	1 (1%)	3 (2%)	1 (2%)	2 (2%)
First Degree Family History, N (%)						
Yes	100 (26%)	10 (19%)	33 (22%)	57 (31%)	25 (39%)	32 (27%)
No	244 (64%)	36 (69%)	98 (66%)	110 (60%)	33 (52%)	77 (64%)
Unknown	40 (10%)	6 (12%)	17 (11%)	17 (9%)	6 (9%)	11 (9%)
DRE status						
Normal	264 (69%)	30 (58%)	115 (78%)	119 (65%)	49 (77%)	70 (58%)
Suspicious	55 (14%)	1 (2%)	15 (10%)	39 (21%)	7 (11%)	32 (27%)
Unknown	65 (17%)	21 (40%)	18 (12%)	26 (14%)	8 (15%)	18 (15%)
Gleason Score/Epstein, N (%)						
6/1				64 (35%)	64 (100%)	
7 (3+4)/2				58 (32%)		58 (48%)
7 (4+3)/3				43 (23%)		43 (36%)
8/4				5 (3%)		5 (4%)
9/5				14 (8%)		14 (12%)



Gleason central pathology review								
Site Gleason	3+3	3+4	4+3	4+4	3+5	4+5	5+4	No cancer
3+3	59	13	1	0	0	0	0	1
3+4	1	43	9	0	1	0	0	0
4+3	0	2	28	0	0	2	0	0
4+4	0	0	5	4	0	1	0	0
5+3	0	0	0	0	0	0	1	0
4+5	0	0	0	0	0	7	0	0
5+4	0	0	0	0	0	1	1	0
5+5	0	0	0	0	0	1	0	0
No cancer	4	0	0	0	0	0	0	199

Figure 1. Concordance between site PSA and central PSA and site and central pathology results
Left panel: Correlation between PSA concentration (ng/ml) obtained from the patient's medical record and the trial sample PSA measured centrally by Cenetron Diagnostics. **Right panel:** Concordance between the central pathology and pathology reported by the clinical site.



	Sensitivity	Specificity	AUC
MiCheck®	80%	68%	0.82
PSA (4ng/ml)	88%	26%	

Test	Sens	Spec	AUC	Reference
MiCheck®	0.80	0.68	0.82	Current Prospective Study
PSA	0.88	0.26	0.57	Current Prospective Study
PSA+Age	0.80*	0.26*	0.52	Nordstrom
PHI	0.75*	0.56*	0.70	Nordstrom
Opko4k	0.75*	0.55*	0.69	Nordstrom

* estimated from ROC curve figures

	Sensitivity	Specificity	AUC
MiCheck®	85%	58%	0.76
PSA (4ng/ml)	95%	27%	

Test	Sens	Spec	AUC	Reference
MiCheck®	0.86	0.58	0.76	Current Prospective Trial
PSA	0.96	0.24	0.60	Current Prospective Study
PSA+age	0.80*	0.35*	0.57	Nordstrom
PHI	0.80*	0.45*	0.71	Nordstrom
Opko4k	0.75*	0.58*	0.72	Nordstrom

* estimated from ROC curve figures

Figure 2. ROC curves and performance of the MiCheck® test. ROC curves are shown for **(A)** Cancer vs no cancer and **(B)** Aggressive vs non-aggressive cancer. Sensitivity, specificity and AUC values are shown for MiCheck® and PSA at the 4ng/ml 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 Opko4K. 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. Centralized 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

1. Shore et al. *Glypican-1 As A Biomarker For Prostate Cancer.* The Journal of Urology 193(4):e496 April 2015

2. Gillatt et al. *A Multi-analyte Assay for Prostate Cancer,* presented at Prostate Cancer World Congress, Cairns August 18-20, 2015.

3. Nordström et al. *Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer.* Eur. Urol. 68.1 (2015): 139

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