Multivariate Index Analyte (MIA) Assays for Differentiating Aggressive from Non- Aggressive Prostate Cancer

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Introduction

There is a need for biomarkers that can assist clinicians and patients to determine treatment pathways when PSA and /or DRE are equivocal. Such biomarkers should establish both sensitivity and specificity for prostate cancer detection in order to improve go-forward decisions to perform prostate biopsy.

Ideally a biomarker test would inform the clinician and patient of the presence of prostate cancer and also an indication of whether the cancer is likely to be indolent or clinically significant.

Specific Aims

Following the successful use of a three-protein marker panel to increase the specificity of prostate cancer detection[1] we have now used the same technology platform to examine whether an MIA assay approach can assist in differentiating aggressive from non-aggressive cancer in prostate cancer patients.

Methods

Serum samples from patients with aggressive prostate cancer or non-aggressive prostate cancer were obtained from two commercial sources (Innovative Research and Proteogenex). Non-aggressive prostate cancer was defined as having a biopsy Gleason score of 6 (n = 37) and aggressive prostate cancer was characterized as Gleason score 7 and above (n = 69). All men were Caucasian with the exception of 3 who were African American. Biomarker levels were determined using a plate based ELISA for Glypican-1 (GPC-1)[2] and a bead-based MIA assay for the other markers.

Results

PSA was a poor predictor of aggressive prostate cancer in this cohort with a sensitivity of 58% and specificity of 43% (AUC 0.55).

By using co-evolutionary fuzzy modeling[3], (SimplicityBio, Switzerland), two multi-analyte models were identified that were able to differentiate between aggressive and non-aggressive prostate cancer. One consisted of a combination of 5 analytes and the other used 6 analytes. Model 1 contained PSA and GPC-1 plus 4 analytes and produced a combined sensitivity of 81% and specificity of 78% (AUC 0.81). The second model comprising GPC-1 with an additional 4 analytes and achieved a sensitivity of 72% with a specificity of 76% (AUC 0.76). Both models had a p value of less than 0.05.

Table 1. Patient characteristics

	Gleason Score	Patient Number	PSA mean	PSA median	PSA range	Age range
Non-Aggressive	3+3	37	13.0	10.0	2.1 - 42.6	49-77
Aggressive	3+4	59	12.9	9.9	0.1 - 85.9	43-79
	4+4	4	20.1	11.3	7.2 - 50.6	57-69
	4+5	3	13.7	5.5	3.8 - 32	64-67
	5+3	1	17.7	17.7	17.7	73
	5+4	1	7.4	7.4	7.4	60
	5+5	1	2.9	2.9	2.9	61

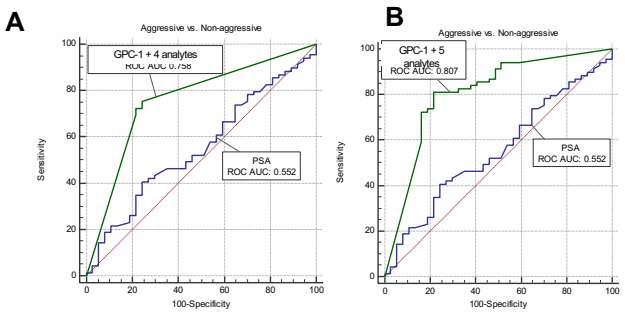
Table 2. Performance of two different biomarker panels

NOTE: the identity of analytes A, B, C, D and H has not been disclosed as patents are in progress.

Combination	AUC	Sensitivity	Specificity
GPC-1 + A + B + C + D	0.758	0.72	0.76
GPC-1 + PSA + A + B + C + E	0.807	0.81	0.78

Figure 1. ROC curves showing performance of two different biomarker panels in differentiating non-aggressive from aggressive prostate cancer

(A) Performance of MIA panel 1 **(B)** Performance of MIA panel 2
The ROC curve for PSA is included in both panels for reference



Conclusions

Conclusions: The MIA panels identified by the two statistical models demonstrate potential utility for using the combined markers as a new means of differentiating aggressive prostate cancer from non-aggressive cancer. Further studies to validate these models are planned.

References and Acknowledgements

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