

Development and Validation of An Serum MiRNA Biomarker panel for the Detection of Early Stage Lung Cancer

Abstract No

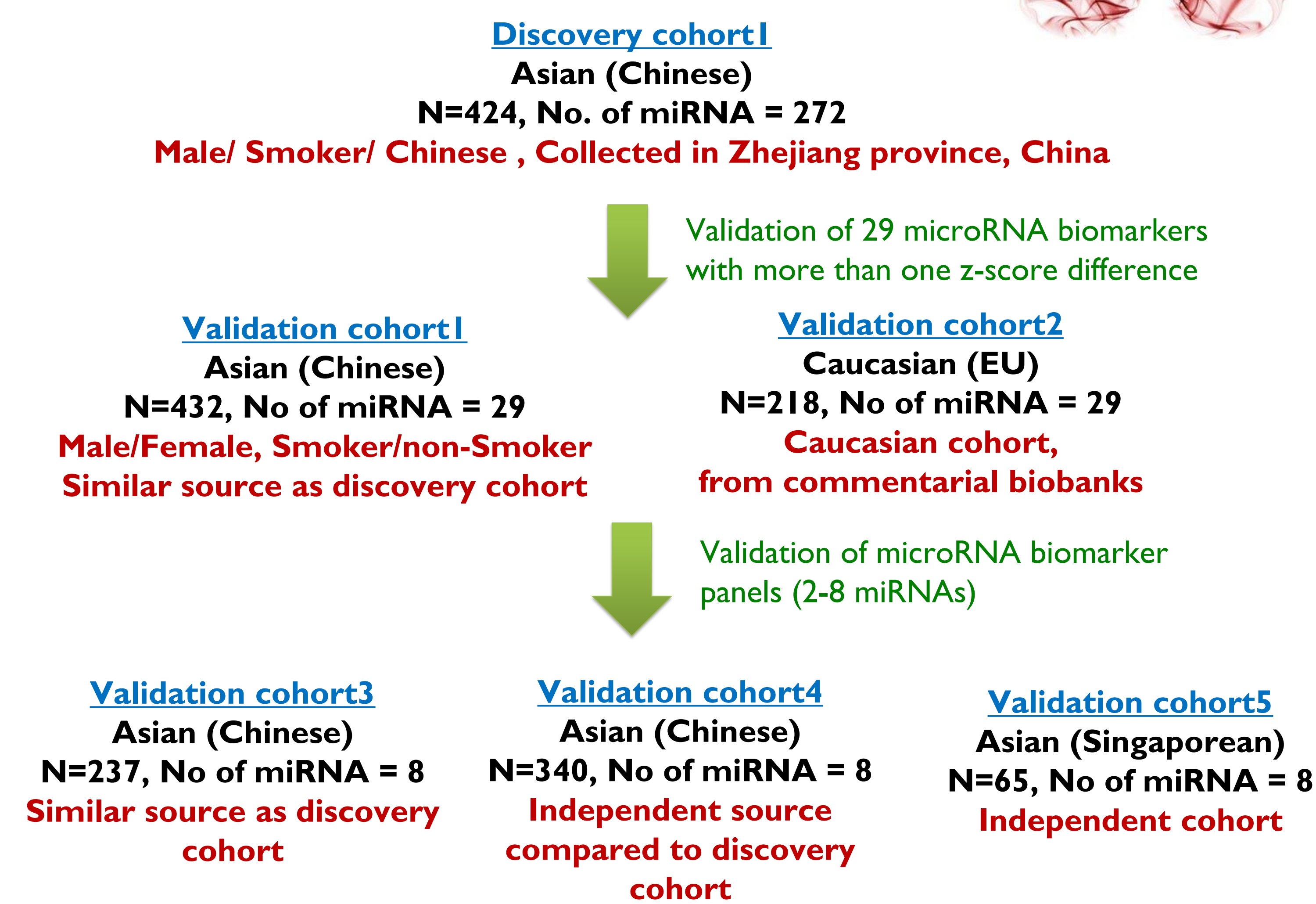
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1, Study design

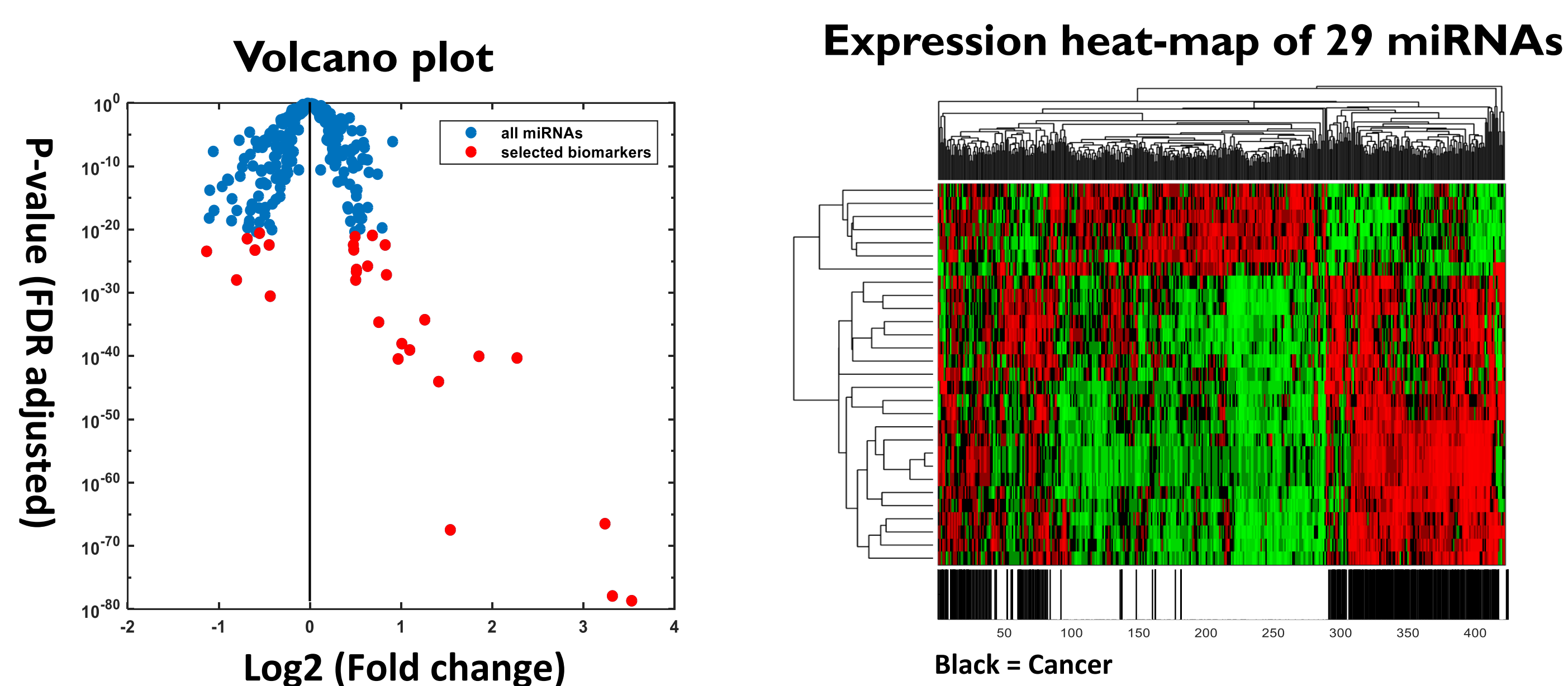
Lung cancer is the most prevalent cancer and leading cause of cancer death worldwide. Low-dose spiral computed tomography (LDCT) scan is being recommended as a screening test for smokers in the U.S. However, the poor specificity (73% specificity at 94% sensitivity) of LDCT has raised significant concern for its high chance of false positive (96% of LDCT positives are benign nodules). This study aims to develop a blood (serum) miRNA based molecular diagnostic test for the detection of early stage lung cancer. In the unbiased discovery phase, more than 400 miRNAs were profiled with MiRXES's qPCR based high through-put assay platform in a Chinese case-control cohort (n=424). And then, 29 miRNA biomarkers were validated in two case-control cohorts (Chinese (n=432) and Caucasian (n=218)). Afterwards, the miRNA biomarker panels (2-8 miRNAs) were built and validated in three additional Asian case-control cohorts with an AUC of > 0.9.



All microRNA were measured with replicates and standard curves using MiRXES® qPCR assays.

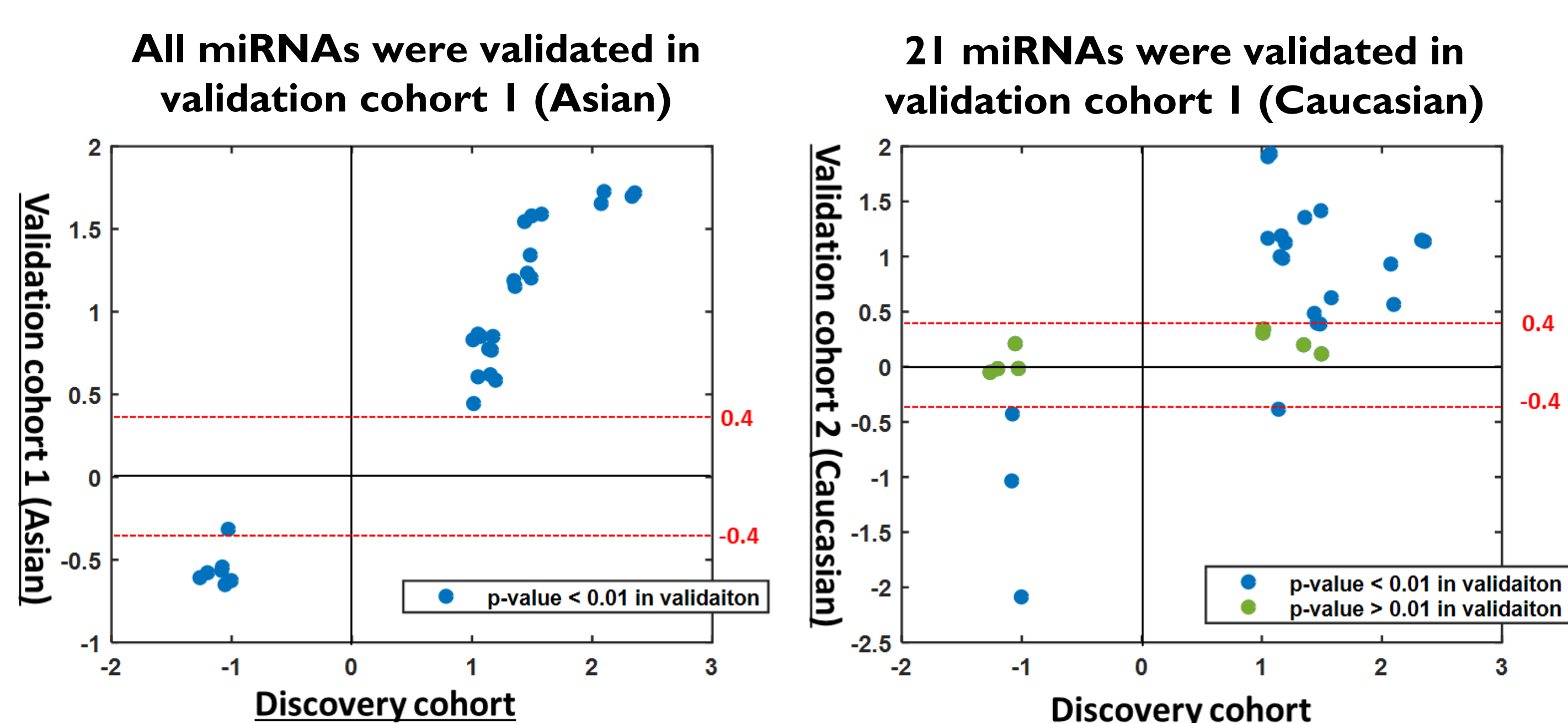
2, Discovery and Validation 1/2

Discovery



29 miRNAs were selected for further validation, 22 miRNAs with standard score > 1 (up-regulated in Cancer), 7 miRNA with standard score < -1 (Down-regulated in Cancer)

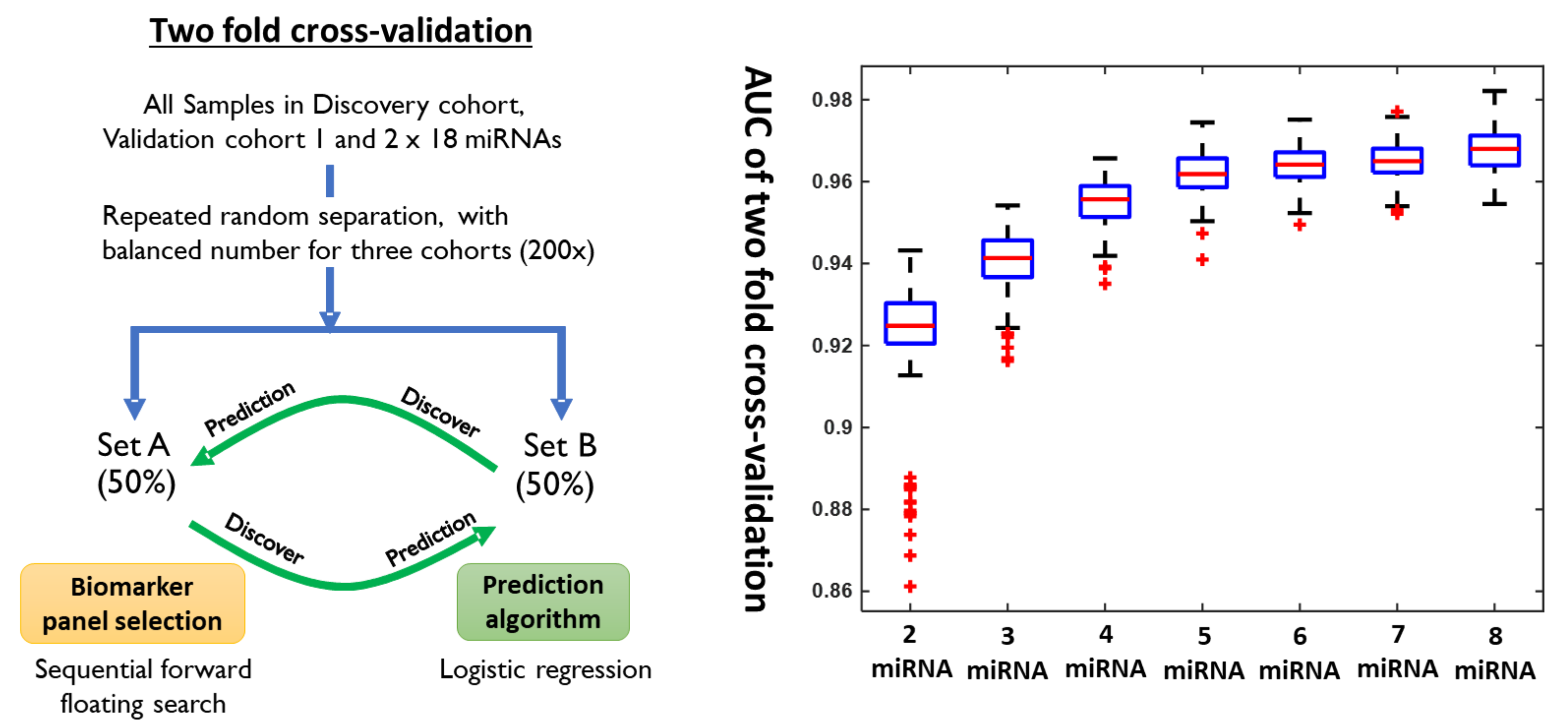
Validation 1 and Validation 2



18 miRNAs with more than 0.4 standard score for both validation cohort 1 (Asian) and validation cohort 2 (Caucasian) were used to build biomarker panels

3, Biomarker panel optimization

Biomarker panels including 2 to 8 miRNAs were constructed and validated in multiple times of two-fold cross validation. Better performances were observed in the validation phases when more than 5 miRNAs were used.



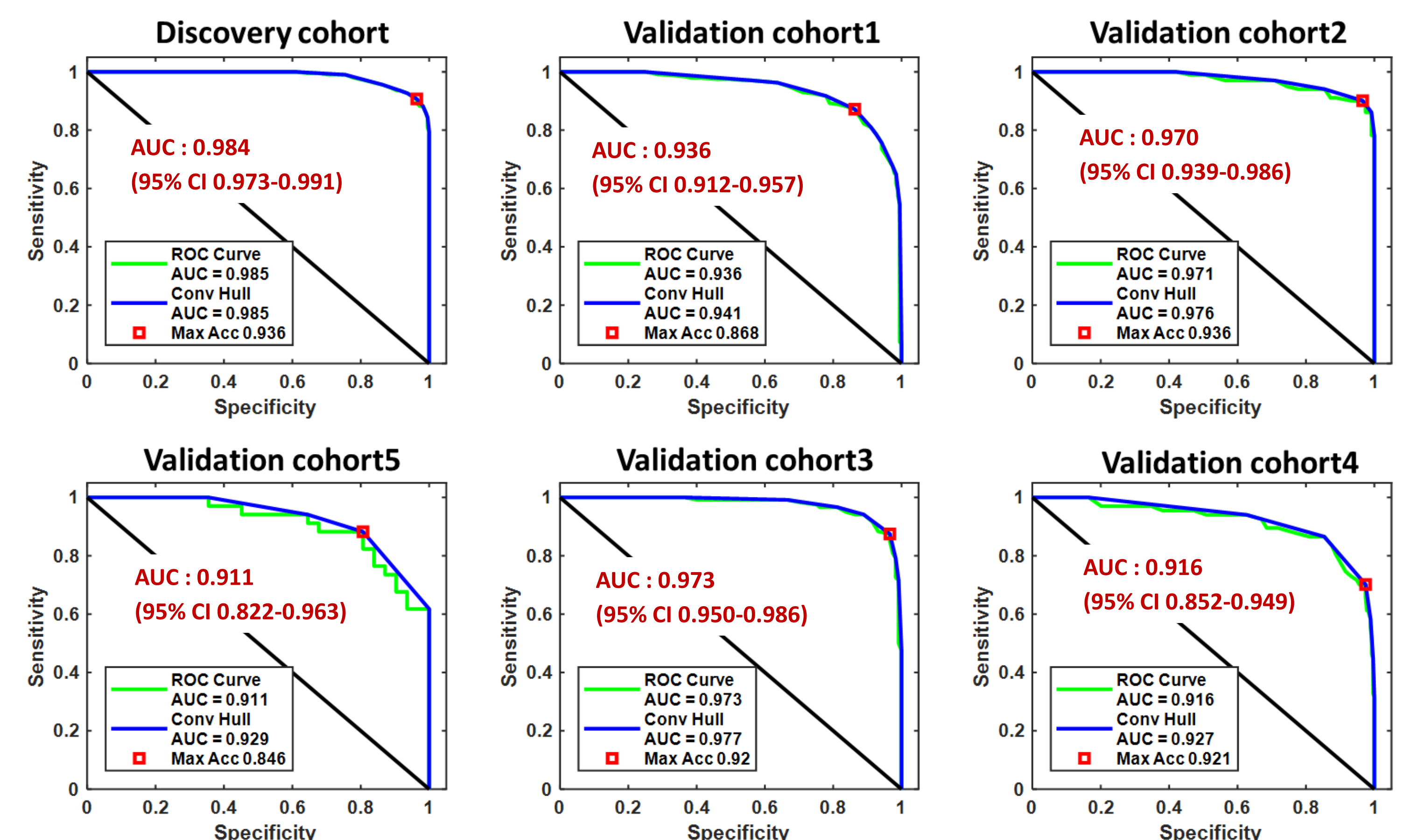
4, Validation cohort 3,4,5

Performance of 2-8 miRNA biomarker panels

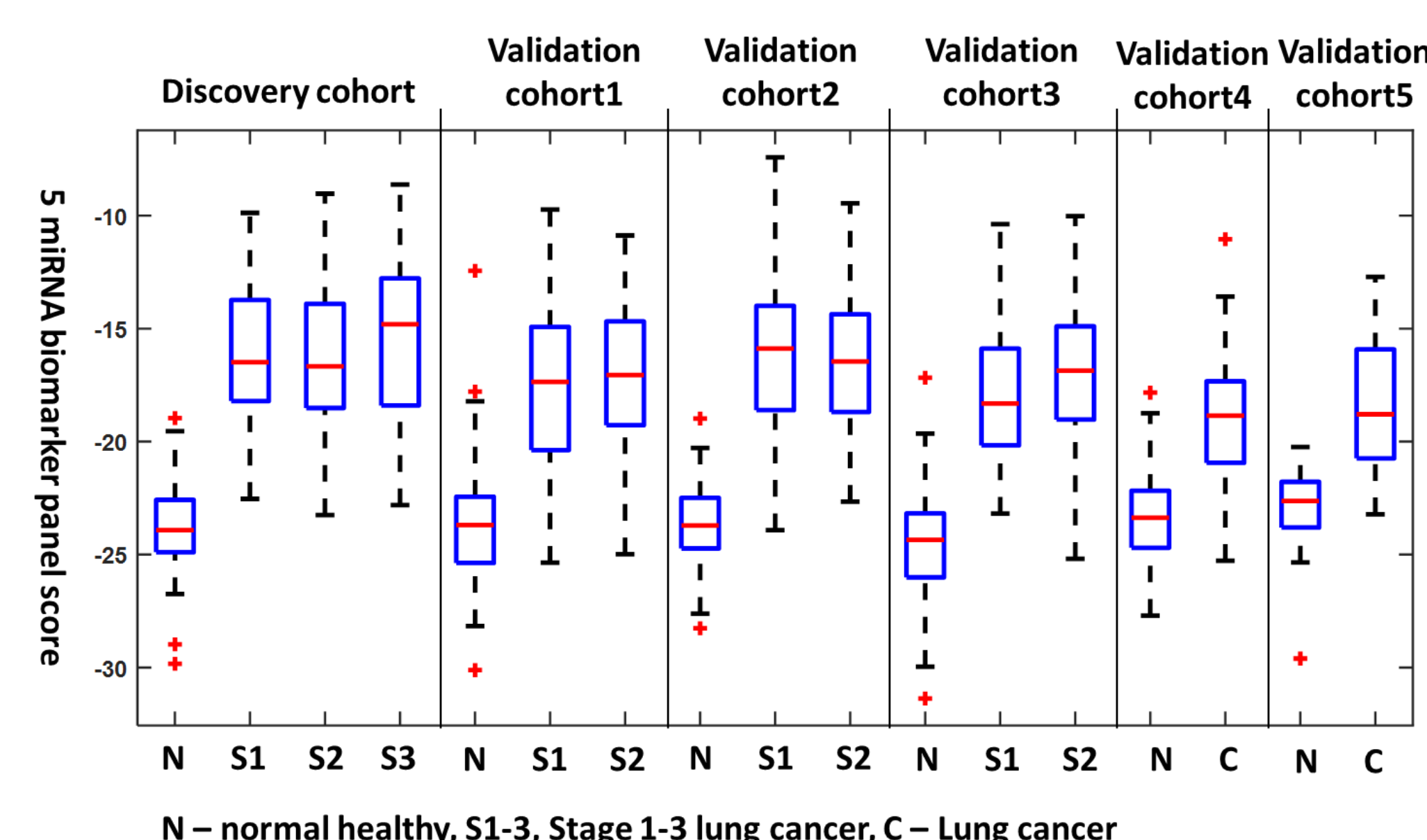
	2 miRNA	3 miRNA	4 miRNA	5 miRNA	6 miRNA	7 miRNA	8 miRNA
Discovery cohort	0.964	0.963	0.984	0.984	0.987	0.982	0.978
Validation cohort 1	0.907	0.907	0.937	0.936	0.942	0.947	0.952
Validation cohort 2	0.925	0.968	0.951	0.970	0.970	0.975	0.983
Validation cohort 3	0.927	0.942	0.967	0.973	0.977	0.975	0.974
Validation cohort 4	0.876	0.888	0.904	0.916	0.903	0.833	0.870
Validation cohort 5	0.838	0.907	0.865	0.911	0.876	0.935	0.947

5 miRNA panel has the most robust performance

ROC curve of 5 miRNA panel



5 miRNA panel score



Cancer diagnostic score

$$= \sum_{i=0}^{24} K_i \times \log_2 \text{microRNA}_i$$

microRNA_i – copy number / ml serum
 K_i – coefficient for microRNA_i