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Predicting Time to Ovarian Carcinoma Recurrence Using Protein Markers

TCGA 2nd Annual Scientific Symposium

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Background

- Standard of care for ovarian cancer: resection, platinum based chemotherapy.

- For about 25% of patients, the tumor does not respond to platinum therapy.

TCGA	RESISTANT	SENSITIVE	TOTAL
	90 (31.1%)	199 (68.9%)	289

- Identification of platinum resistant patients at time of diagnosis may result in a change in therapeutic approach.

CLOVAR model predicts outcome in ovarian cancer

- ‘CLassification of OVARian cancer’ (CLOVAR) predicts survival using gene expression signatures.
- Using TCGA, subtypes and survival gene expression signatures were identified, which would provide a prognostic model.

Verhaak RG et al., *JCI 2012 (in press).*

CLOVAR model predicts outcome in ovarian cancer

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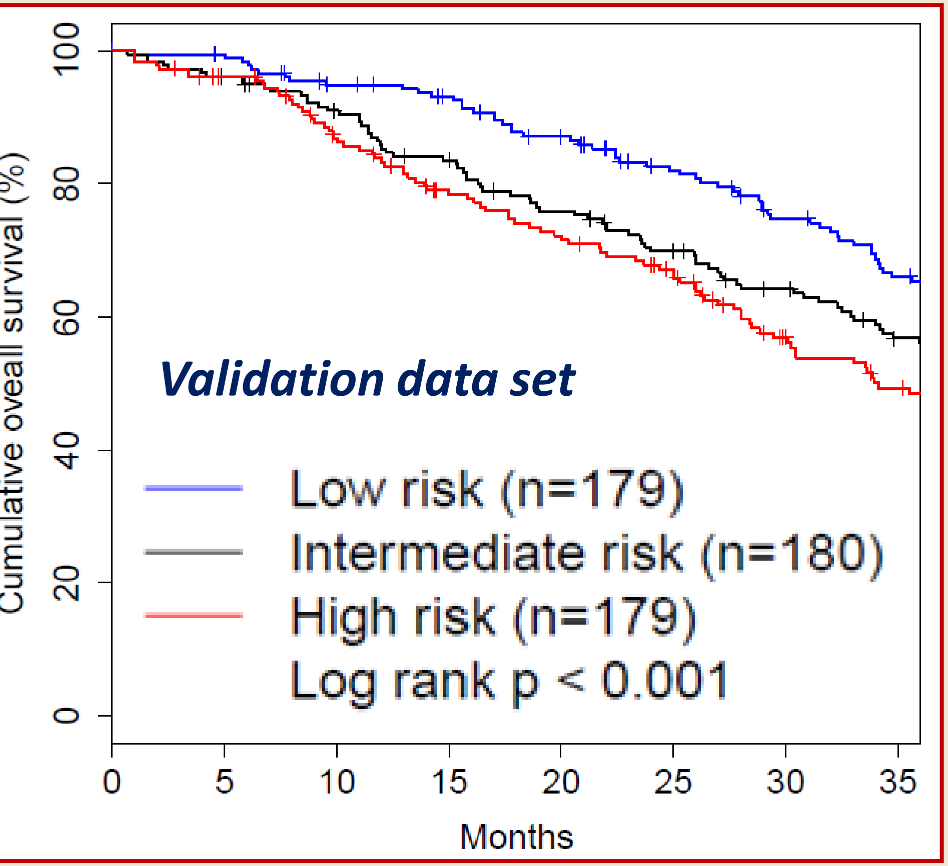
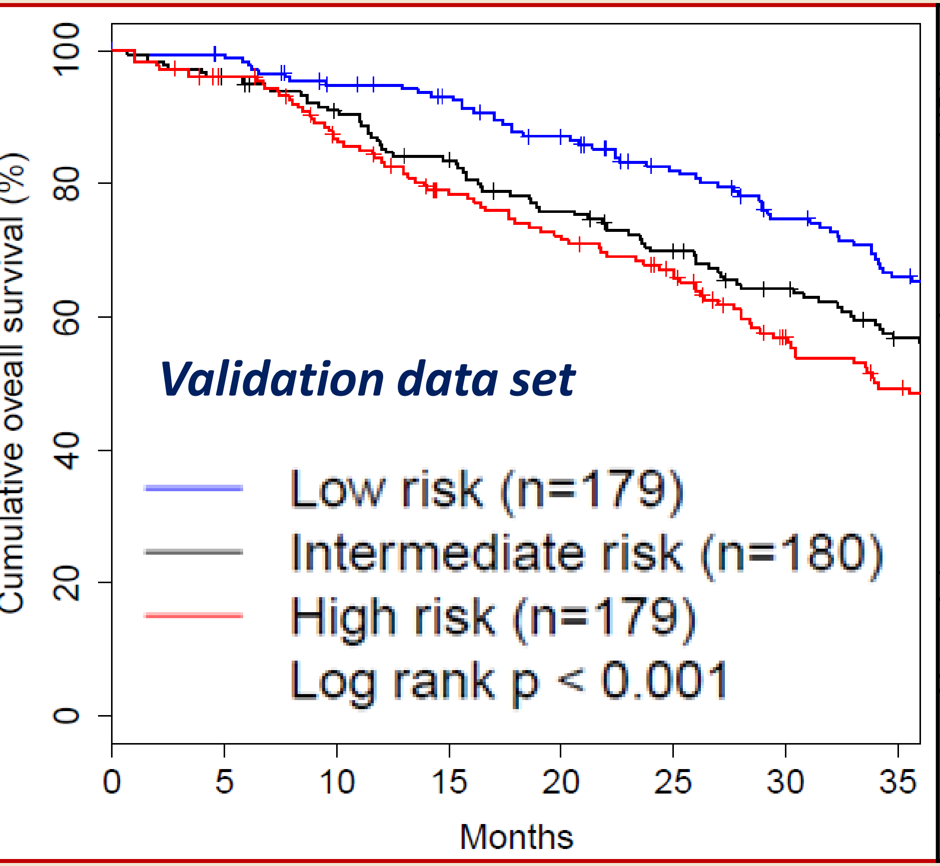
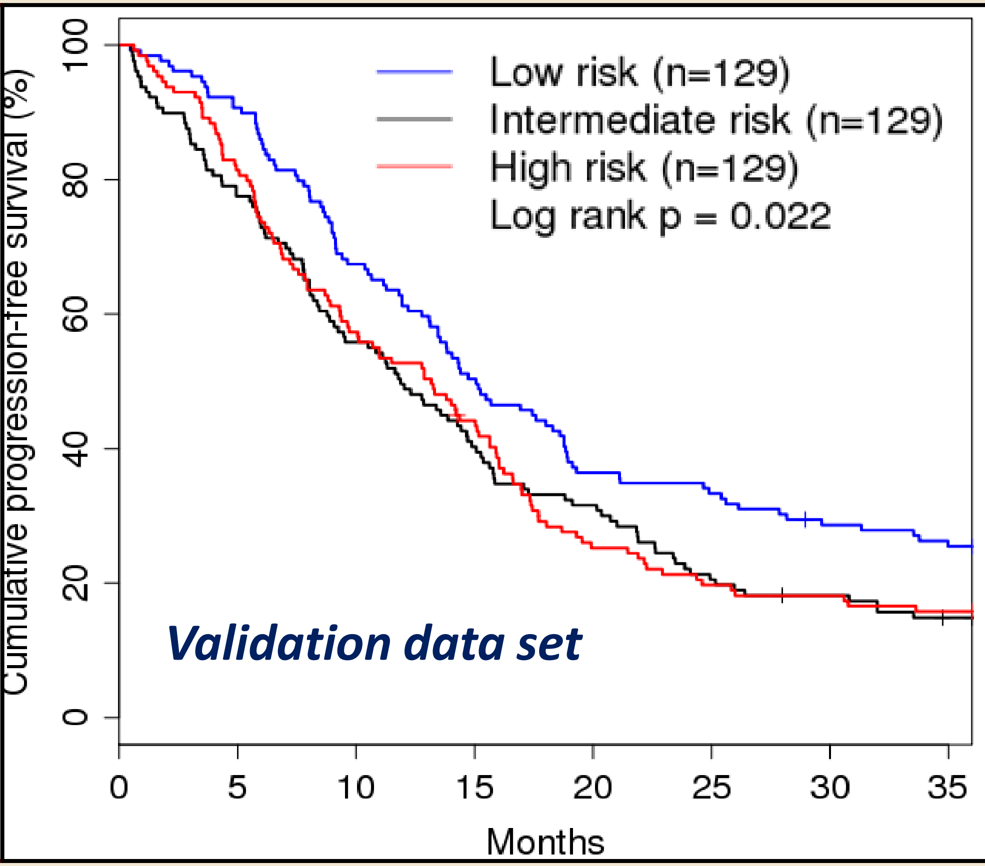


Verhaak RG et al., *JCI 2012 (in press).*

CLOVAR is less effective to predict progression free survival

- ‘CLassification of OVARian cancer’ (CLOVAR) predicts survival using gene expression signatures.





Verhaak RG et al., *JCI 2012 (in press).*

Can we use protein markers to predict PFS?

- Aim to develop a predictor of platinum resistance that is based on protein markers.

- RPPA (reverse phase protein arrays):

  172 proteins and phosphoproteins in 412 TCGA samples with serous ovarian cancer.

  222 cases were included in the model construction (non-missing values for PFS, advanced stage)

PROVAR

PRotein-driven index of OVARian cancer

TCGA

Training set (n=222 samples)

LASSO

Selected 9 proteins most associated with PFS & estimated β

PROVAR =

$$\hat{\beta}_1 X_1 + \hat{\beta}_2 X_2 + \ldots + \hat{\beta}_9 X_9$$

Feature Selection & Estimation

LASSO (Least Absolute Shrinkage and Selection Operator)

L1-constrained (lasso) Cox regression (Tibshirani,1997), sparse interpretable models by shrinking some variables to exactly zero.

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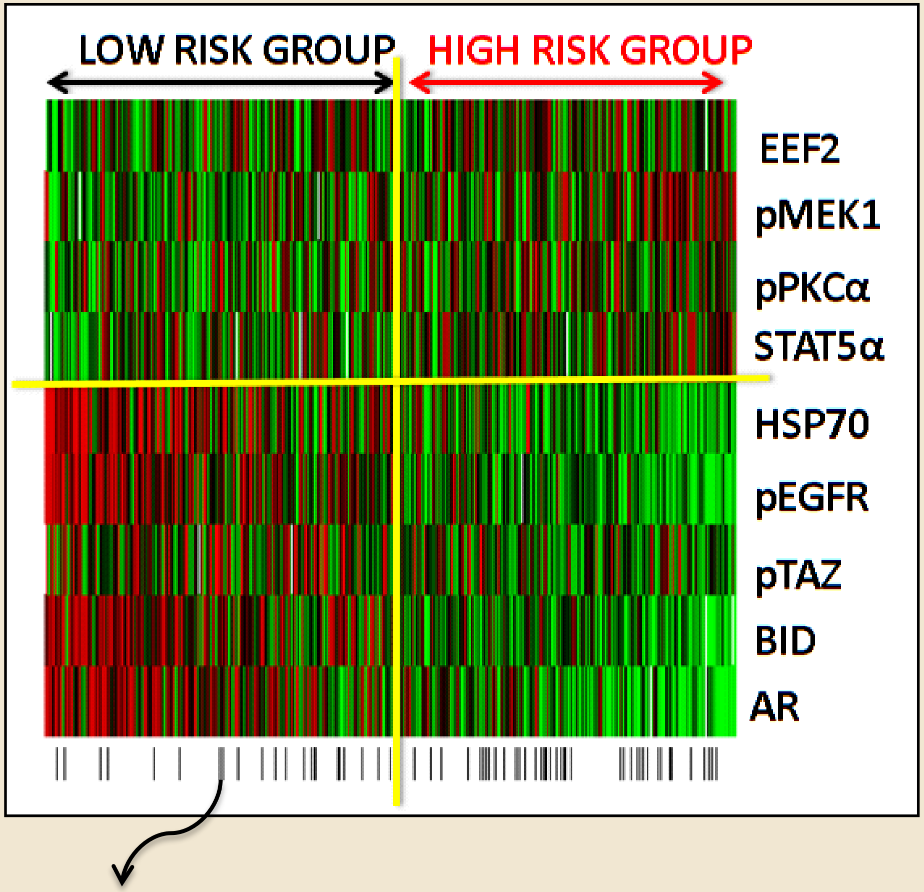
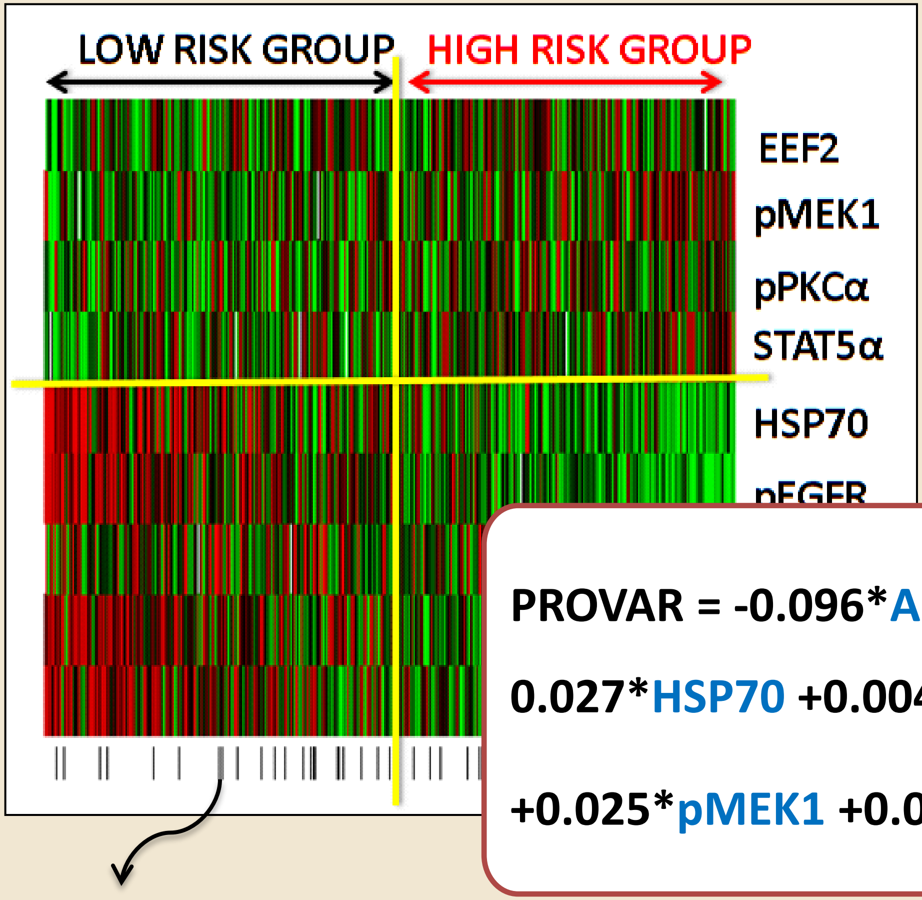
AR	BID	pTAZ	pEGFR	HSP70	STAT5α	pPKCα	pMEK1	EEF2
-0.096	-0.075	-0.058	-0.052	-0.027	0.004	0.022	0.025	0.029

9 proteins most associated with progression-free survival.

Numbers, lasso coefficients.



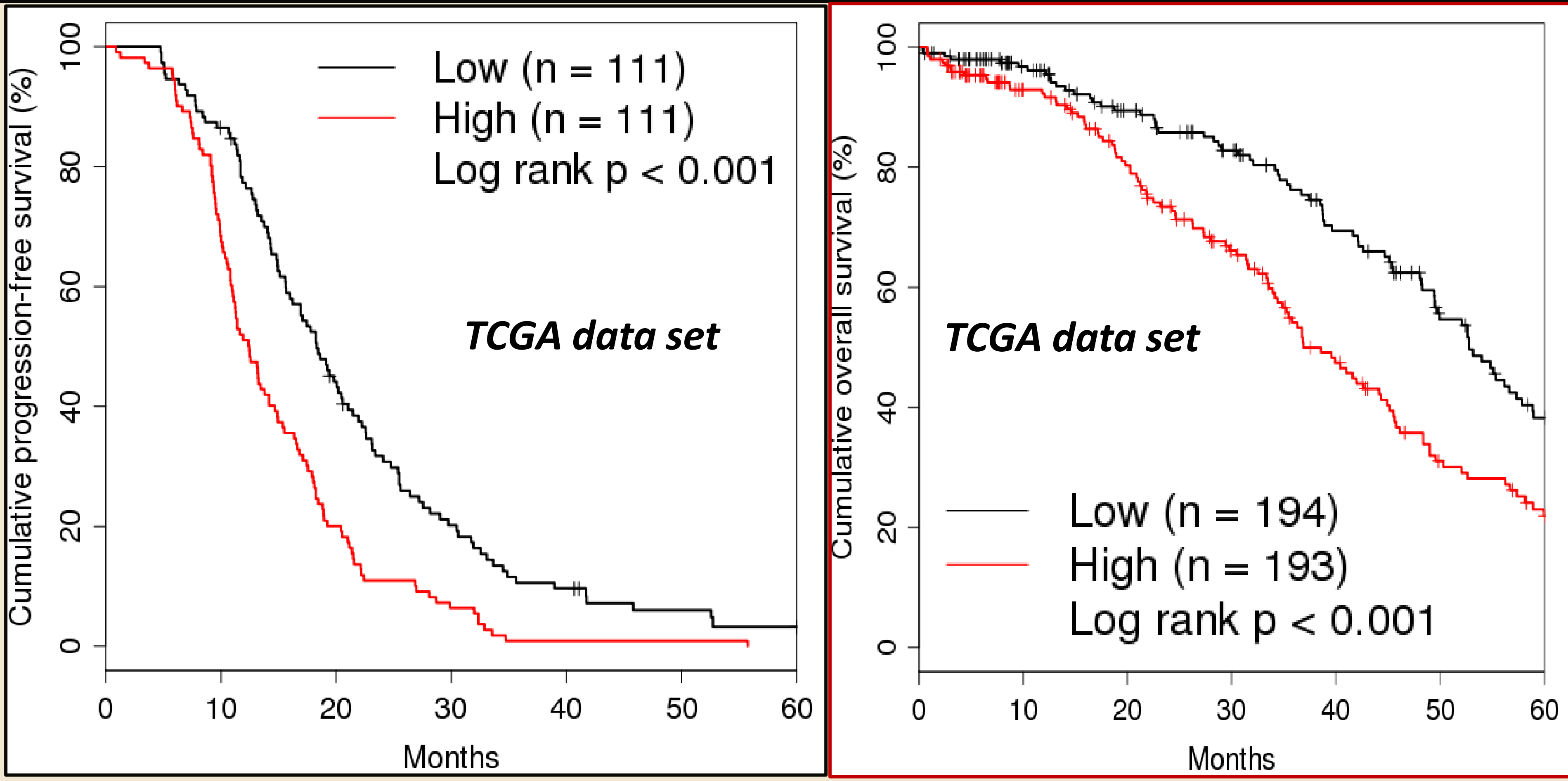
platinum resistant



platinum resistant

PROVAR = -0.096*AR -0.075*BID -0.058*pTAZ -0.052*pEGFR -0.027*HSP70 +0.004*STAT5.ALPHA +0.022*pPKC.ALPHA +0.025*pMEK1 +0.029*EEF2

PROVAR is predictive of both OS & PFS in the TCGA data set



Progression-free survival

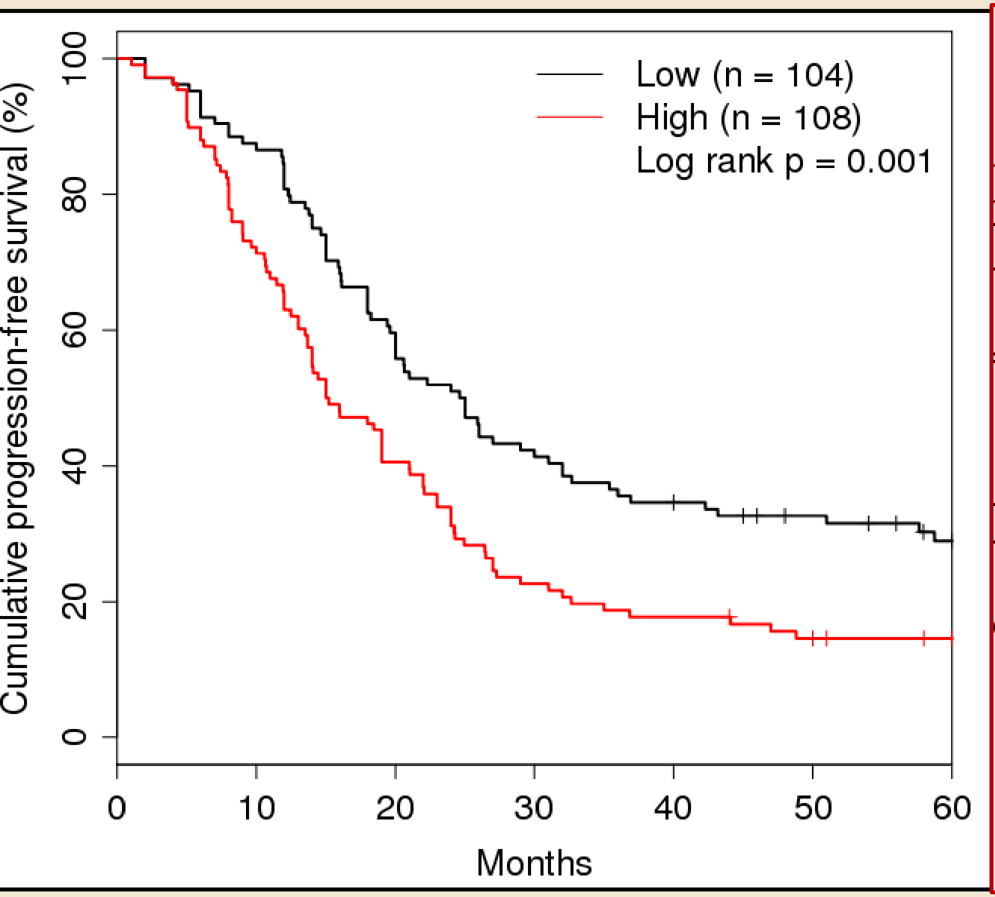
Overall survival

Validation of PROVAR in an independent data set

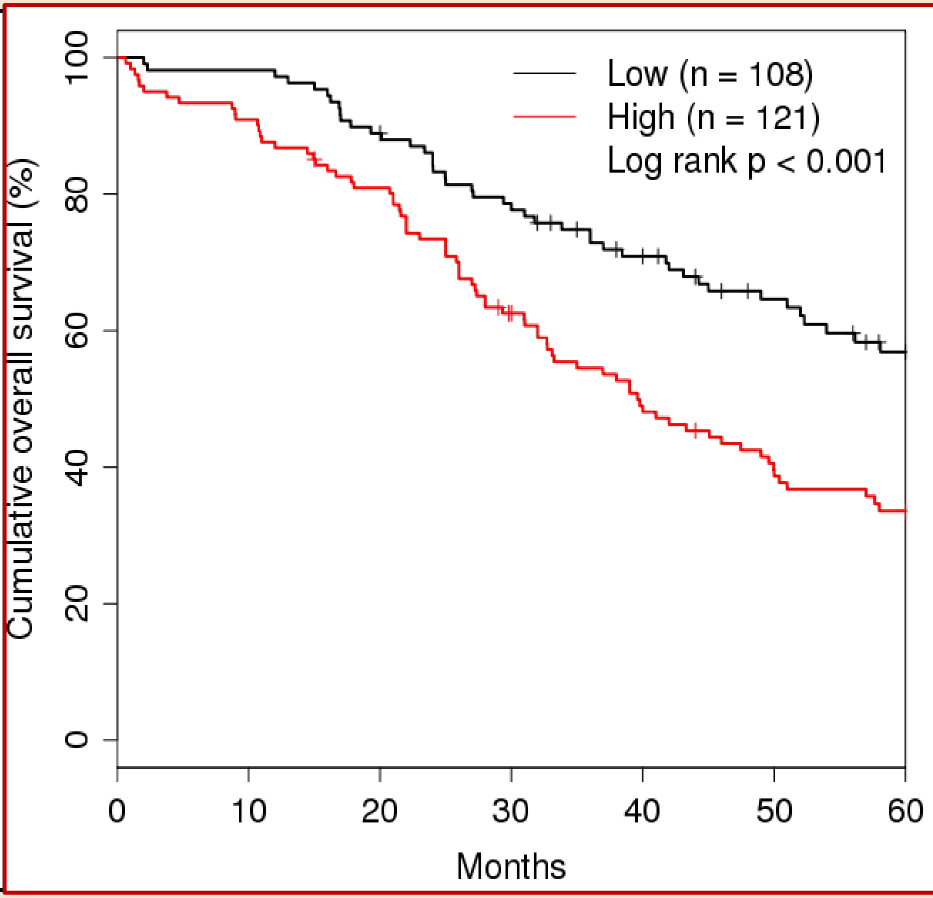
- 229 high-grade serous samples from Japan and Philadelphia.

- Expression levels of 144 proteins and phosphoproteins were measured by RPPA.

PROVAR is predictive of time to tumor recurrence in an independent dataset.



Progression-free survival



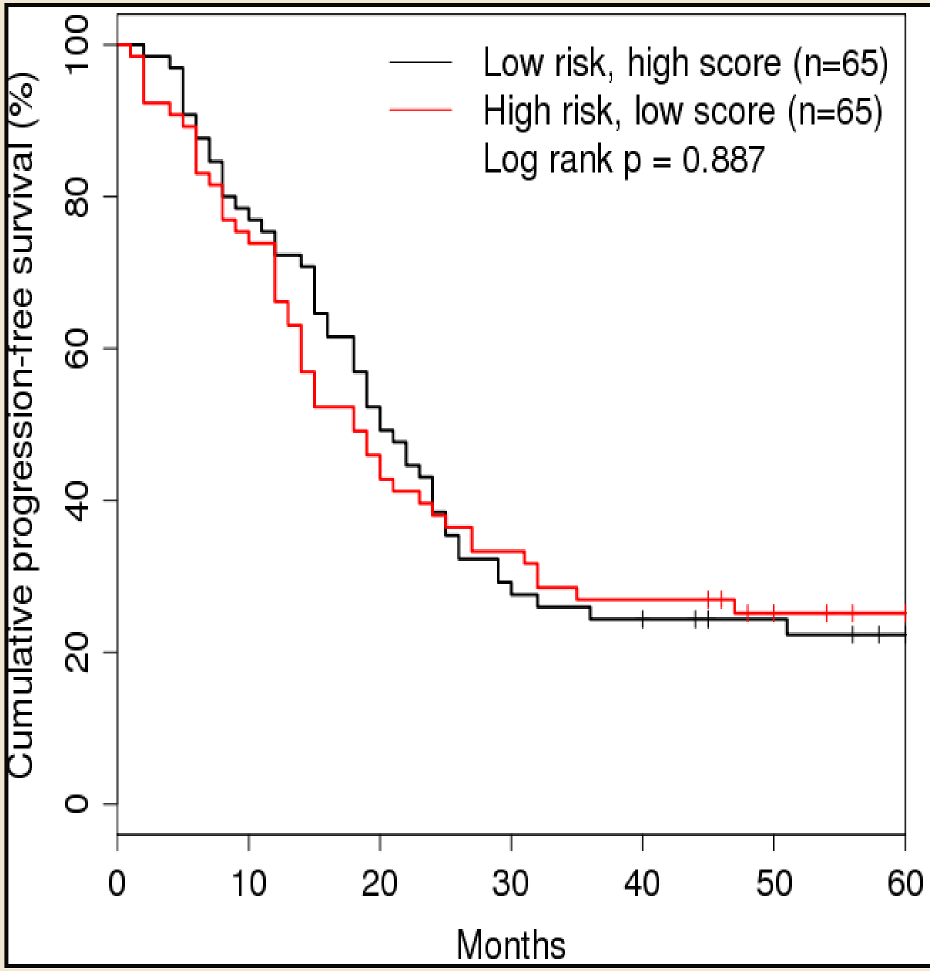
Overall survival

PROVAR (protein-driven) vs. CLOVAR (gene-driven)

n=130 samples with gene expression data available

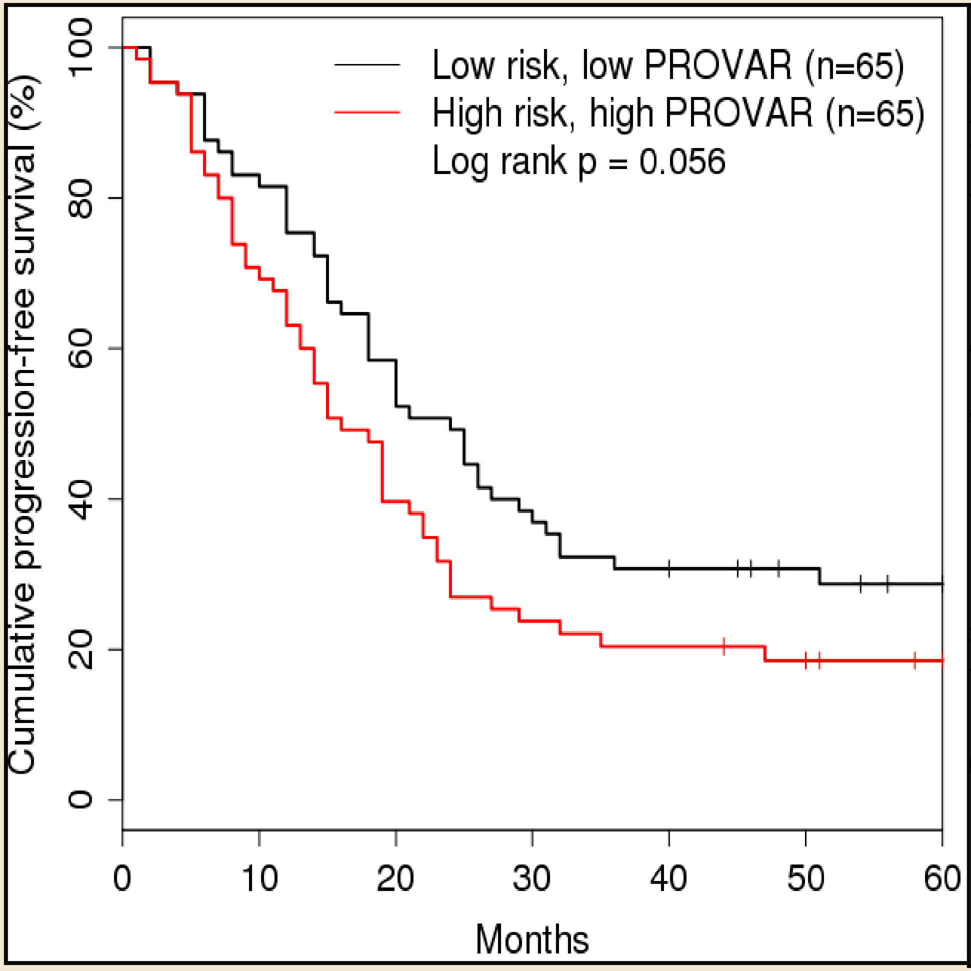
PROVAR (protein-driven) vs. CLOVAR (gene-driven): PFS, n=130 samples with gene expression data available

CLOVAR

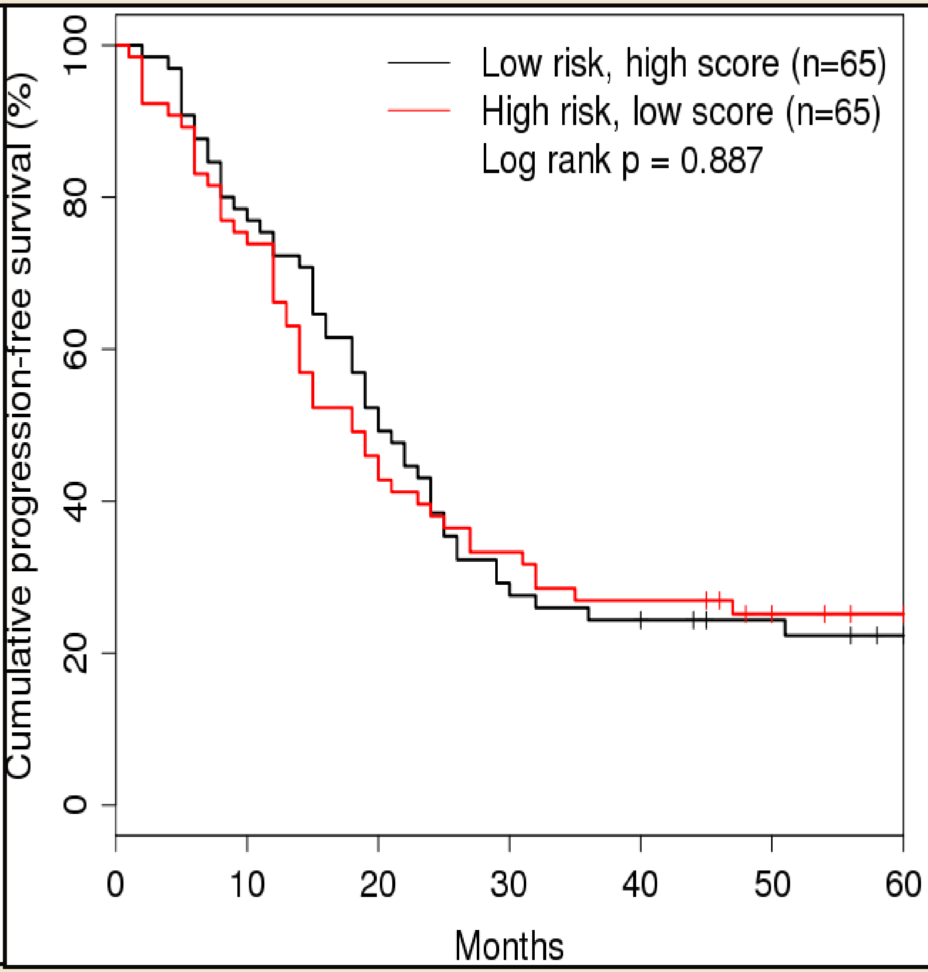


PROVAR (protein-driven) vs. CLOVAR (gene-driven): PFS, n=130 samples with gene expression data available

PROVAR



CLOVAR



Robustness of the nine proteins markers

Robustness of proteins markers

Using the validation samples,

COX2	VASP	CYCLINB1	pNFKB	AR
-0.006	0.057	0.050	-0.028	-0.014

Numbers are lasso coefficients.

Robustness of proteins markers

Using the validation samples,

COX2	VASP	CYCLINB1	pNFKB	AR
-0.006	0.057	0.050	-0.028	-0.014

Using the TCGA samples,

BID	pEGFR	HSP70	EEF2	pPKCα	STAT5α	pTAZ	pMEK1	AR
-0.075	-0.052	-0.027	0.029	0.022	0.004	-0.058	0.025	-0.096

Numbers are lasso coefficients.

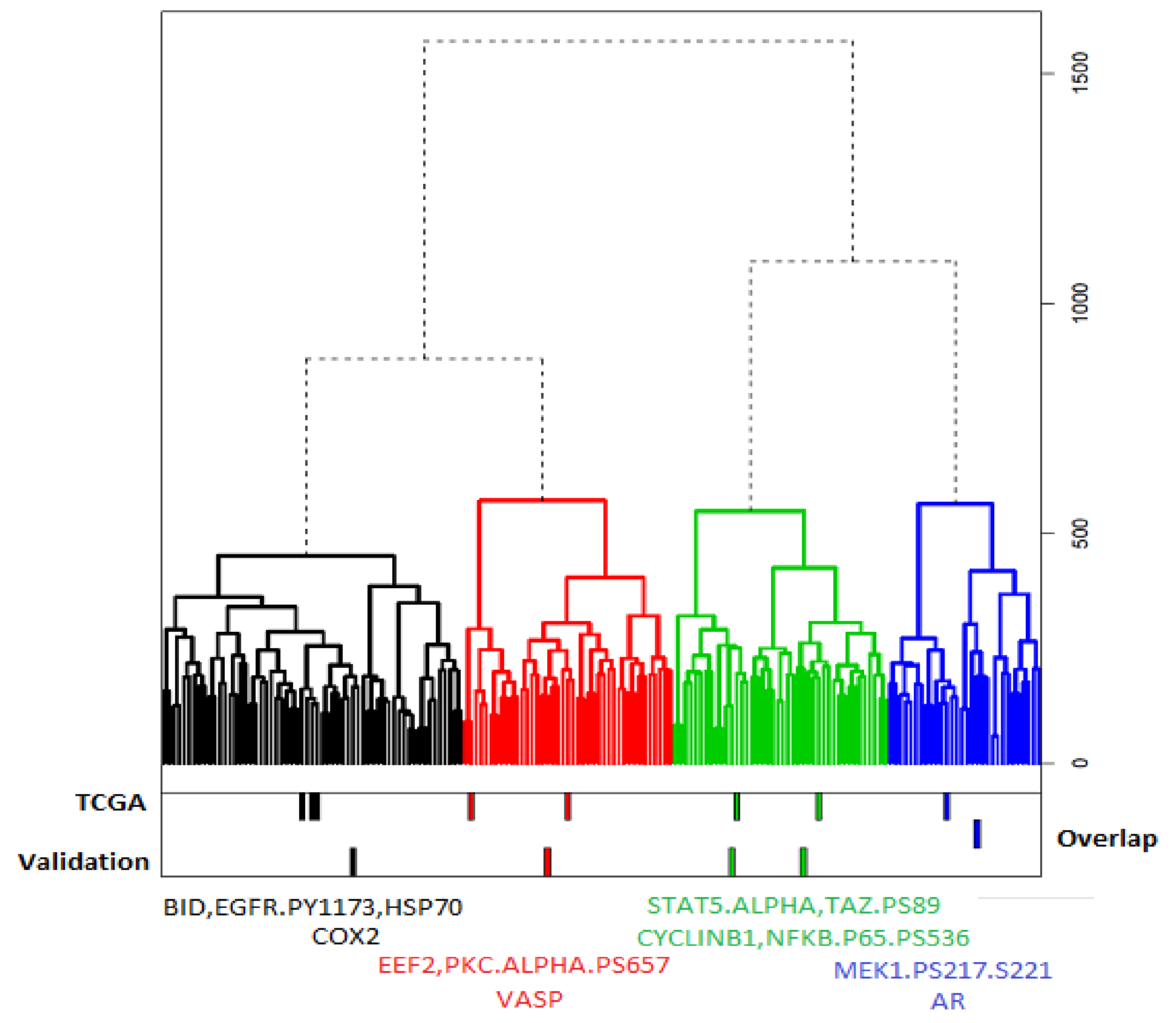
Hierarchical clustering of 172 proteins from TCGA

[Cluster1]
BID, pEGFR, HSP70
COX2

[Cluster2]
EEF2, pPKCα
VASP

[Cluster3]
STAT5α, pTAZ
CYCLINB1, pNFKB

[Cluster4]
pMEK1, AR
(AR: overlap)



Conclusions

- We developed a 'PRotein-driven index of OVARian cancer', PROVAR using progression-free survival,
- and successfully validated its discriminative ability to predict both progression-free and overall survival in high-grade serous ovarian cancers
- Unlike genetic signatures in previous studies that often contained a large number of genes, PROVAR is simple but still predictive of progression and survival, making it useful in clinical practice.

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