Most Random Gene Expression Signatures are Significantly Associated with Breast Cancer Outcome

Venet, et al.
PLoS Computational Biology, 2011

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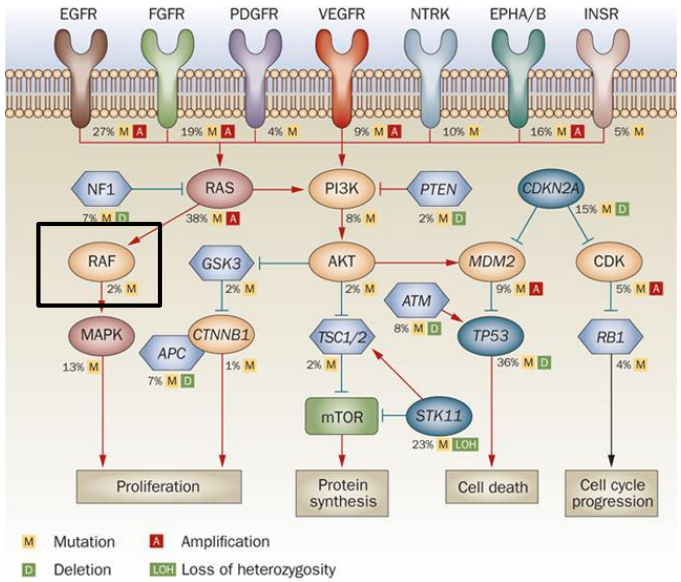
Biomedical Research Methods

1. Characterize mechanism in the model
2. Derive a marker that changes when the mechanism is altered
3. Show correlation of marker with disease outcome



Ding, L. et al. Nature (2008).

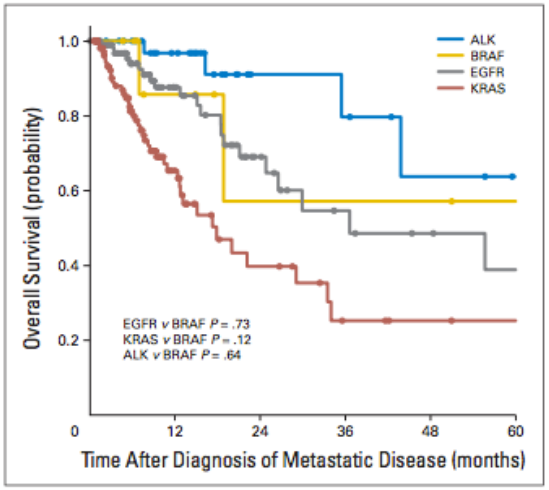


Fig 2. Kaplan-Meier curve for overall survival in patients with advanced stage (IIIB/IV) disease.

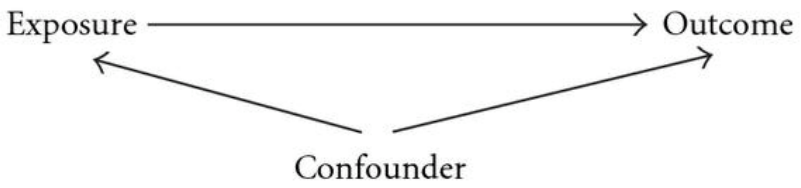
Paik, PK. et al. Journal of Clinical Oncology (2011)

Hazard Ratio:

$$\frac{\text{chances of an event (death) occurring in variable condition}}{\text{chances of an event (death) occurring in control condition}}$$

Confounding Variable Problem

- Some signatures are markers of mechanisms- ie. Epithelial mesenchymal transition
- Several signatures have equivalent prognostic outcome
- Are all mechanisms independent drivers or is there a confounding factor?



(Proliferation?)

Advances made in Methods

Step 2: Increase in genome-wide expression profiling leading to automated screen for markers and increased signatures

Step 3: Rise of cohorts with genome-wide expression profiles and patient follow-ups

Need to test negative controls to check relation of signature to outcome

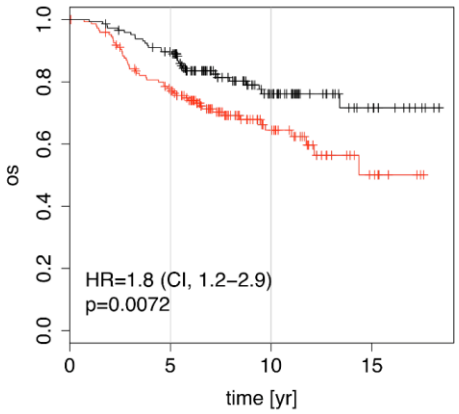
Typical: Signature of interest more strongly related to outcome than signature of no oncological rationale

Proposed: Random signature is more likely to be correlated with cancer outcome than not

Results- Fig 1

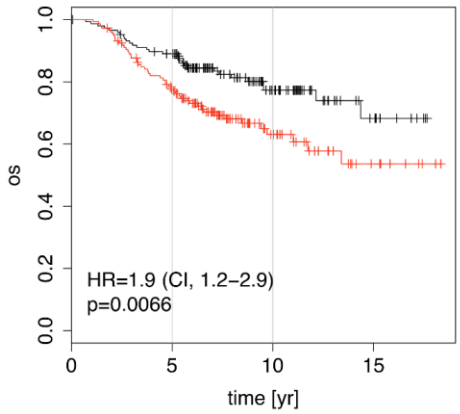
A

Post-prandial laughter sig.



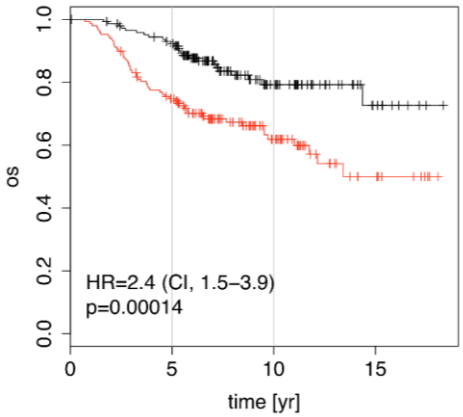
B

Localization of skin fibroblasts sig.

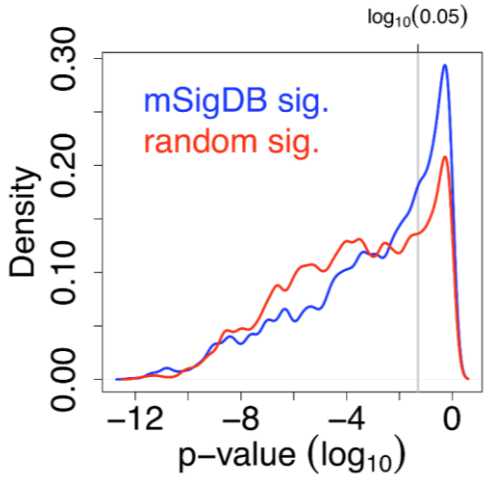


C

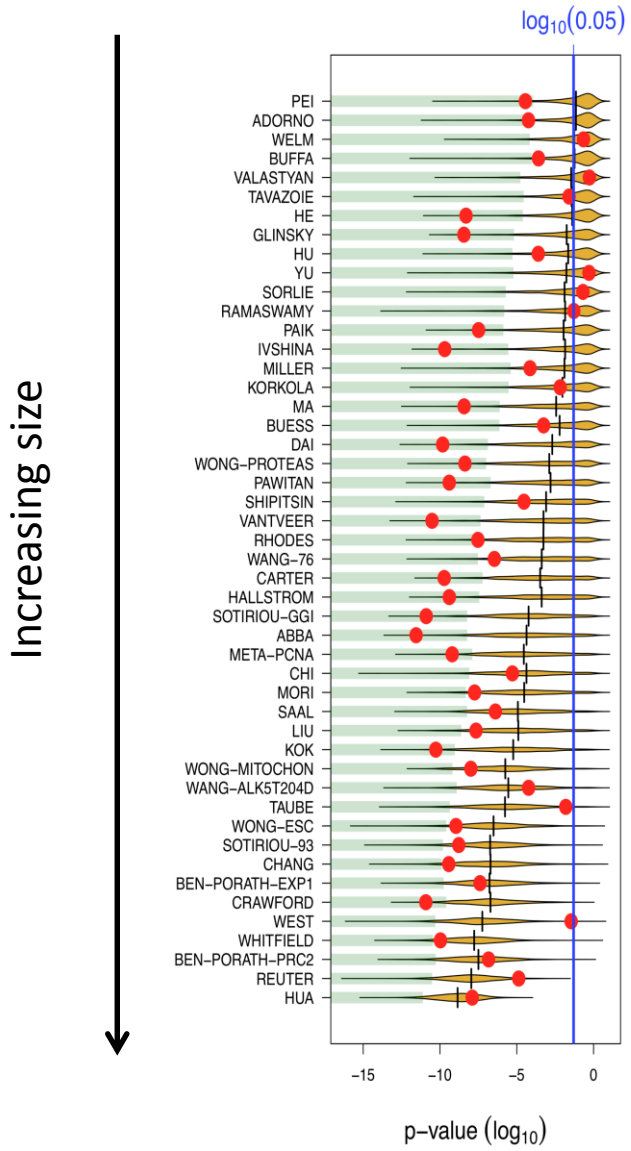
Social defeat in mice sig.



D

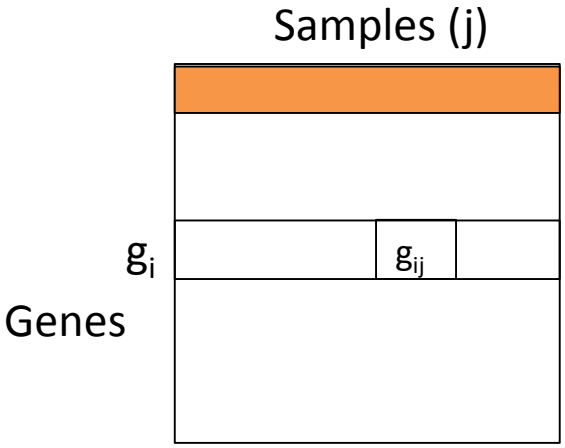


Results- Fig 2



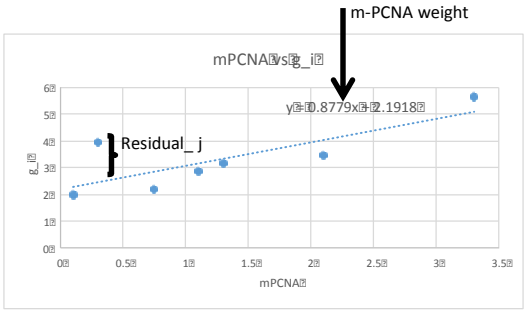
- Compared published breast cancer signature p-value of association with random signatures of equal size
- Used NKI cohort of patients

Methods: Meta-PCNA and Data Adjustment



m-PCNA index

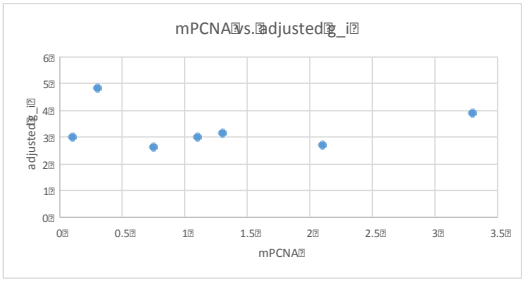
j	mPCNA_j	g_ij
1	0.1	1.957143
2	0.3	3.957143
3	0.75	2.157143
4	1.1	2.857143
5	1.3	3.157143
6	2.1	3.457143
7	3.3	5.657143



j	g_ij	linear fit	residual_j
1	1.957143	2.279579	-0.32244
2	3.957143	2.455137	1.502006
3	2.157143	2.850143	-0.693
4	2.857143	3.157369	-0.30023
5	3.157143	3.332927	-0.17578
6	3.457143	4.035159	-0.57802
7	5.657143	5.088507	0.568636

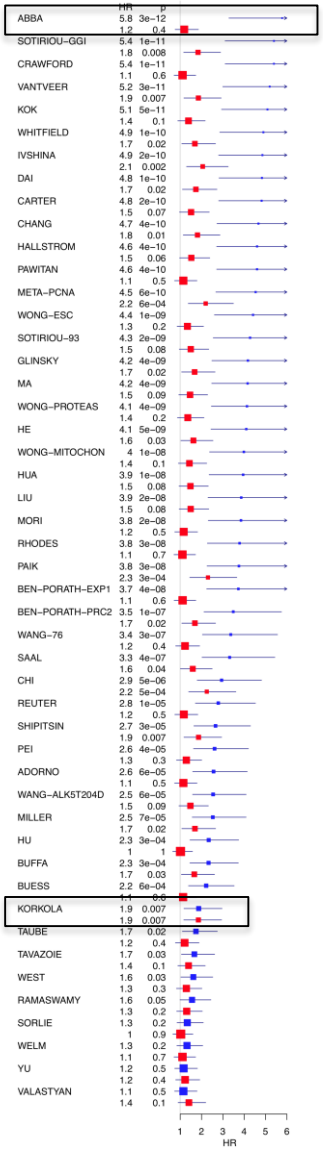
g_ij=weight*(mPCNAj) + intercept +error_ij

adj_g_ij = avg(g_i) + error_ij

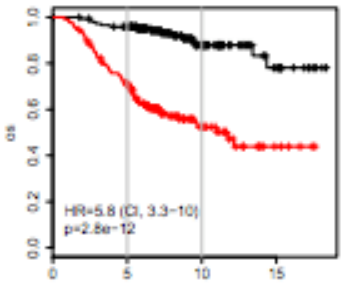


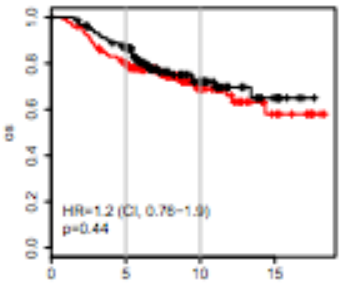
- Pearson correlation between PCNA and all genes in by Ge et al. via genome-wide expression profiling of healthy tissues
- 131 genes were top 1% that correlated with PCNA=> meta-PCNA sig.
- m-PCNA index of tissue: median expression of the genes
- Used linear regression (R's 'lm' function) to fit a sample's individual gene expression to m-PCNA gene

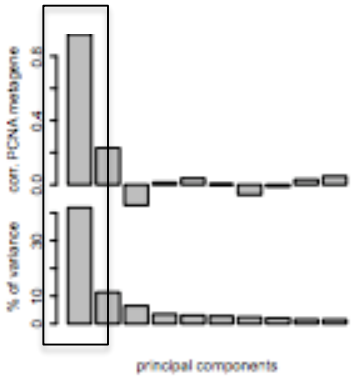
Results: Figure 3 and Supplmental



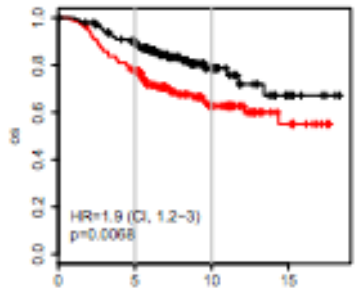
Abba Signature

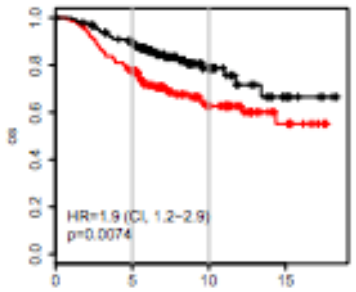


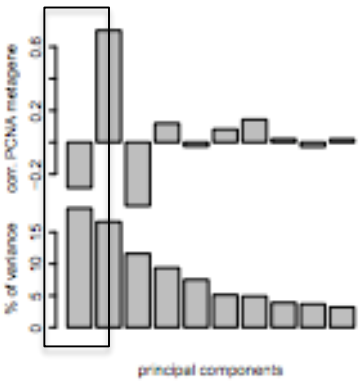




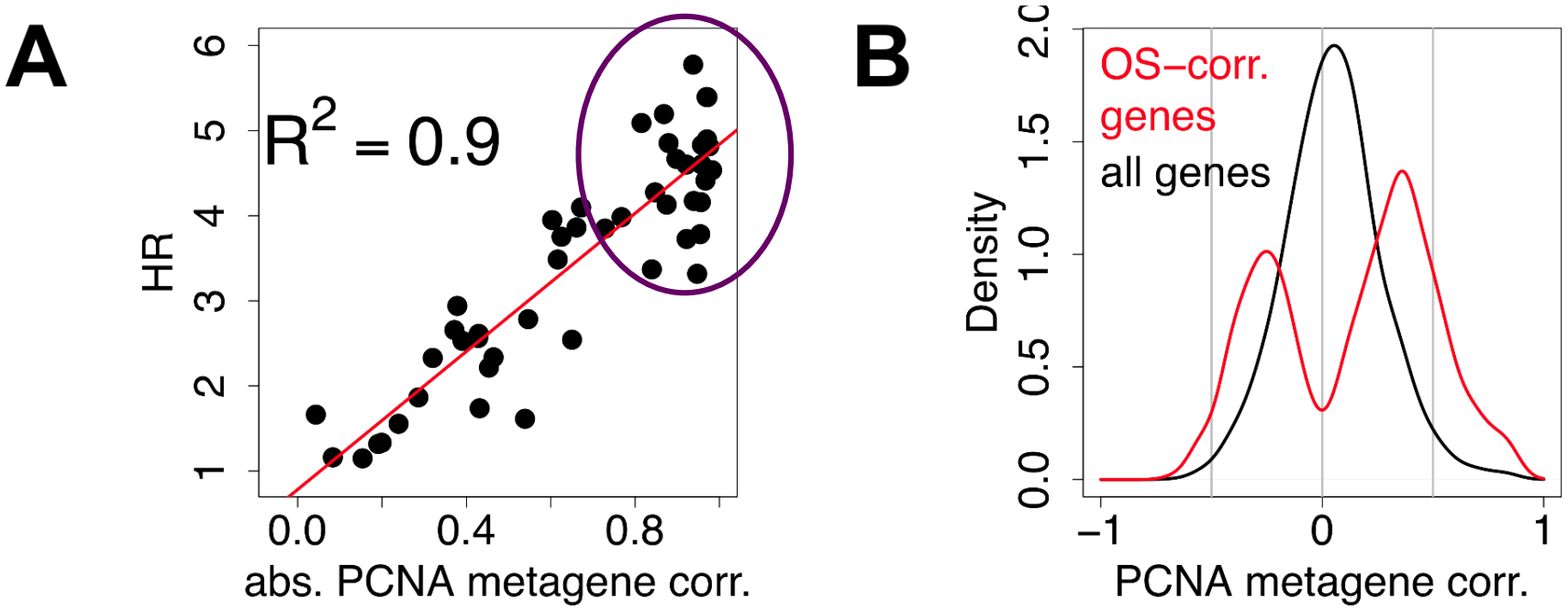
Korkola Signature



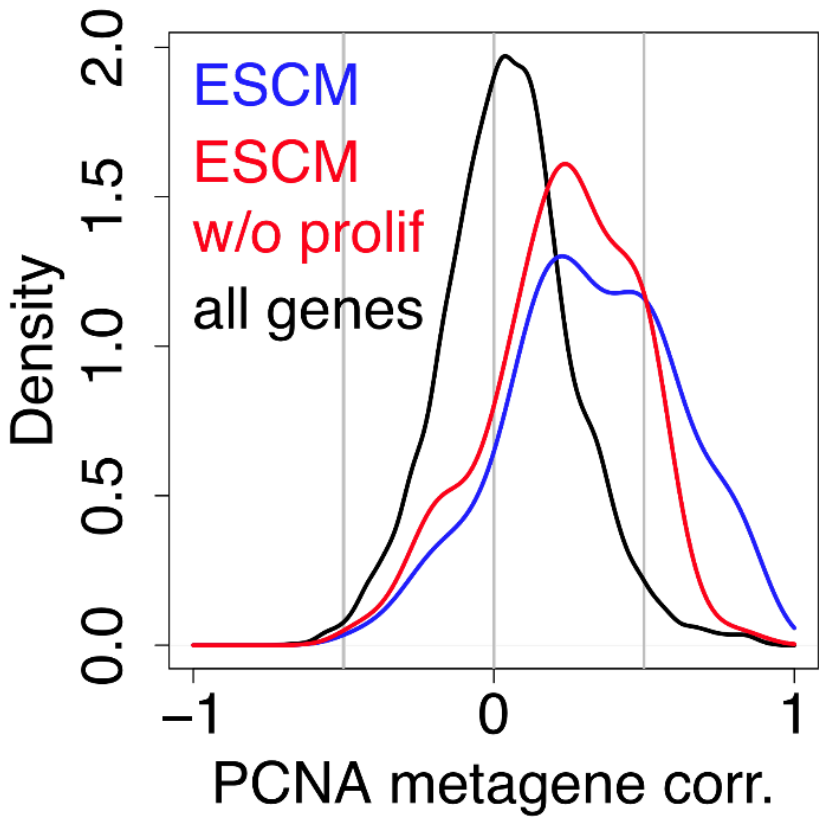




Results: Figure 4



Results: Figure 5



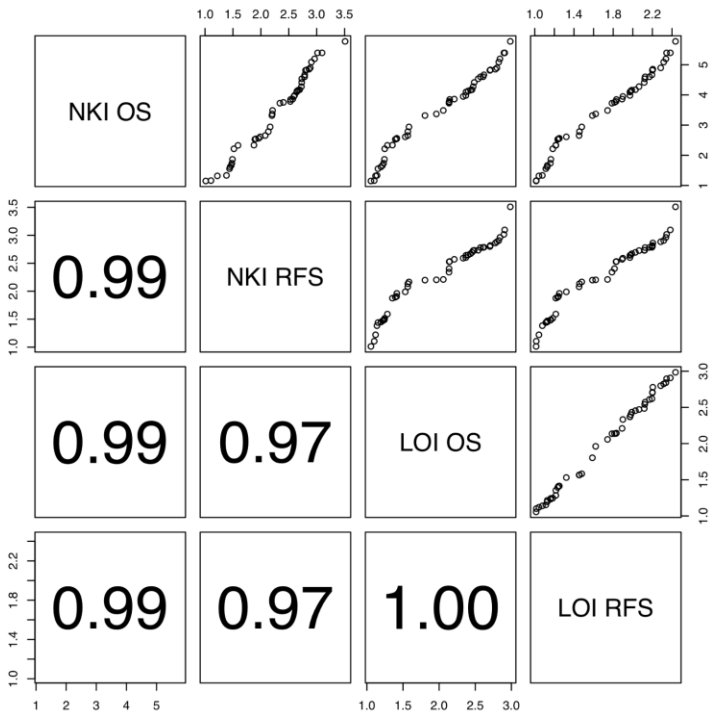
- ESCM: signature of gene sets associated with embryonic stem cell identity from Wong et al.
- Purging of cell cycle genes did not eliminate high correlation of ESCM with PCNA metagene

Correlations with meta-PCNA extend far beyond cell-cycle genes

Results: Figure 6

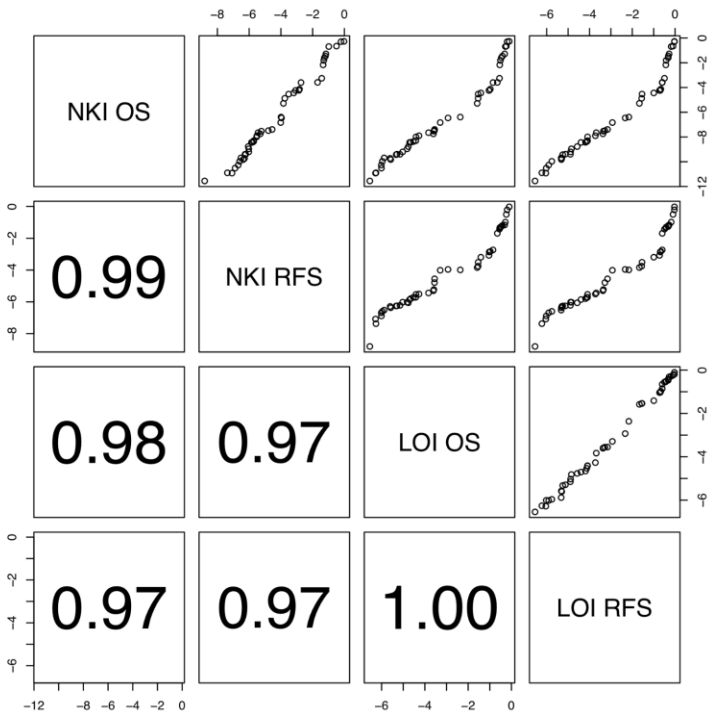
A

Hazard Ratio



B

Log rank p-values



Conclusions and Moving Forward

- Random single and multiple genes expression markers have high probability to be associated with BC outcome
- Most published signatures are not significantly more associated with outcome than random signatures
- Meta-PCNA metagene integrates most of the outcome-related information in BC transcriptome
- This information is present in 50% of the transcriptome and can't be removed by purging cell cycle genes from a signature

- Development of larger cohorts with various sub-types of a cancer included may help find better prognostic signatures
  - The NKI cohort represented bulk tumors from a wide spectrum of patients
  - Couldn't use NKI cohort to detect transcriptional signatures in specific cells (stromal, epithelial, etc) or patient groups (ER+, HER2 amplification)