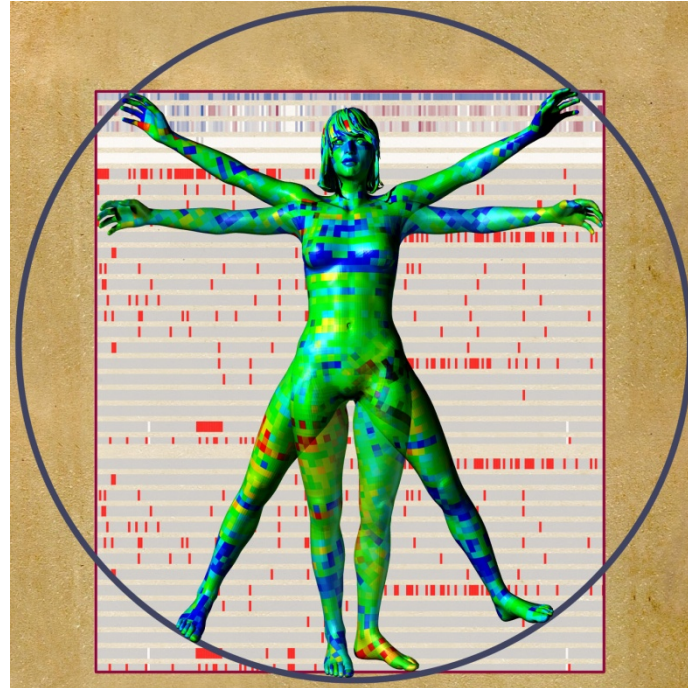


A Pan-Cancer Proteomic Perspective on The Cancer Genome Atlas



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UT MD Anderson Cancer Center

Overview



- Analyzed 3,467 samples across 11 tumor types:
 - BLCA, BRCA, COAD, READ, GBM, HNSC, KIRC, LUAD, LUSC, OVCA, UCEC
- 181 proteins
 - 128 total proteins
 - 1 cleaved
 - 1 acetylated
 - 51 phosphorylated forms
- Data produced in 6 Reverse-Phase Protein Array (RPPA) batches
 - Developed Replicates Based Normalization (RBN) method to reduce batch effects

Protein vs. other platforms

- Gene:protein matched (*cis*) comparisons
 - **mRNA:protein** Spearman correlation global mean = 0.3

Disease	BLCA	BRCA	COAD	GBM	HNSC	KIRC	LUAD	LUSC	OVCA	READ	UCEC
Corr	0.26	0.27	0.16	0.25	0.23	0.19	0.24	0.24	0.33	0.18	0.24

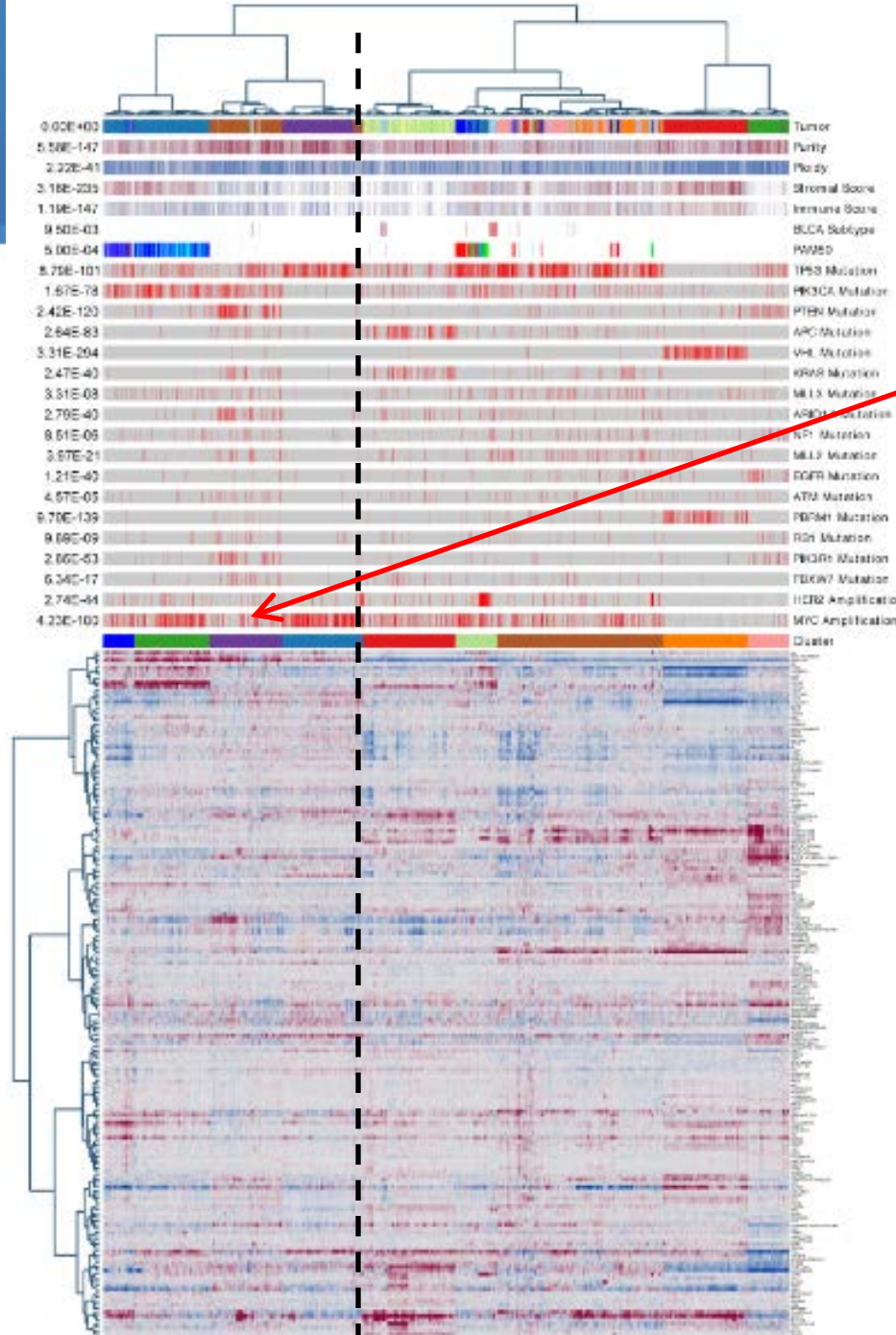
- **CNV:protein** mean fold change
 - Amplifications = 1.05, Deletions = 0.95
- **Mutation:protein** mean fold change
 - Elevating mutations = 1.2, Suppressing mutations = 0.9
- Other comparisons (all vs. all)
 - **miRNA:protein** mean Spearman correlation = ± 0.07
 - **Protein:protein** mean Spearman correlation = ± 0.15

Focus: ERBB2 CNV vs. mRNA vs. protein



Disease	CNV ERBB2 (%)	mRNA ERBB2 (%)	Protein HER2 (%)
BLCA	7	8	22
BRCA	15	11	15
CRC	7	3	37
GBM	0	0	1
HNSC	2	1	2
KIRC	0	0	0
LUAD	4	2	18
LUSC	3	1	3
OVCA	4	2	2
UCEC	6	4	9

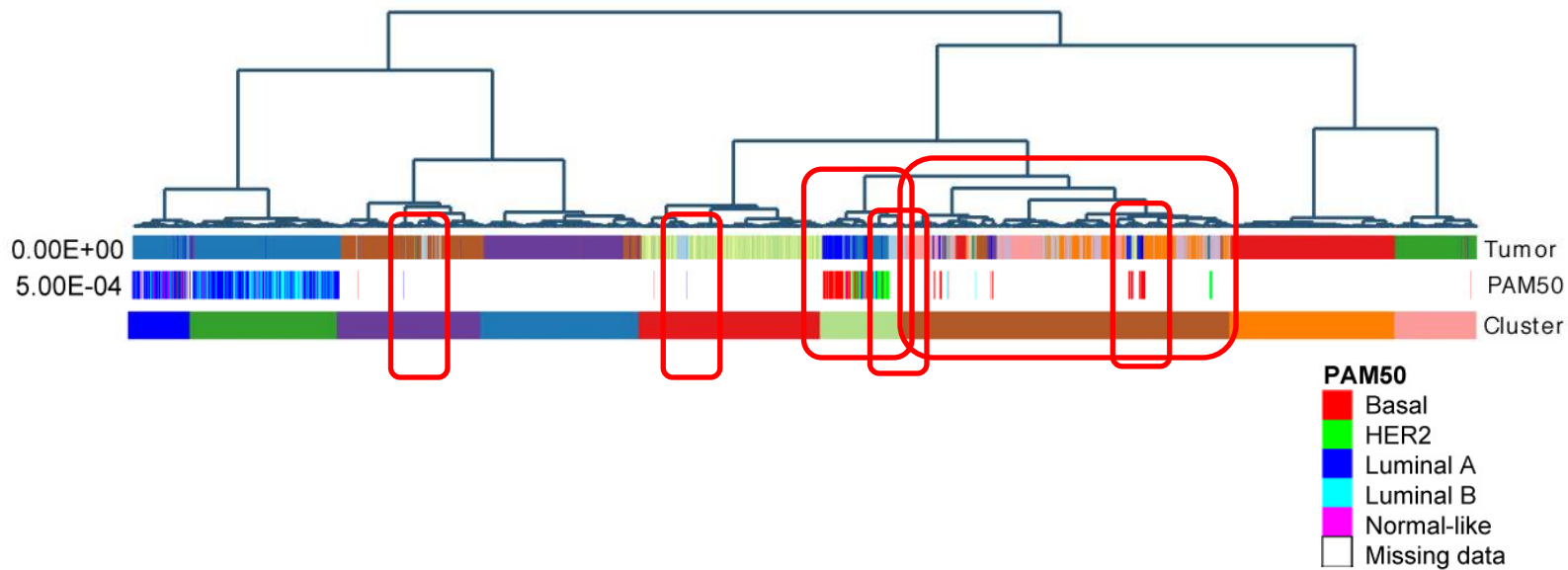
Unsupervised clustering shows 8 clusters



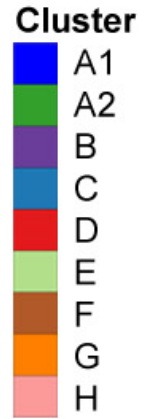
Women's cancers:
OV, UCEC, BRCA
(except basal, HER2+)

<http://bioinformatics.mdanderson.org/main/TCGA/Pancan11/RPPA>

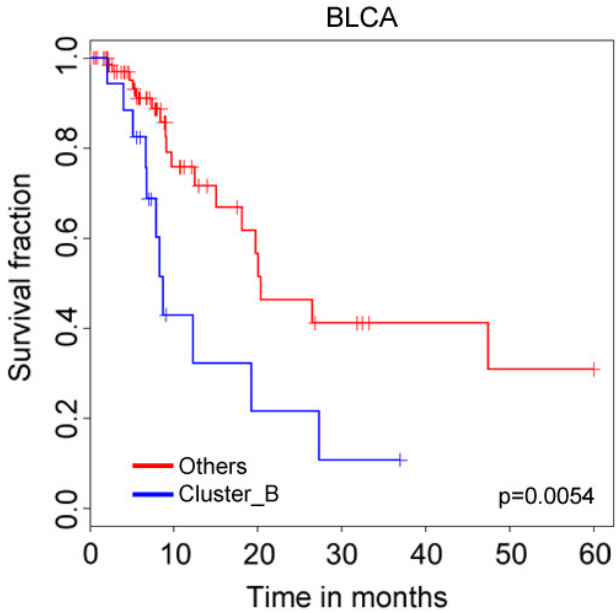
Next Gen Clustered Heat Maps (NG-CHM)



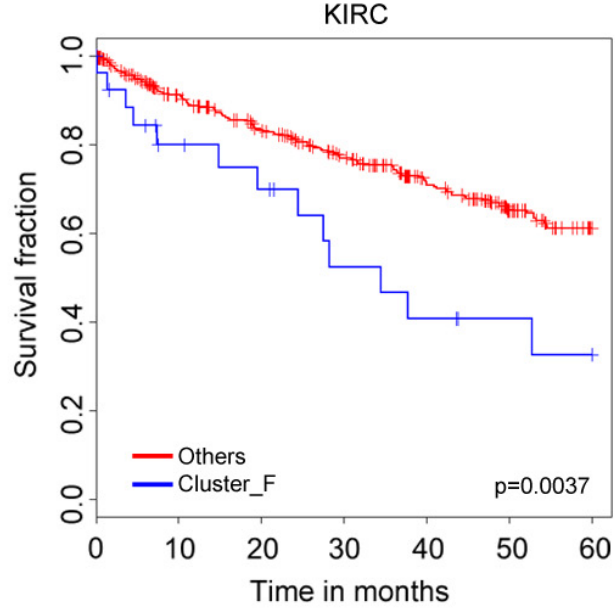
	A1	A2	B	C	D	F	F	G	H
BLCA	1	0	18	0	30	44	34	0	0
BRCA-Basal	1	1	2	0	1	89	32	0	2
BRCA-HER2	0	3	0	0	0	53	5	0	0
BRCA-LuminalA/B	2	344	0	0	0	17	2	0	0
BRCA-Reactive	144	31	1	0	1	7	9	0	0
COAD	1	0	3	0	314	0	16	0	0
GBM	0	0	2	0	0	0	6	0	207
HNSC	0	0	2	0	0	0	210	0	0
KIRC	0	0	2	0	0	0	27	424	1
LUAD	0	0	4	0	0	0	233	0	0
LUSC	0	0	5	0	0	2	188	0	0
OVCA	9	0	5	368	0	1	28	0	1
READ	0	0	1	0	120	0	9	0	0
UCEC	0	0	324	39	0	0	41	0	0



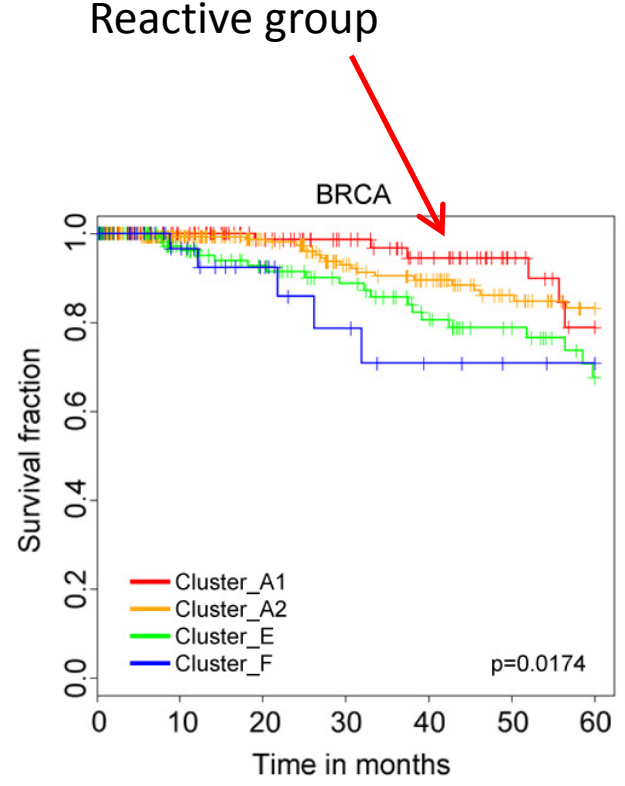
Some outcome differences



Endo-like BLCA



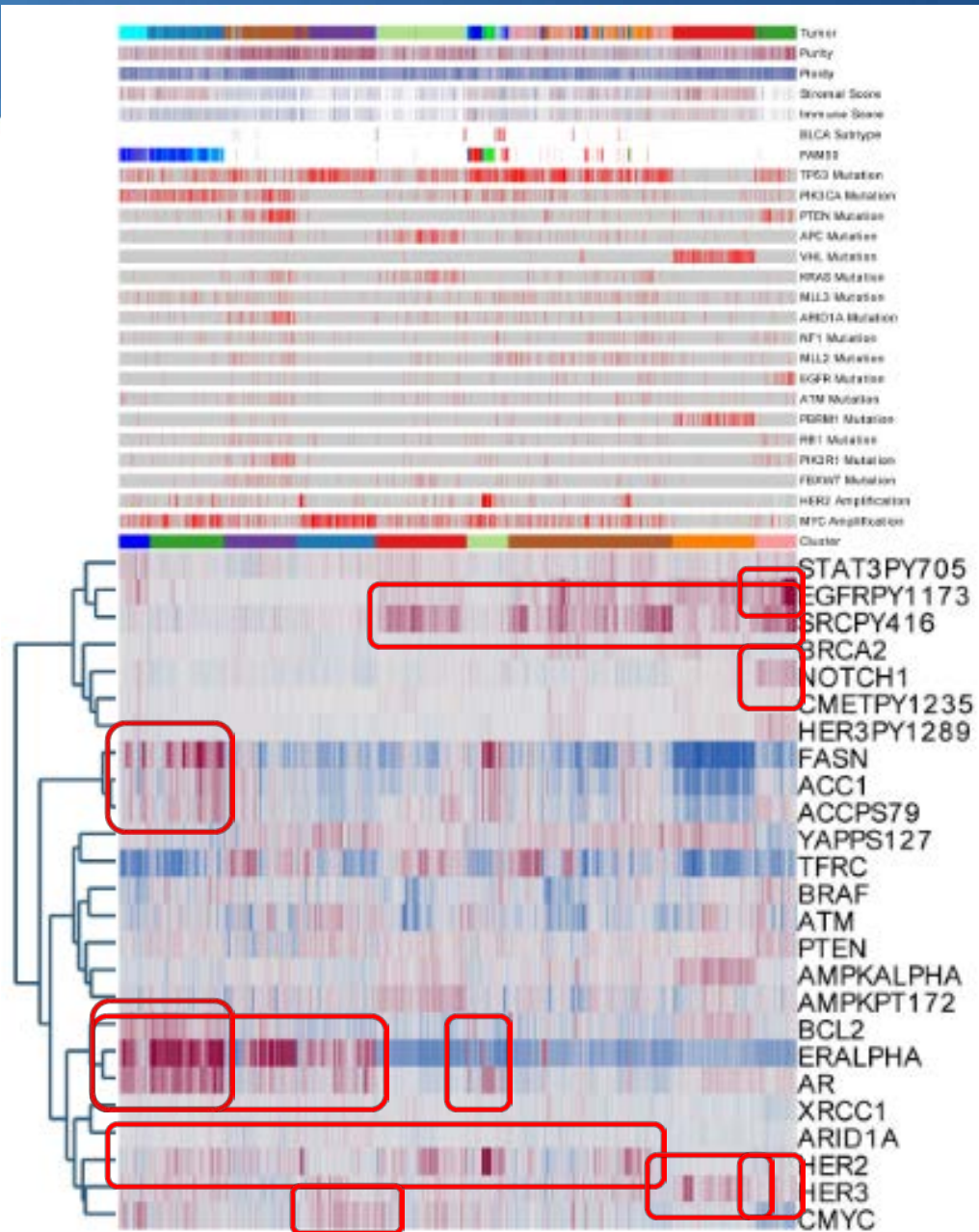
Squamous-like KIRC



BRCA

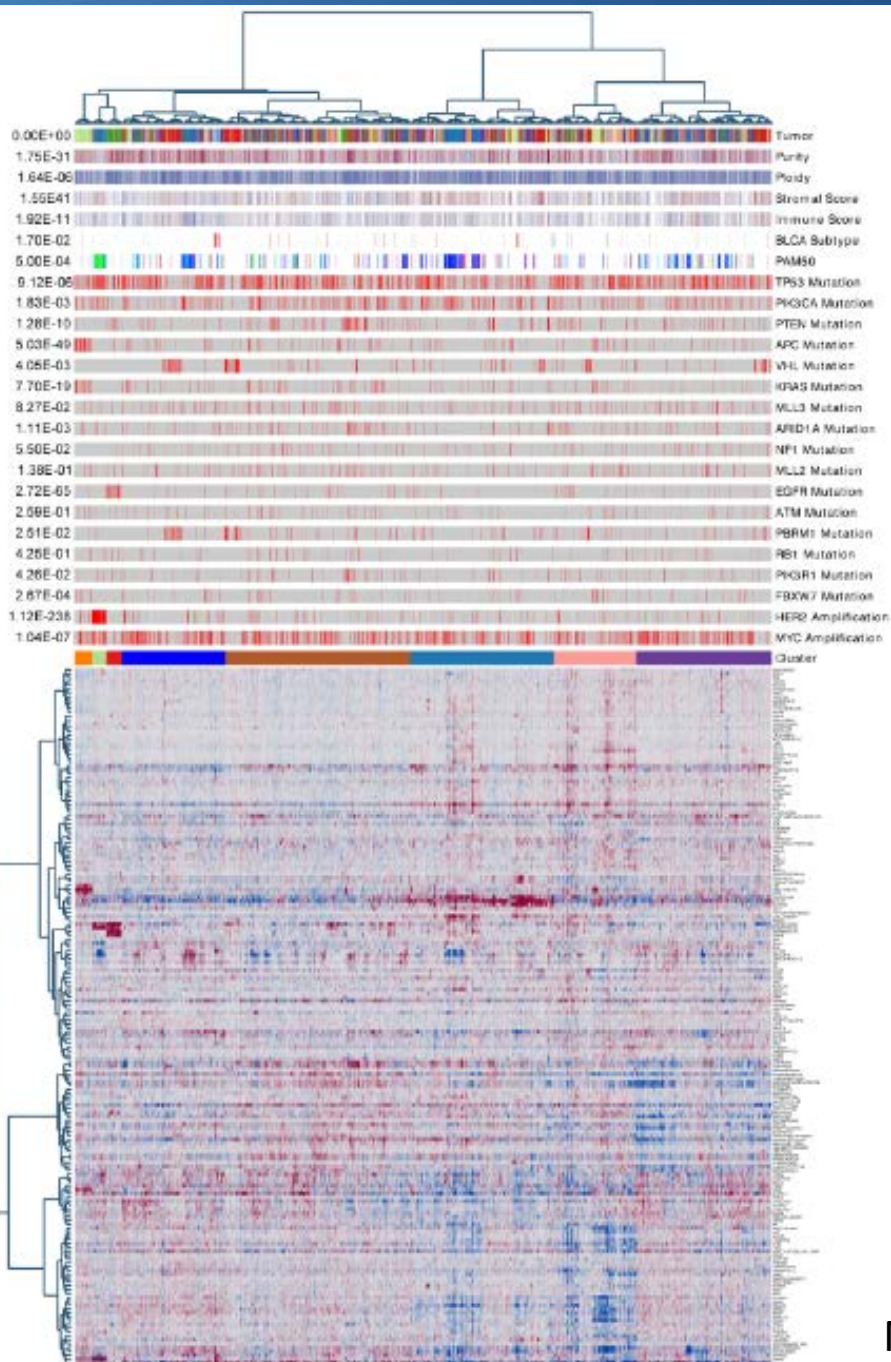
BRCA reactive group markers: Caveolin, Collagen, MHY11, Rictor

Marker proteins (potential targets)



- Women's cancers: ER-alpha, AR
- Luminal breast: AR, BCL2, FASN, ACC1, and pACC
- OV: CMYC (new MYC therapies under development)
- All except women's cancers and bladder: pSRC
- HNSC: pSRC, a downstream target of EGFR (sensitive to EGFR therapy?)
- UCEC, BLCA, BRCA, COAD/READ: HER2
- KIRC: HER3
- GBM: pEGFR with NOTCH1 and HER3 activation (combination therapy?)

Adjustment for tissue effects



Unsupervised clustering shows 7 clusters

Tumor lineage

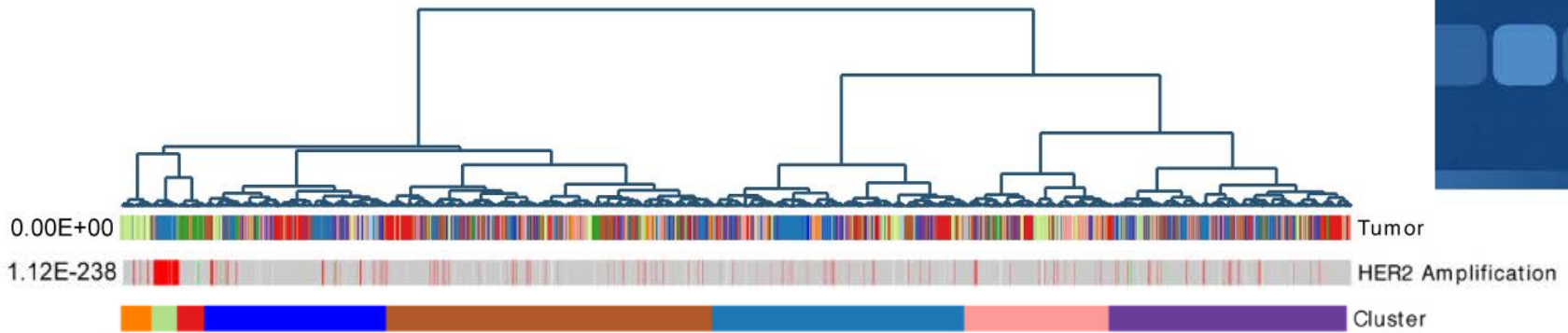
- Basal
- BLCA
- BRCA
- COAD
- GBM
- HNSC
- KIRC
- LUAD
- LUSC
- OVCA
- READ
- UCEC

Cluster

- I
- IIa
- IIb
- III
- IV
- V
- VI
- VII

<http://bioinformatics.mdanderson.org/main/TCGA/Pancan11/RPPA>

Next Gen Clustered Heat Maps (NG-CHM)

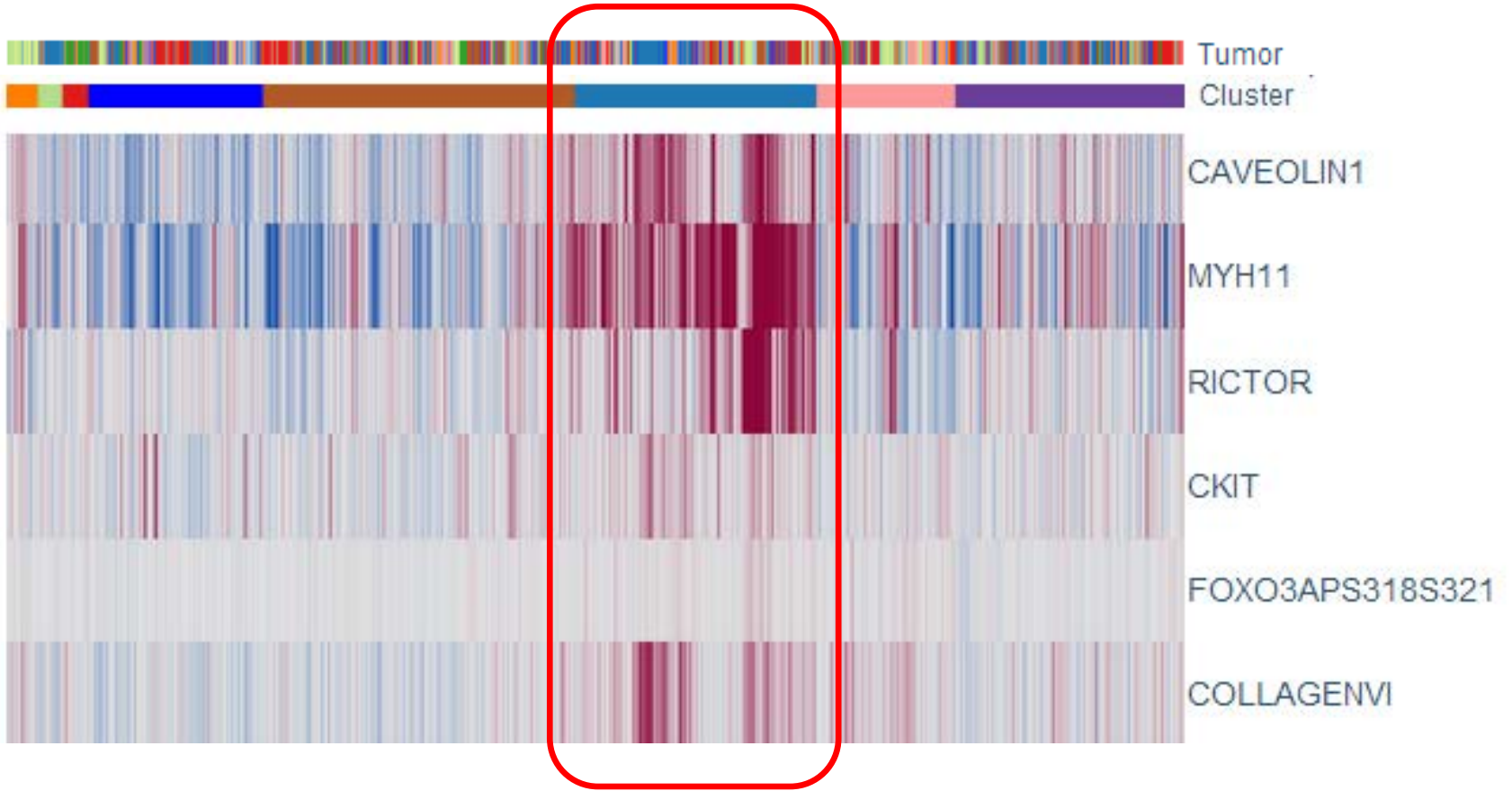


- Tumors cross clusters
- Sanity check: Her2 amplified cases cluster together

	I	IIa	IIb	III	IV	V	VI	VII
BLCA	1	3	0	23	28	33	19	20
BRCA-Basal	1	1	1	20	42	22	11	30
BRCA-HER2	0	40	0	1	15	0	0	5
BRCA-LuminalA/B	2	16	0	105	84	24	15	119
BRCA-Reactive	0	1	0	0	11	147	6	28
COAD	58	0	0	31	56	78	63	48
GBM	0	0	61	22	78	7	23	24
HNSC	0	0	6	24	61	38	49	34
KIRC	0	0	1	77	136	107	53	80
LUAD	0	3	5	41	71	33	37	47
LUSC	0	0	2	31	65	30	32	35
OVCA	0	3	0	80	106	86	34	103
READ	25	1	0	19	17	28	29	11
UCEC	0	4	0	41	151	81	38	89

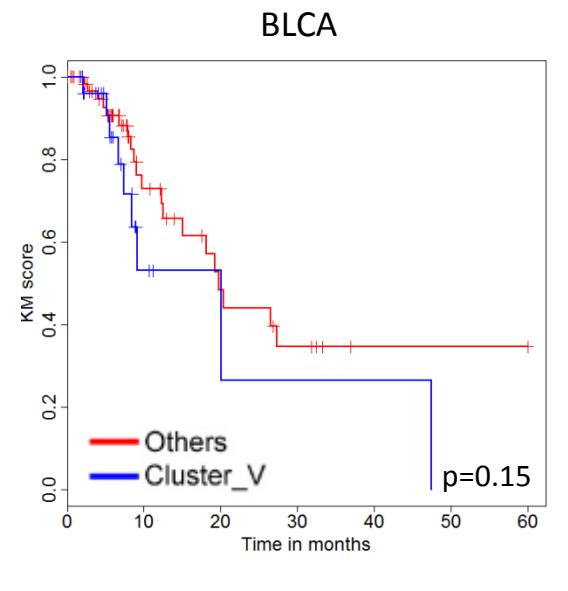
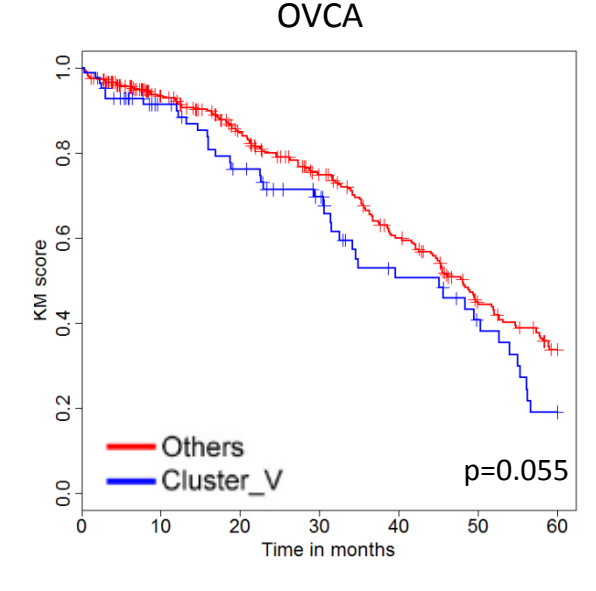
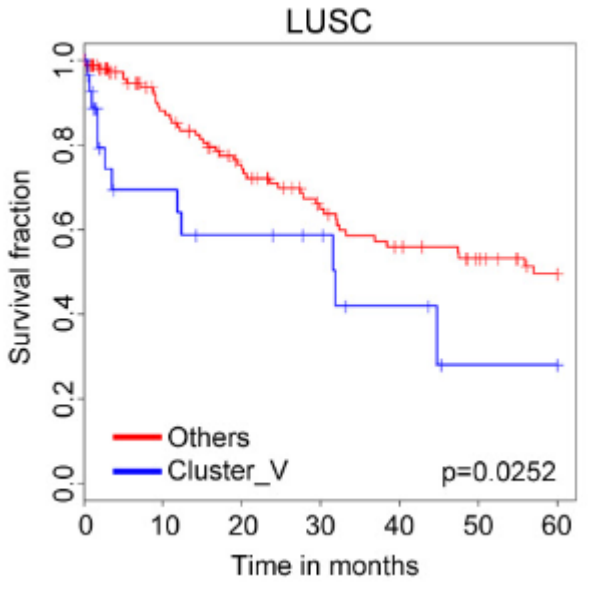
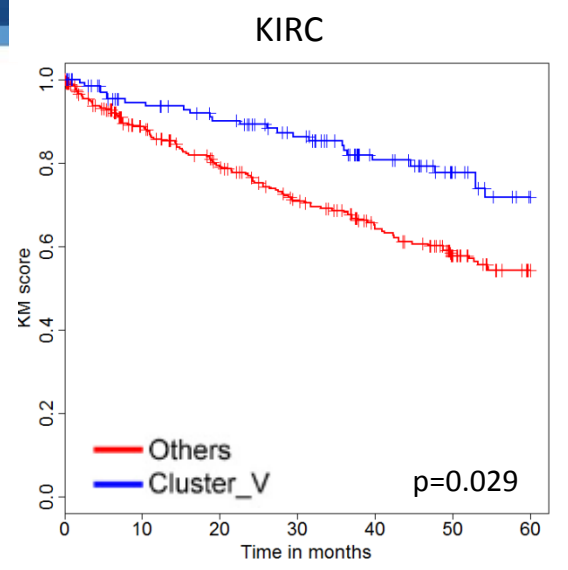
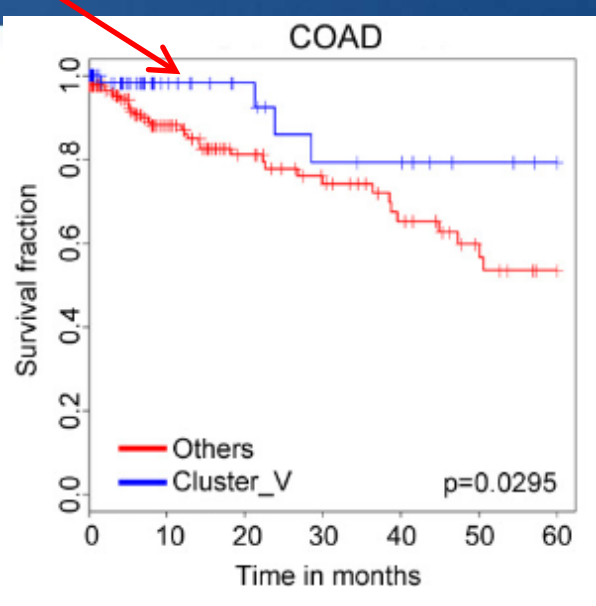
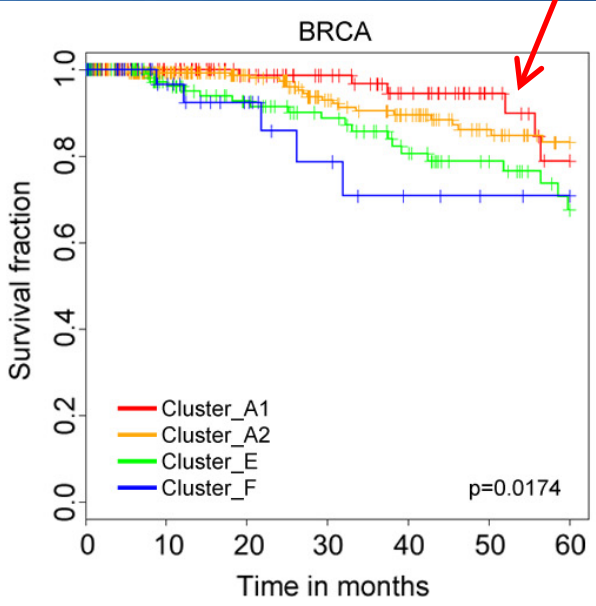
↑ PEA15 ↑ HER2 ↑ HER2 ↑ ERG ↑ Wnt signaling high ↑ Wnt signaling high ↑ Wnt signaling low ↑ AKT ↑ Wnt signaling low

Reactive cluster (V)

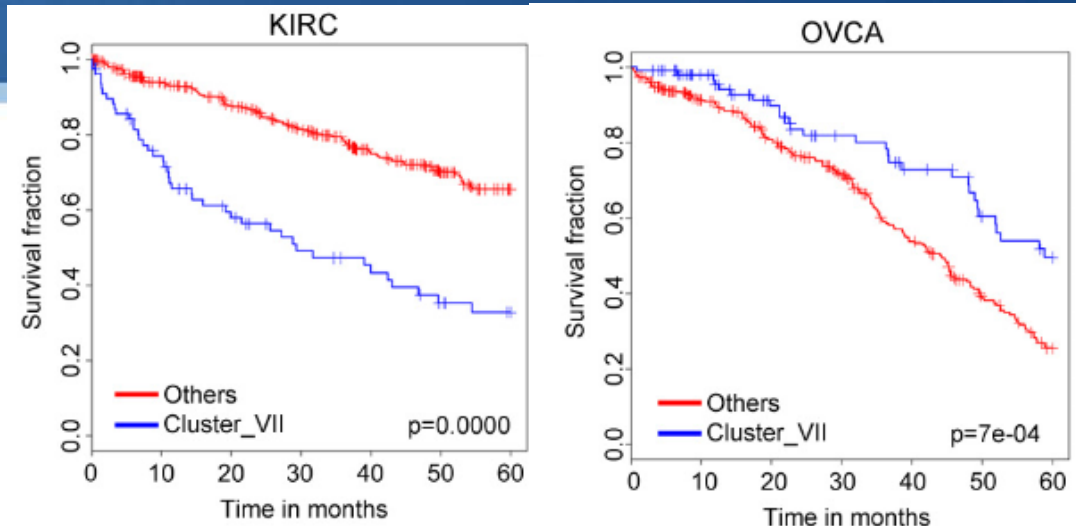


Some outcome differences – Reactives

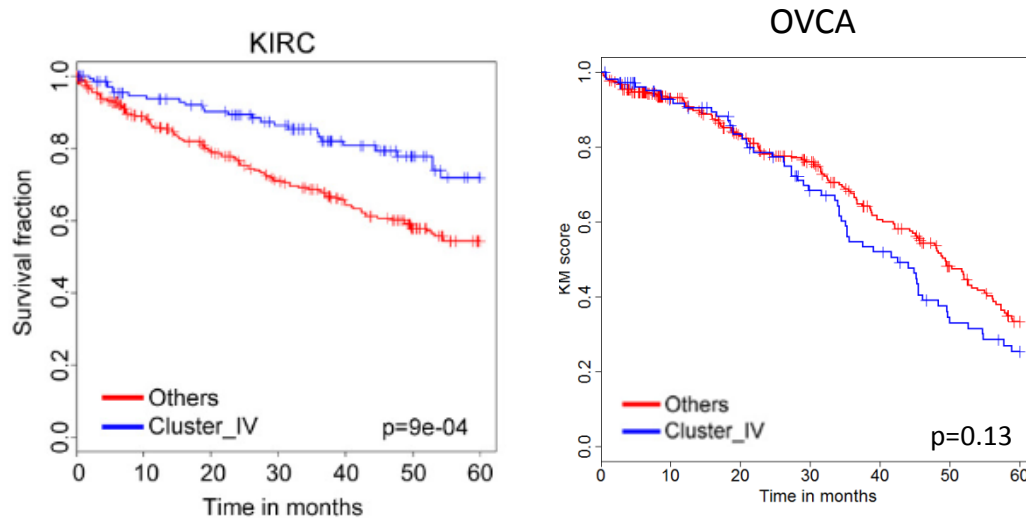
Reactive group



Some outcome differences – AKT pathway



Cluster VII - AKT pathway suppressed



Cluster IV - AKT pathway activated

Take-home findings



- Cross platform comparisons
 - Mutations have greater mean fold changes than CNV
 - mRNA:protein correlations can vary widely by disease
 - HER2 protein levels not predicted well by CNV or mRNA in certain diseases (e.g. CRC, LUAD, BLCA)
- Several novel markers identified
- Outcome differences seen across clusters, possibly driven by pathway differences
- Pathways effects are not equal by disease
 - Certain pathway activations may have good or bad prognosis depending on disease
- Protein:protein correlations vary by disease

Acknowledgments and publication

Akbani, R. *et al.* A pan-cancer proteomic perspective on The Cancer Genome Atlas. Nature Communications, *In Press.*

Poster #1

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The Netherlands Cancer Institute

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Nicolas Stadler

Sach Mukherjee

UT Southwestern Medical Center

John D. Minna

