

# Systematic analysis of mutational signature interactions with cancer states

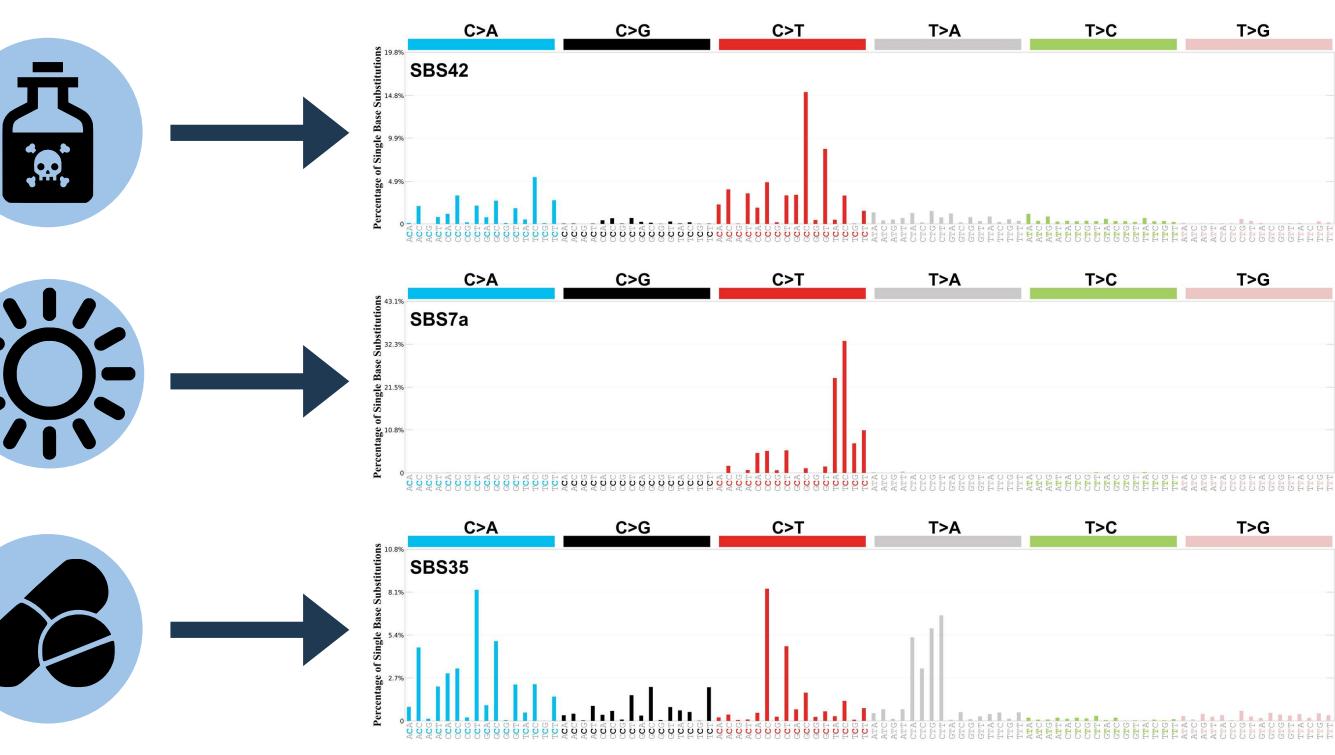
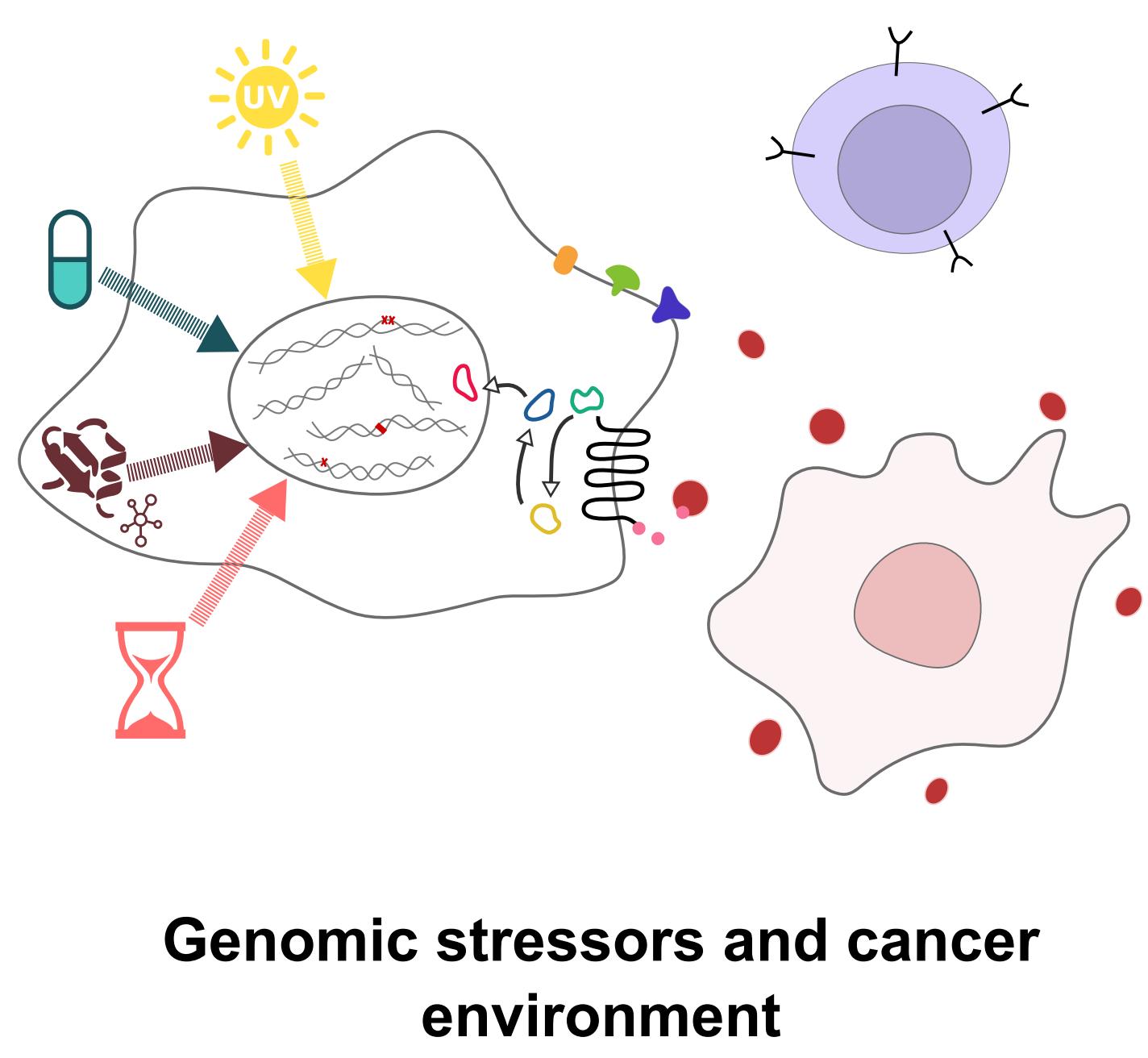
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## Introduction

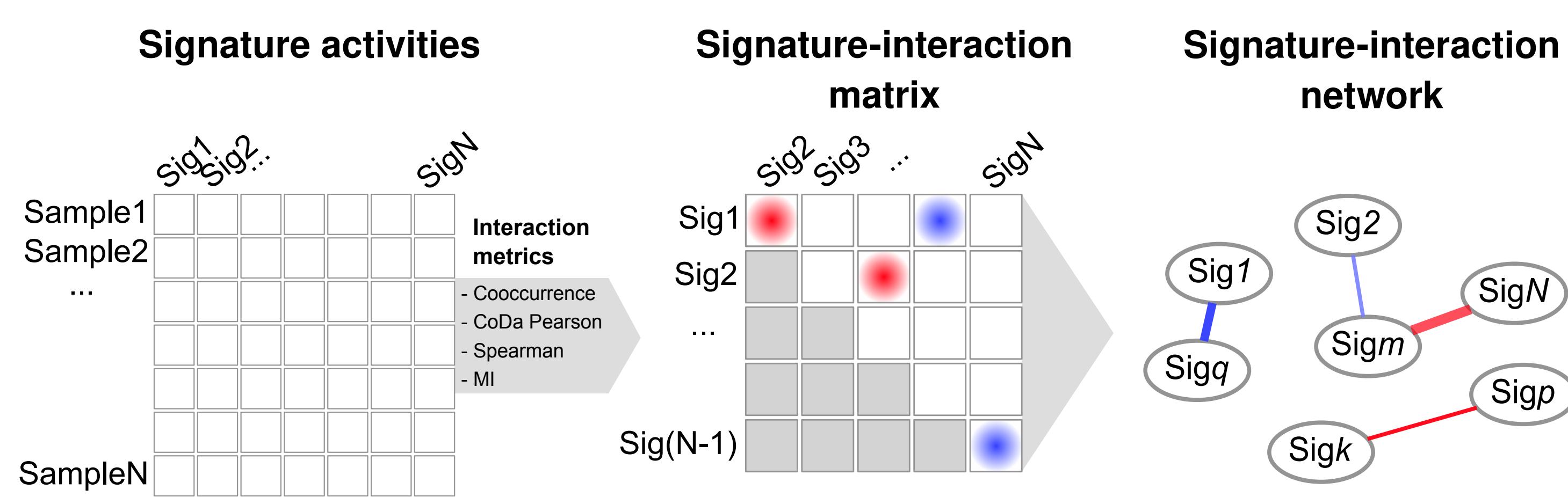
Genomes are constantly exposed to mutagenic processes which can lead to carcinogenesis. These exposures leave characteristic footprints - mutational signatures<sup>1,2</sup>. Multiple mutagenic processes can be active simultaneously, hence the cells can be challenged to repair mutations of different types and origin concurrently. Cancer genomes frequently harbor DNA repair deficiencies, hence they may be able to repair certain types of mutations, while not others. Further, cancer is constantly affected by the tumor microenvironment, the immune state, metabolic state, and potentially other tumor states. In this study, across TCGA and PCAWG we examine patterns of mutational signature interactions and other tumor characteristics with the aim of identifying interactions between signatures and tumor states that are tolerated by the cancer or are lethal and affect the disease outcome.



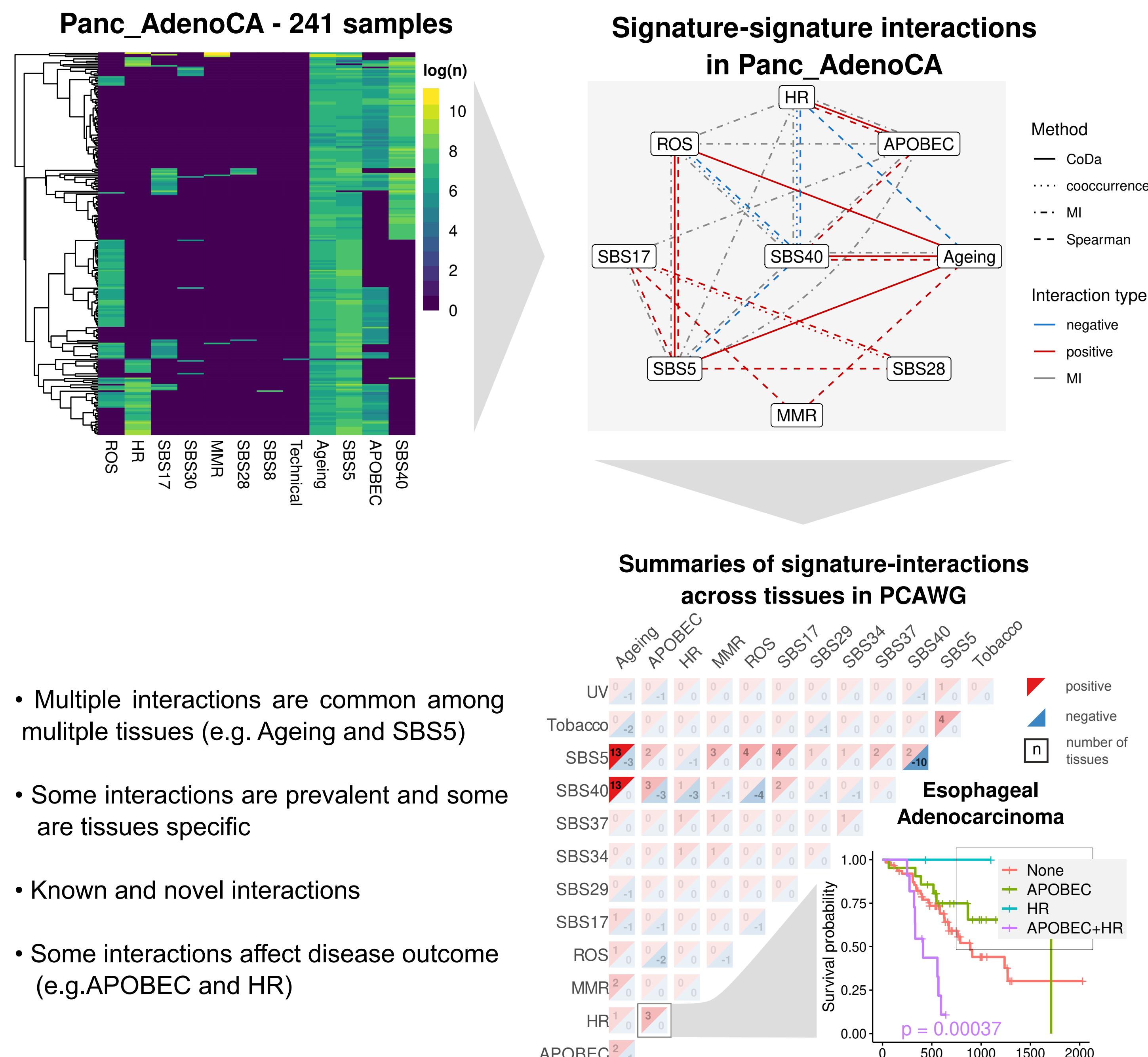
Exposures and DNA damaging processes can leave characteristic mutational signatures

## Signature-signature interactions

Signature interactions were calculated using several orthogonal techniques. Among them methods from compositional data analysis<sup>3</sup> (CoDa) to capture the compositional nature of signatures. Signature interactions were represented through interaction networks.



Signature activities heatmap and the resulting interaction-network reveal how individual metrics behave and contribute to interaction assessment.

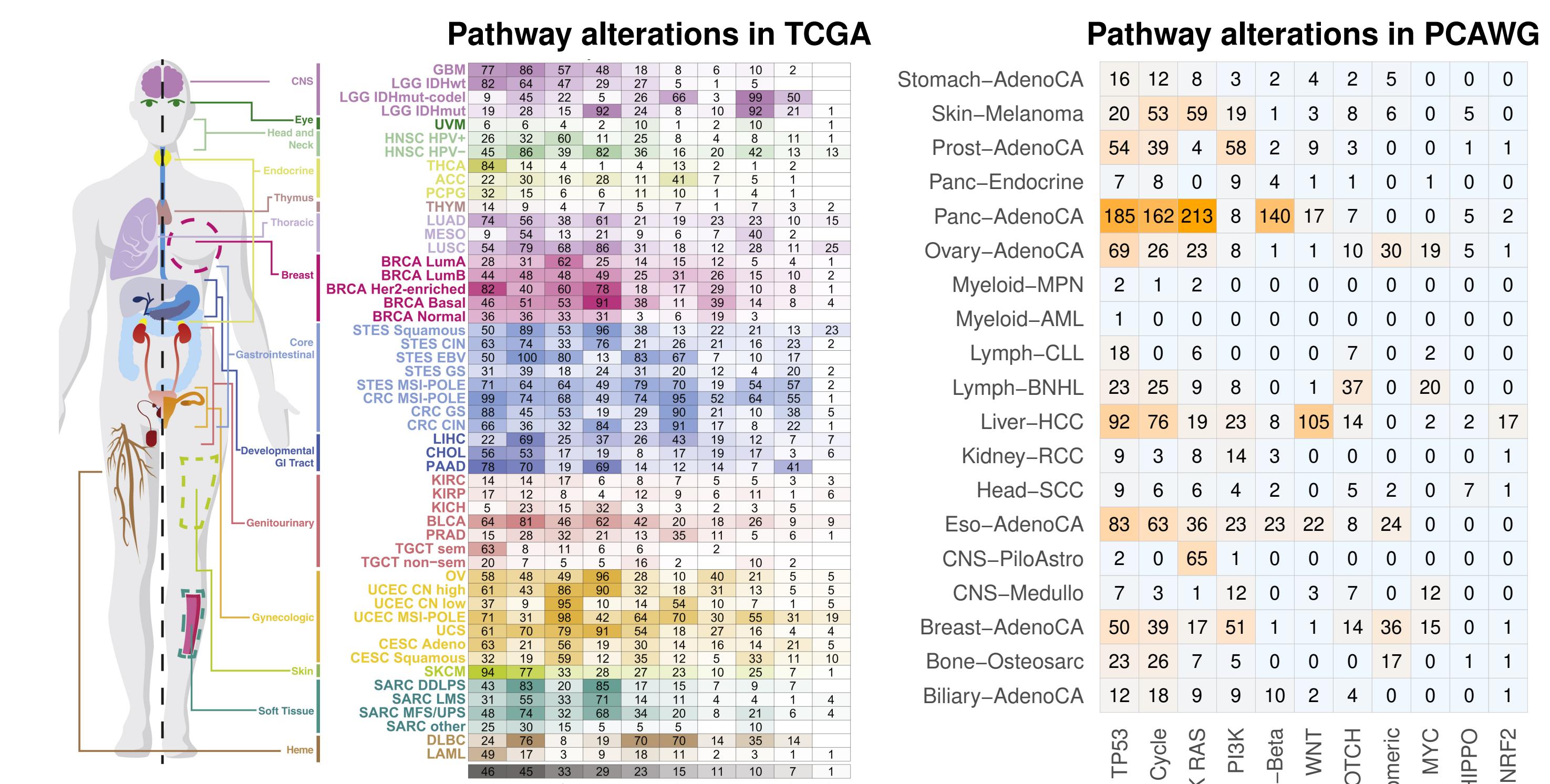


## References

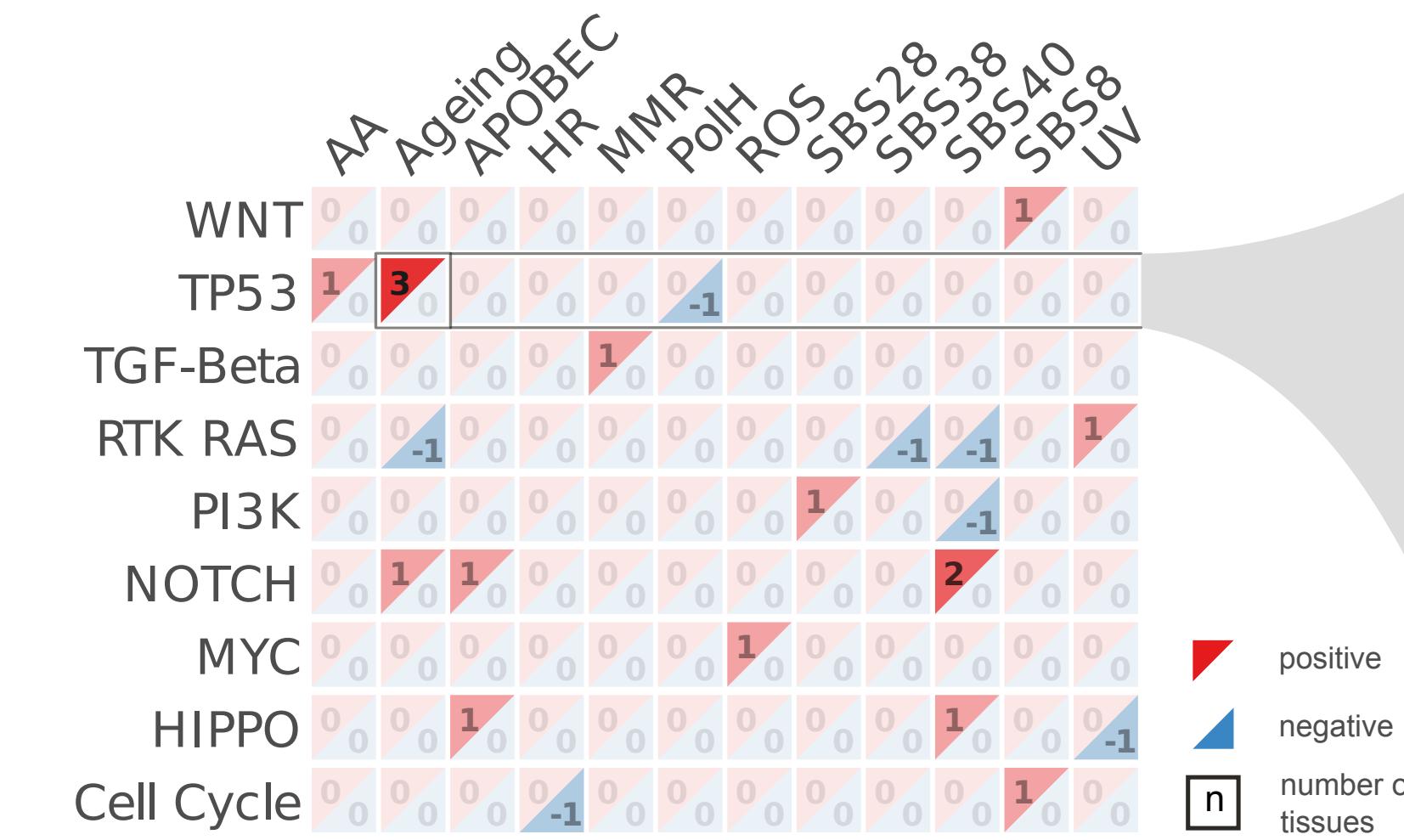
- Alexandrov et al., 2013, *Nature*, Signatures of mutational processes in human cancer
- Alexandrov et al., 2020, *Nature*, The repertoire of mutational signatures in human cancer
- Filzmoser et al., 2010, Springer Series in Statistics, Applied compositional data analysis

## Signature-oncogenic pathway interactions

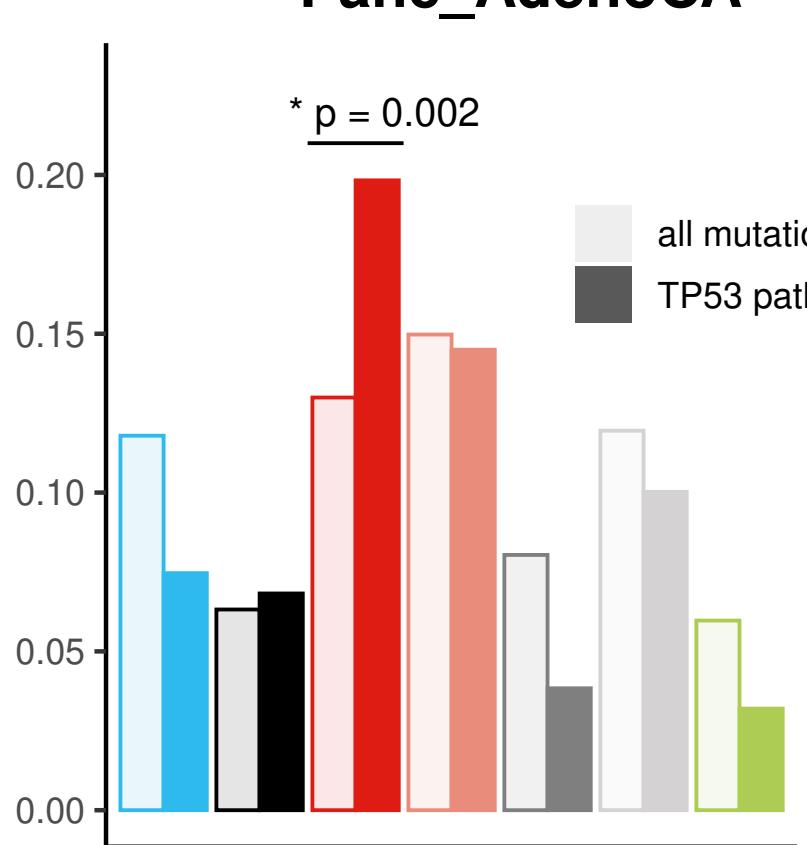
Analysis of TCGA<sup>4</sup> showed that about 89% of tumors have a driver alteration in one of 10 common oncogenic pathways. We mapped driver mutations in PCAWG to genes in these pathways and got a list of mutated pathways. Signature-pathway interactions were assessed using co-occurrence and regression models.



## Signature-pathway interactions across tissues

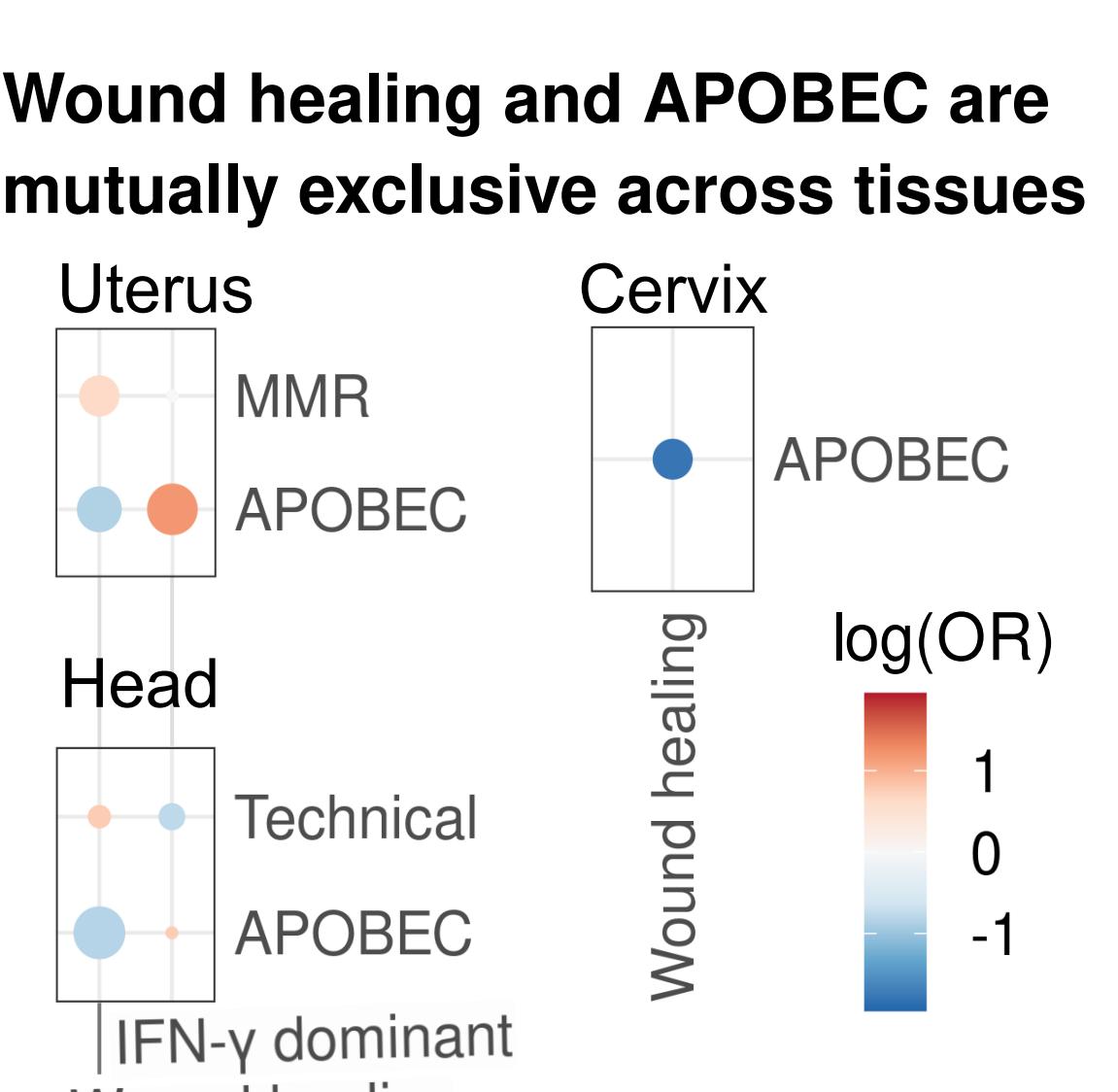
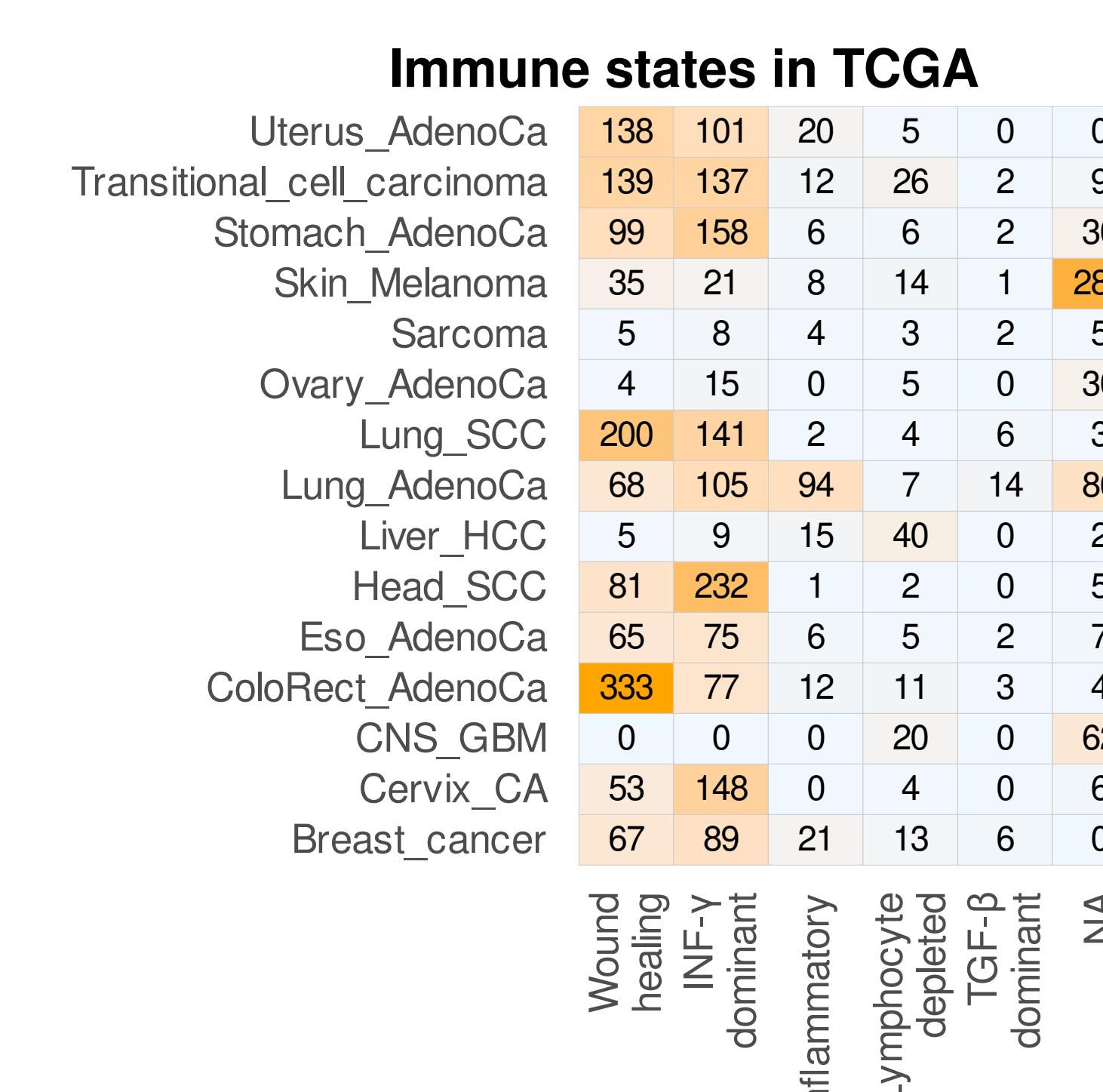


## The context of driver mutations in TP53 pathway in Panc\_AdenoCA



## Signature-immune state interactions

6 immune gene signatures were identified in TCGA samples. We trained and fit three different models and predicted the immune states in PCAWG samples. PCAWG and TCGA immune states were used for immune-signature interaction analysis.



## Immune states in PCAWG

Uterus_AdenoCa	11	38	1	1	0	0	0
Thy_AdenoCA	1	5	39	0	0	0	0
Stomach_AdenoCA	7	21	1	1	0	0	0
Skin_Melanoma	2	5	0	0	0	0	29
Prost_AdenoCA	0	2	13	2	0	0	3
Panc_AdenoCA	10	68	0	0	0	0	0
Ovary_AdenoCA	12	75	0	1	0	0	0
Lymph CLL	7	29	36	0	0	0	0
Lymph_BNHL	0	33	0	0	0	0	72
Lung_SCC	26	22	0	0	0	0	0
Lung_AdenoCA	9	20	7	1	0	1	0
Liver_HCC	2	20	33	45	0	0	0
Kidney_RCC	1	9	99	9	0	0	0
Kidney_ChRCC	2	0	38	3	2	0	0
Head(SCC)	7	36	0				