Passenger mutations in >2500 cancer genomes: Overall molecular functional impact

Mark Gerstein, Yale

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from **Lectures.GersteinLab.org**
& “tweetable” (via **@markgerstein**)
See last slide for more info.

No Conflicts for this Talk

Canonical model of drivers & passengers in cancer

Drivers
directly confer a selective growth advantage to the tumor cell.

A typical tumor contains 2-8 drivers.

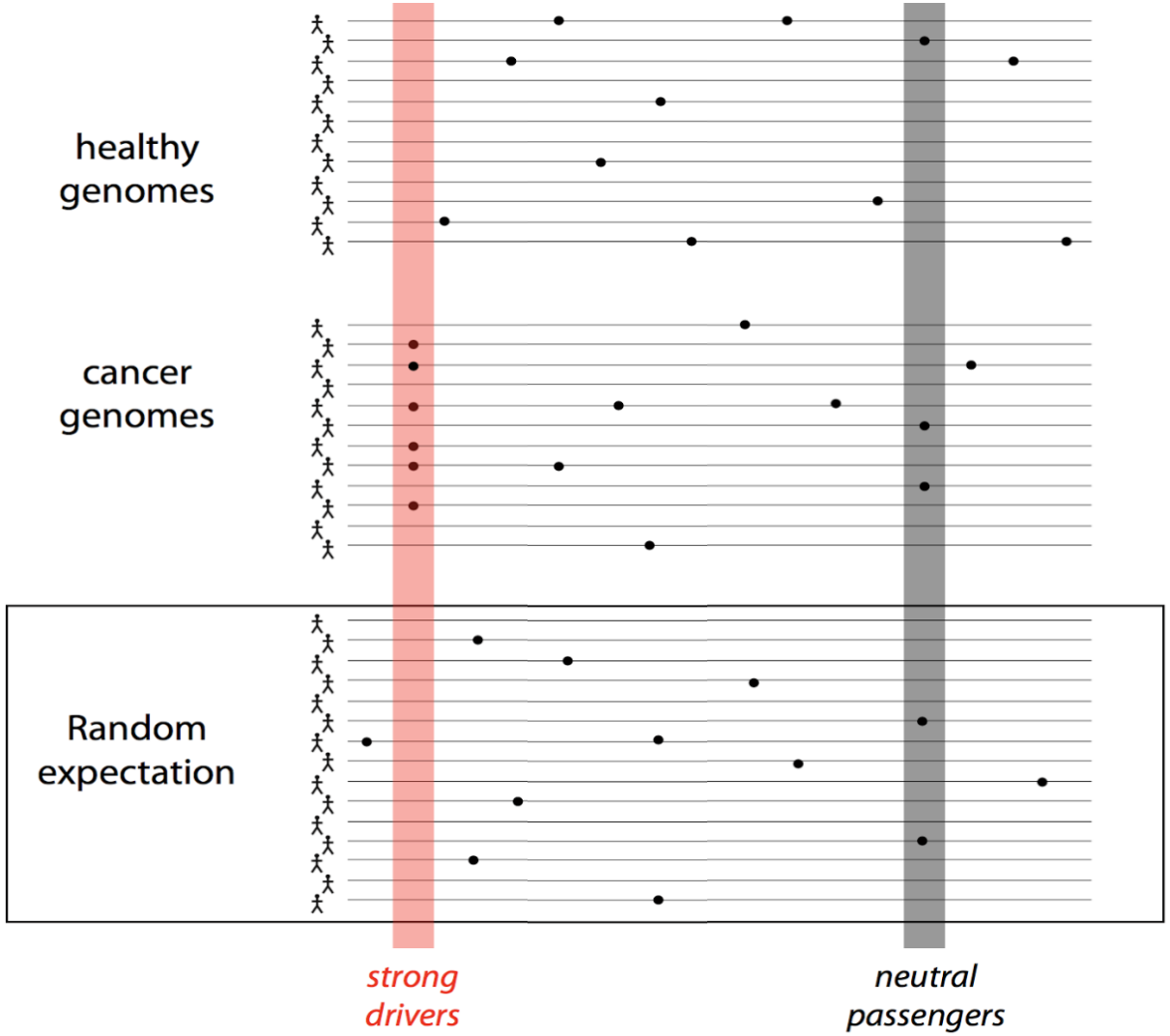
identified through signals of positive selection.

Existing cohorts of ~100s give enough power to identify

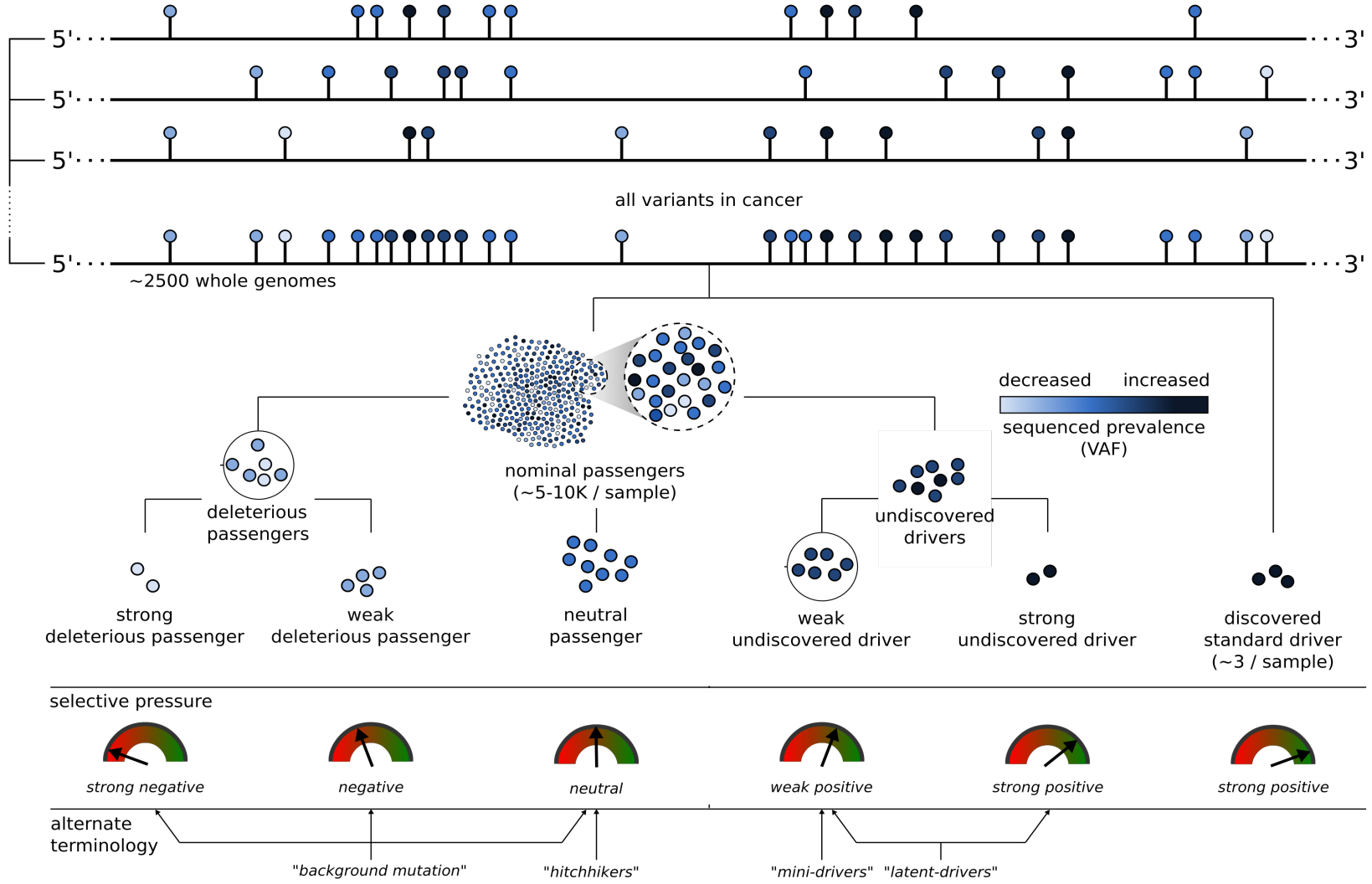
Passengers
Conceptually, a passenger mutation has no direct or indirect effect on tumor progression.

There are 1000s of passengers in a typical cancer genome.

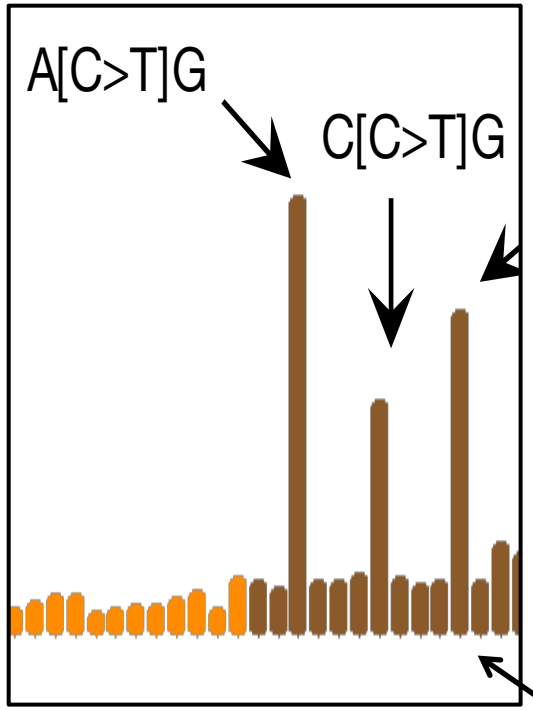
[Vogelstein Science 2013. 339:1546]

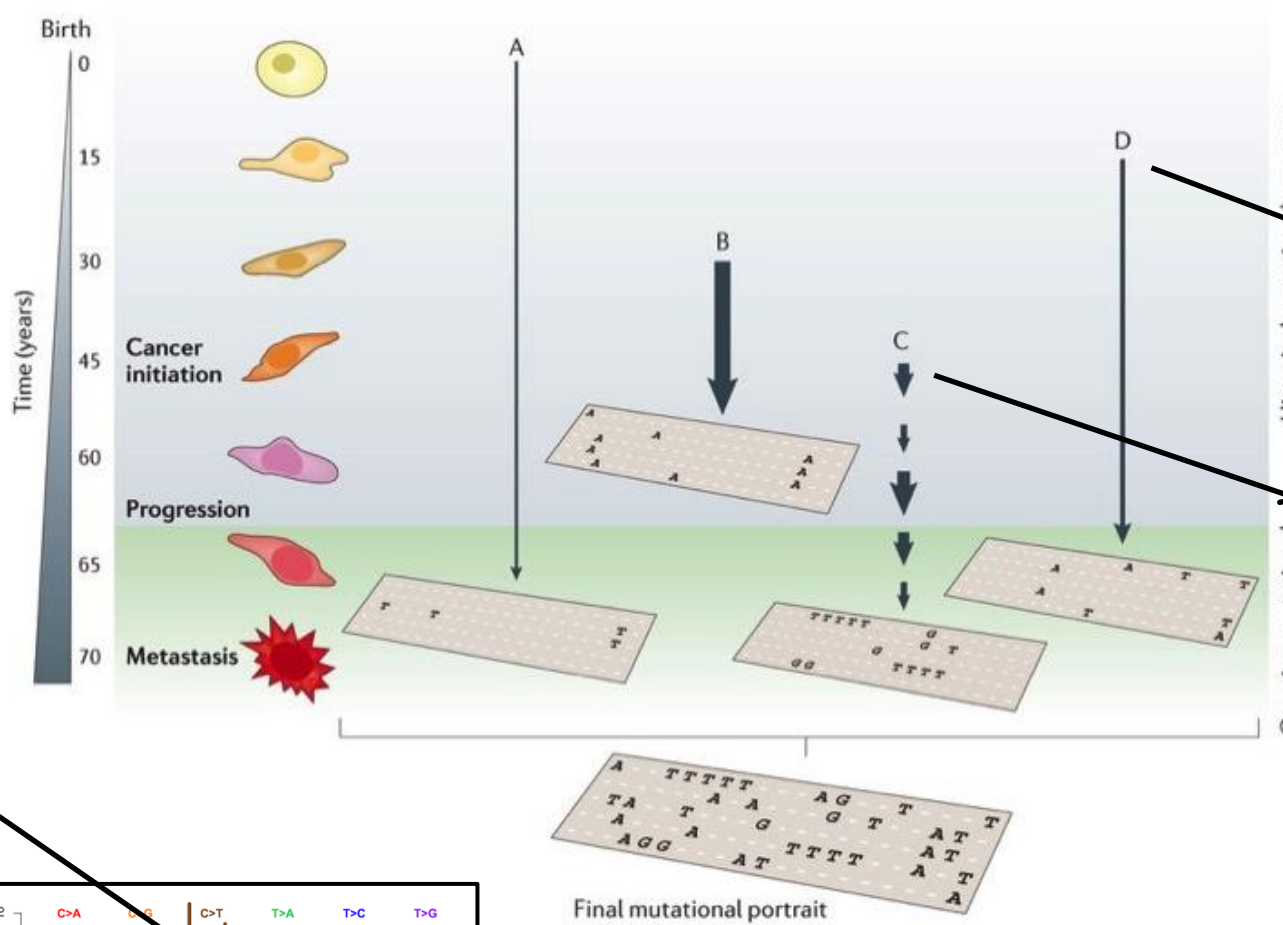


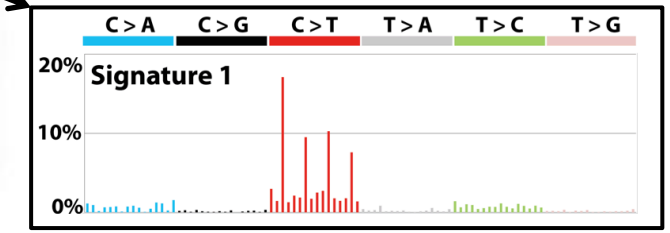
Conceptual extension of the canonical model of drivers & passengers

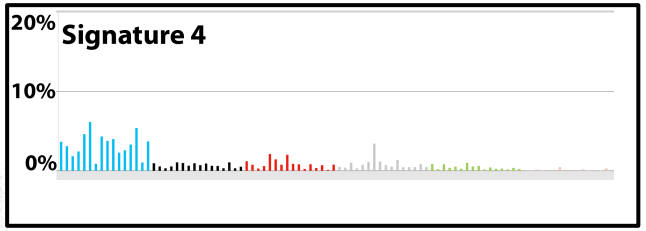


Mutational processes carry context-specific signatures

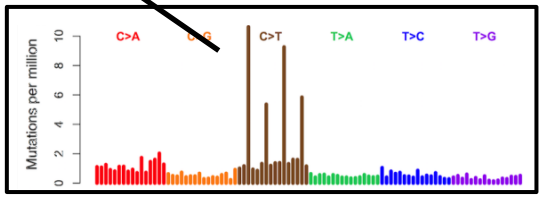








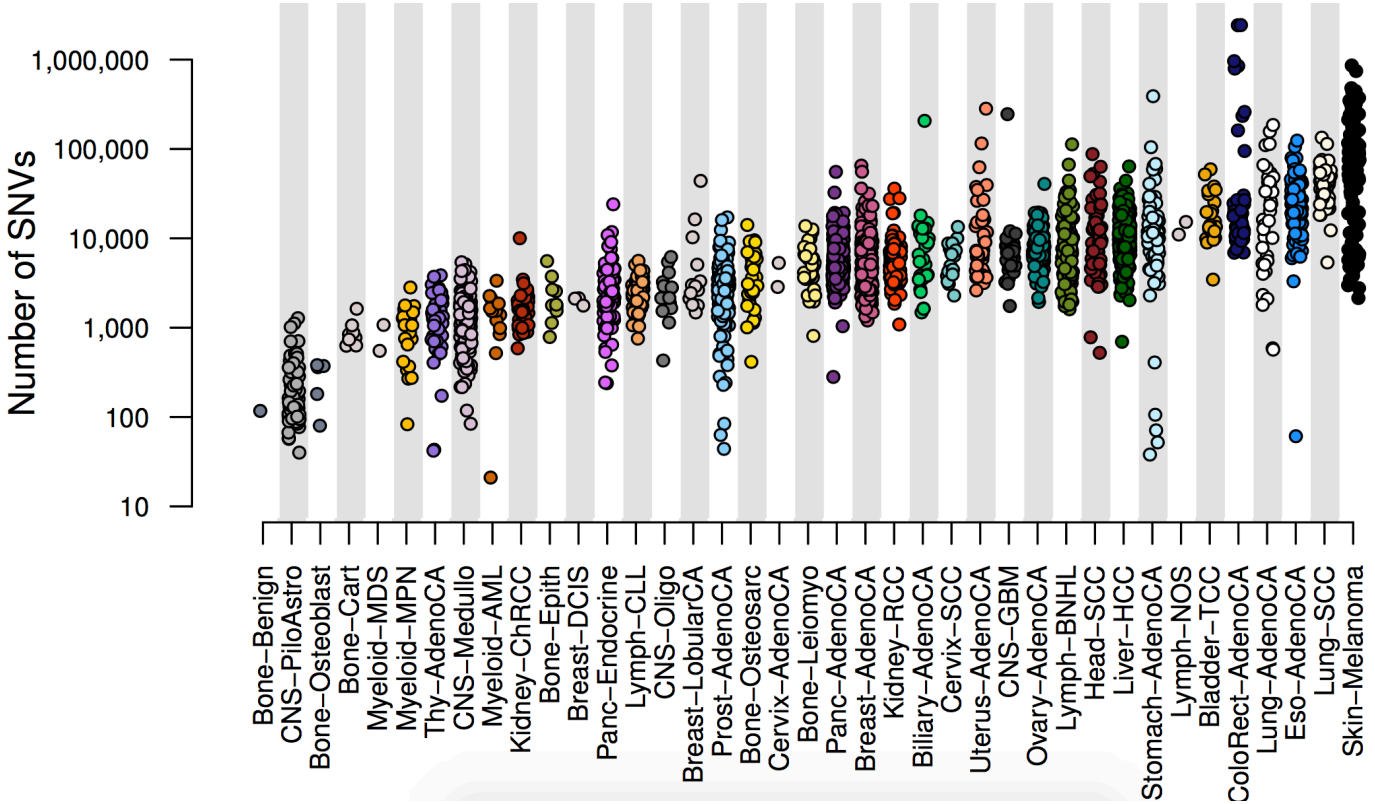
Mutation signature *inferred*



Mutation spectrum *observed*

[T. Helleday, S. Eshtad & S. Nik-Zainal,
Nature Reviews Genetics ('14), L. Alexandrov et al., Nature ('13)]

PCAWG : most comprehensive resource for cancer whole genome analysis



Adapted from Campbell et. al., bioRxiv ('17)

Goal of PCAWG:

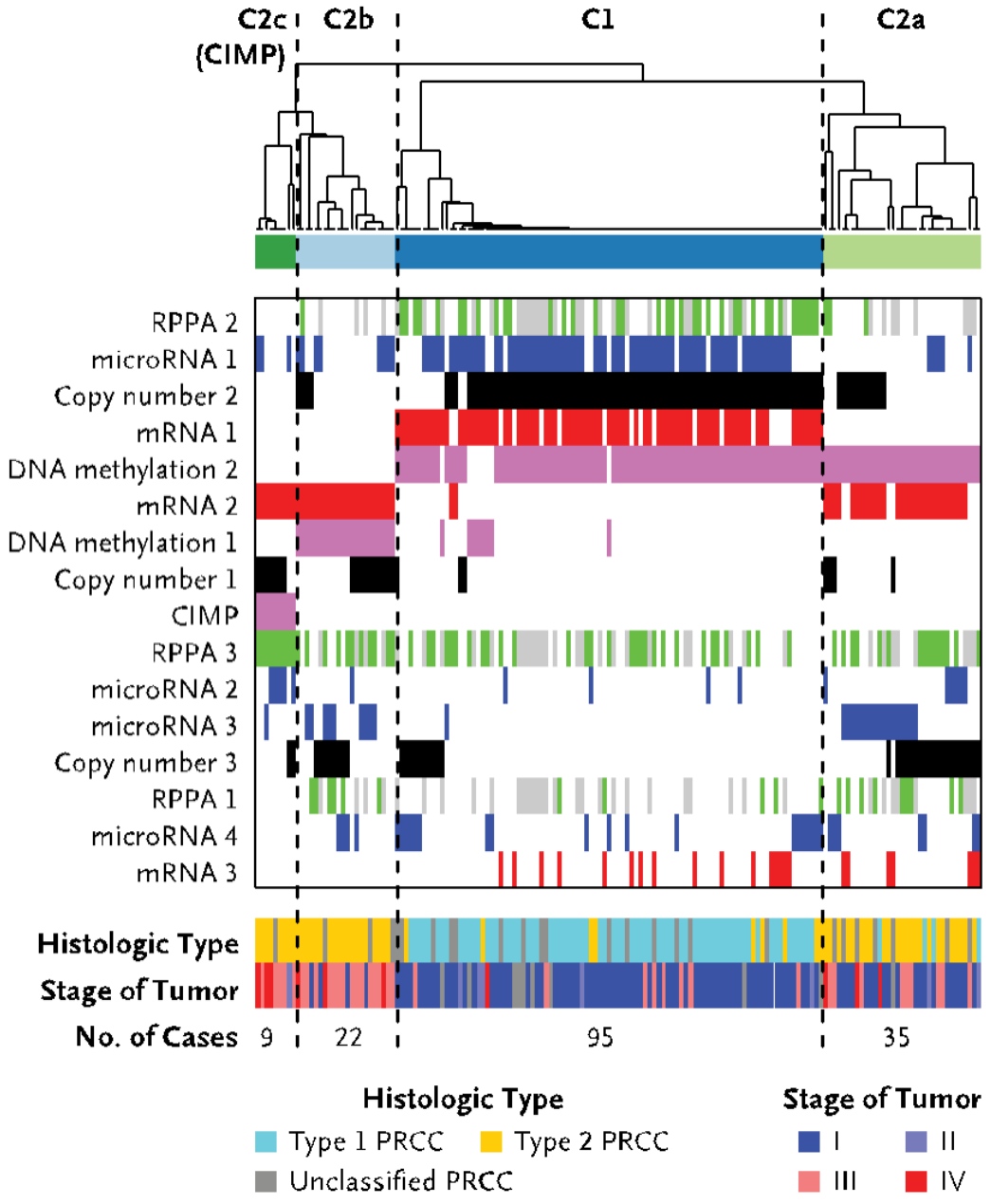
- To understand role of non-coding regions of cancer genomes in cancer progression.
- Union of TCGA-ICGC efforts

- Jointly analyzing ~2800 whole genome tumor/normal pairs
  - > 580 researchers
  - 16 thematic working groups
  - ~30M total somatic SNVs

PCAWG
PanCancer Analysis of WHOLE GENOMES

A case study: pRCC

- Kidney cancer lifetime risk of 1.6% & the papillary type (pRCC) counts for ~10% of all cases
- TCGA project sequenced 161 pRCC exomes & classified them into subtypes
- Also, 35 WGS of TN pairs



[Cancer Genome Atlas Research Network N Engl J Med. ('16)]

Passenger mutations in >2500 cancer genomes: Overall molecular functional impact

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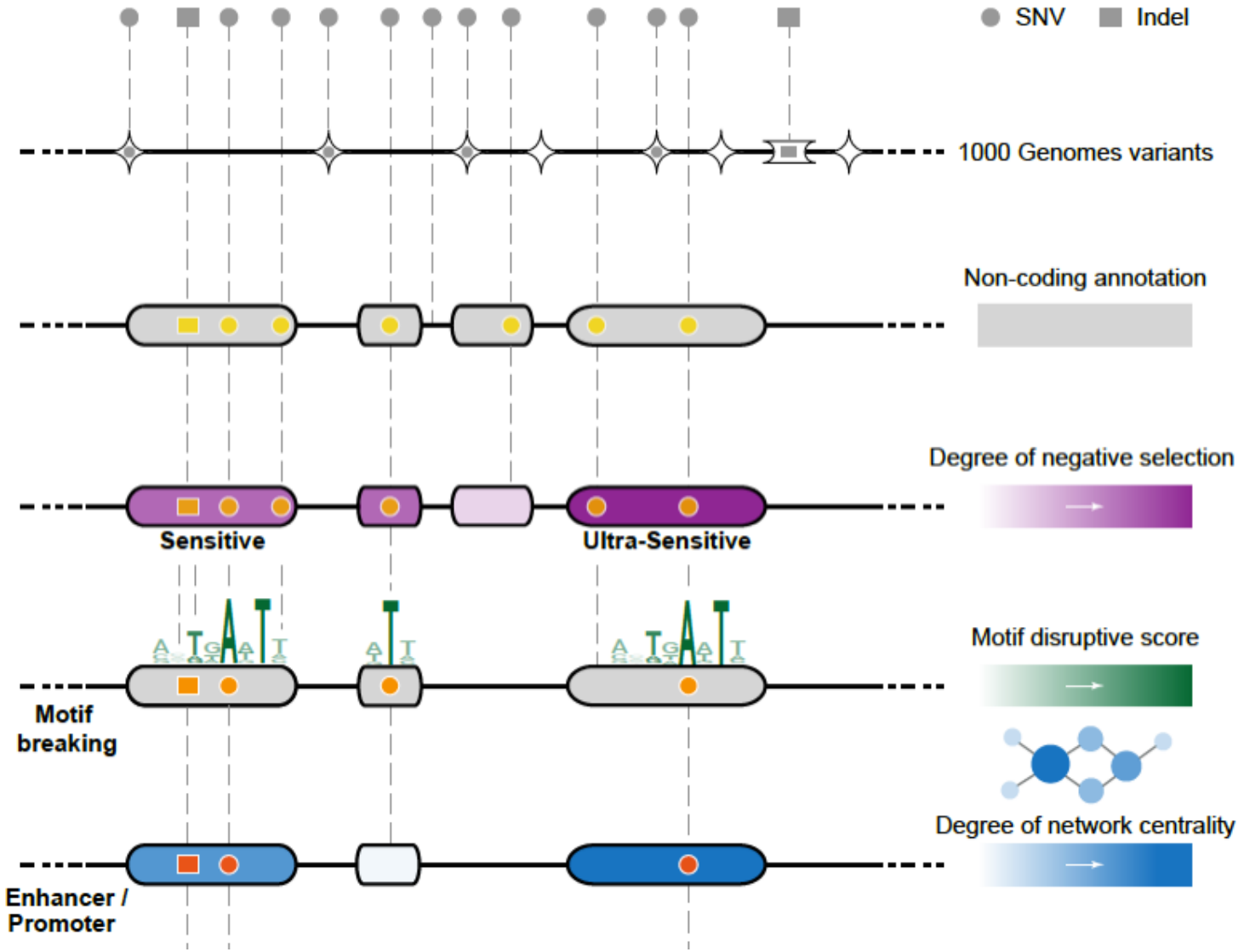
Funseq: a flexible framework to determine functional impact & use this to prioritize variants

Annotation (tf binding sites open chromatin, ncRNAs) & Chromatin Dynamics

Conservation (GERP, allele freq.)

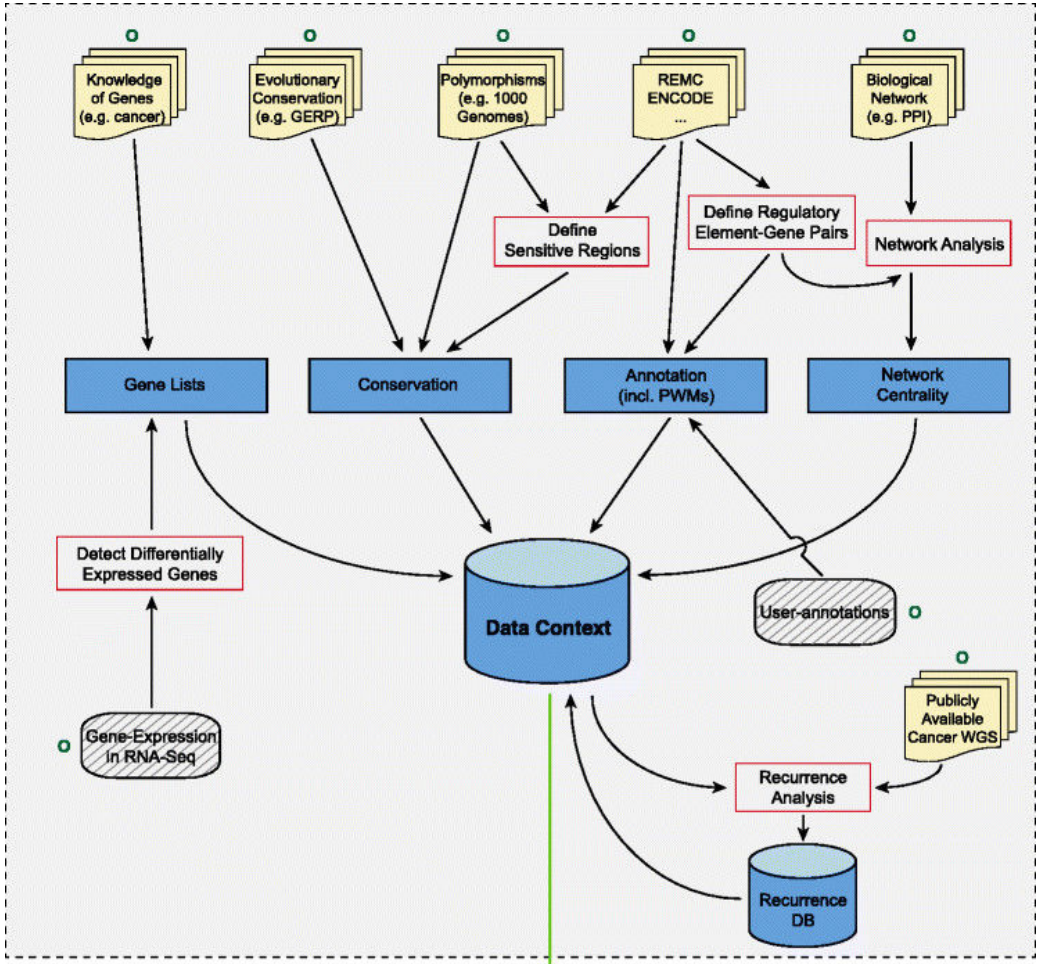
Mutational impact (motif breaking, Lof)

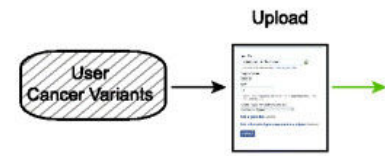
Network (centrality position)

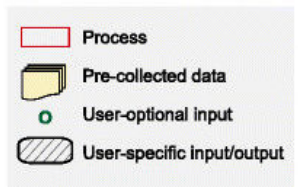


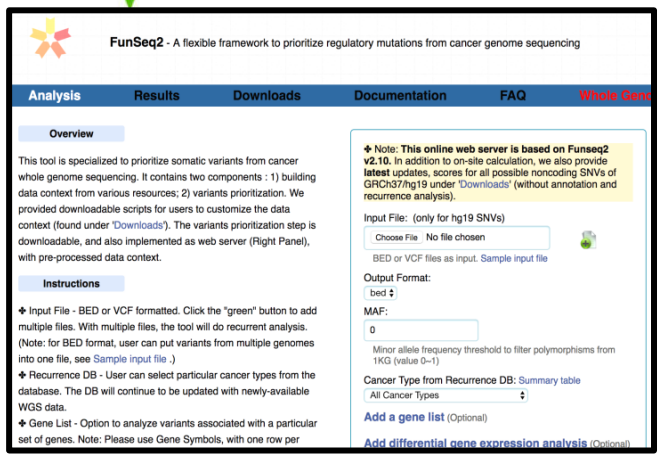
[Fu et al., GenomeBiology ('14), , Khurana et al., Science ('13)]

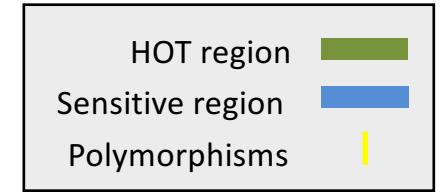
FunSeq.gersteinlab.org











Genome

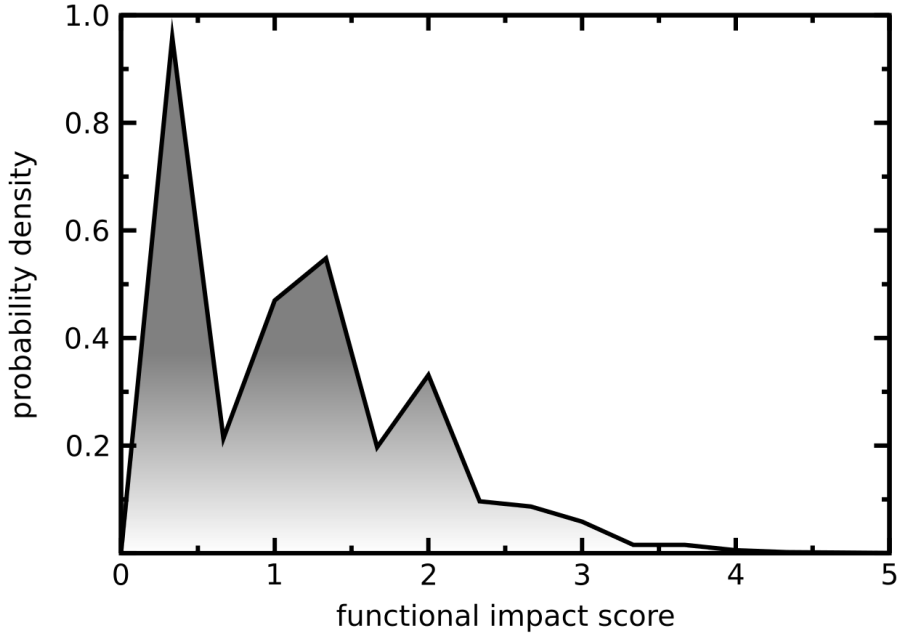
$$w_d = 1 + p_d log_2 p_d + (1 - p_d) log_2 (1 - p_d)$$

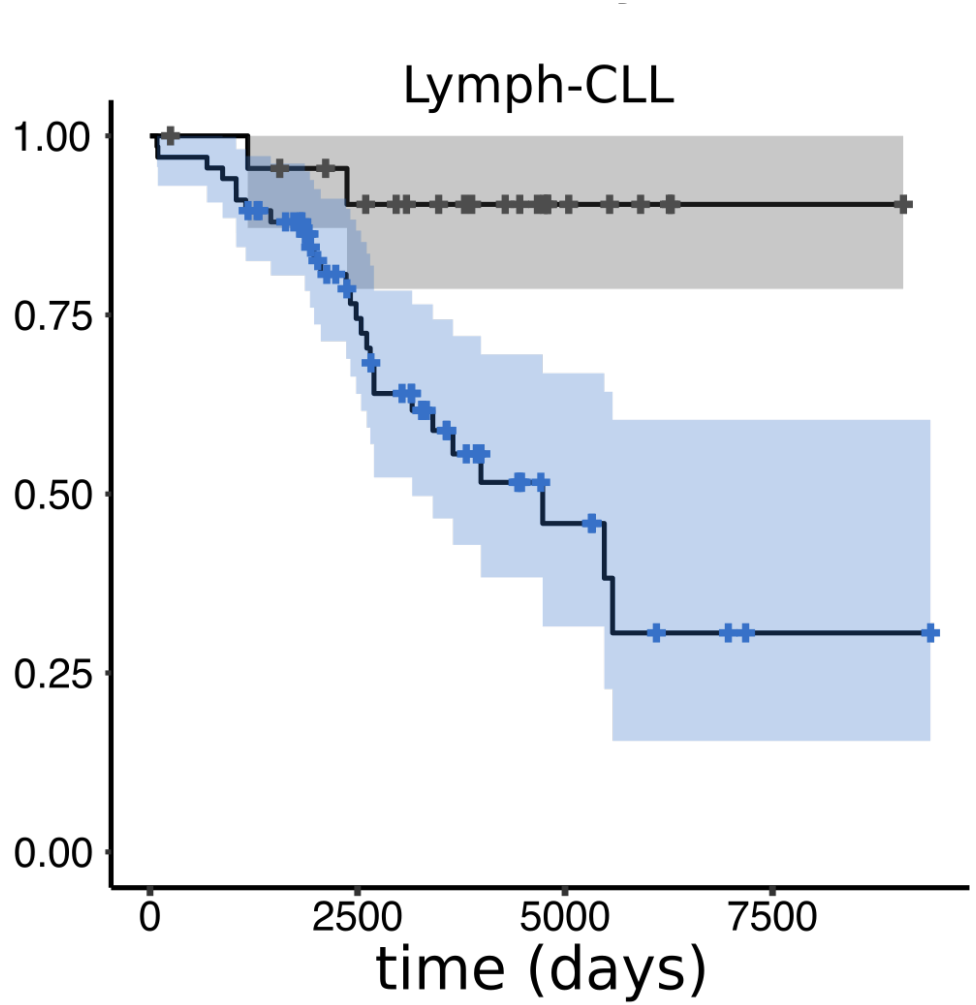
- Entropy based method for weighting consistently many genomic features

- Practical web server
- Submission of variants & pre-computed large data context from uniformly processing large-scale datasets

[Fu et al., GenomeBiology ('14)]

Overall functional impact distribution of PCAWG mutations

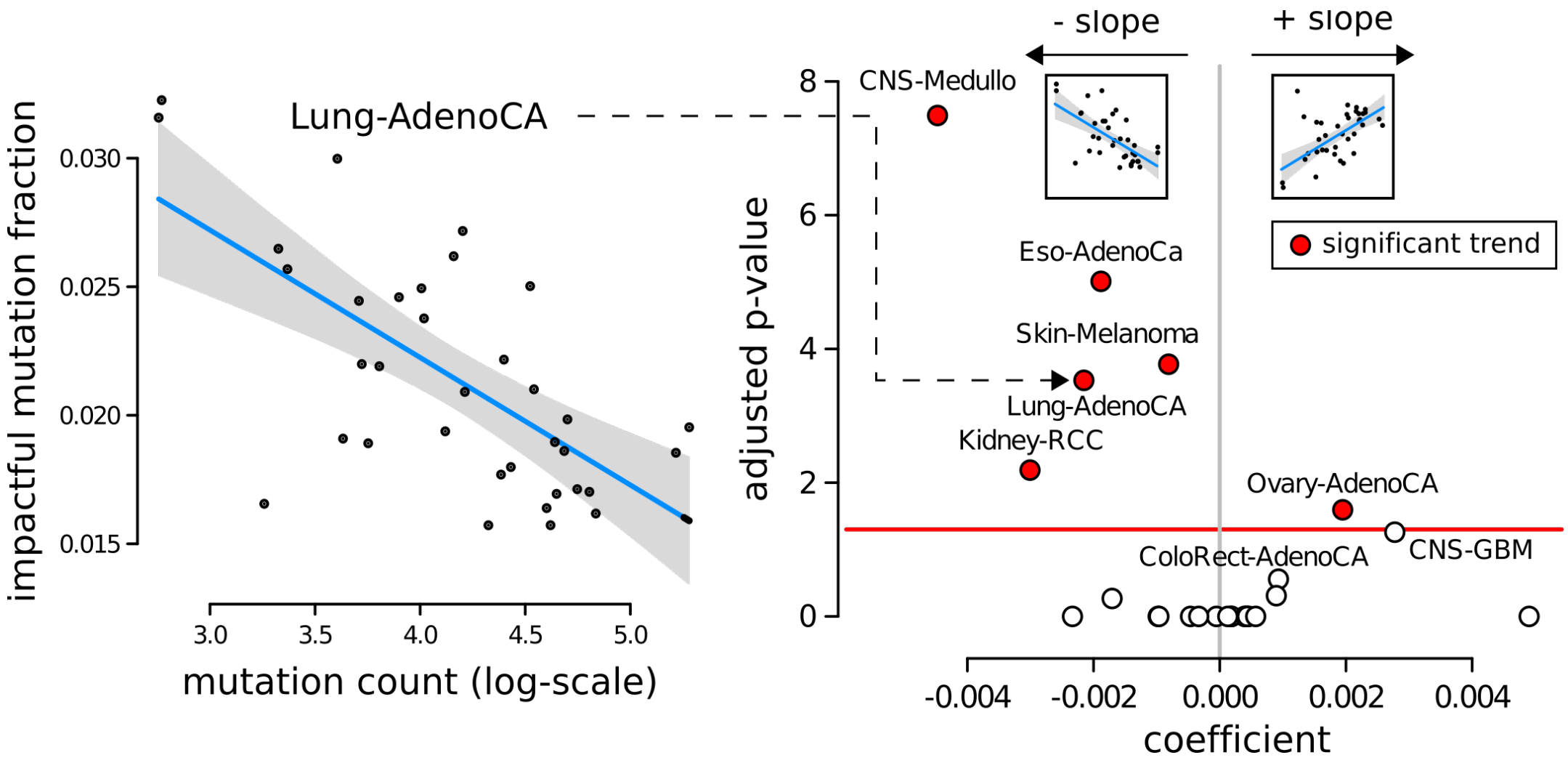




- Funseq molecular functional impact of ~30M variants in >2500 PCAWG samples

Division of PCAWG Lymph-CLL cohort based on average impact of non-driver variants (high v low)

In many PCAWG cohorts, we observe the fraction of impactful "passengers" decreases with increase in total mutation burden.



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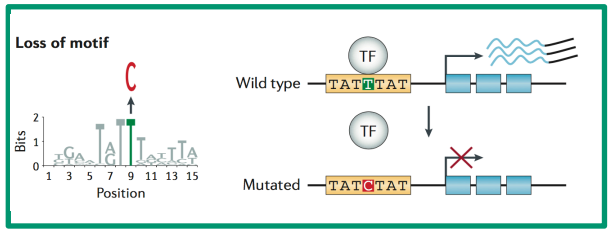
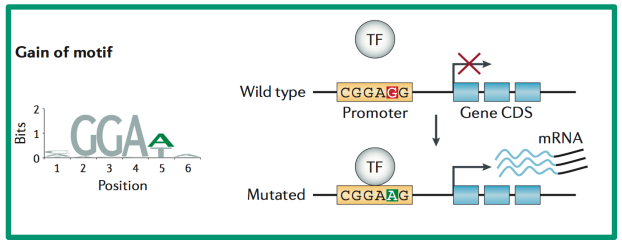
Mutational burdening of TF-subnetworks due to SNVs breaking & creating binding sites



LOSS



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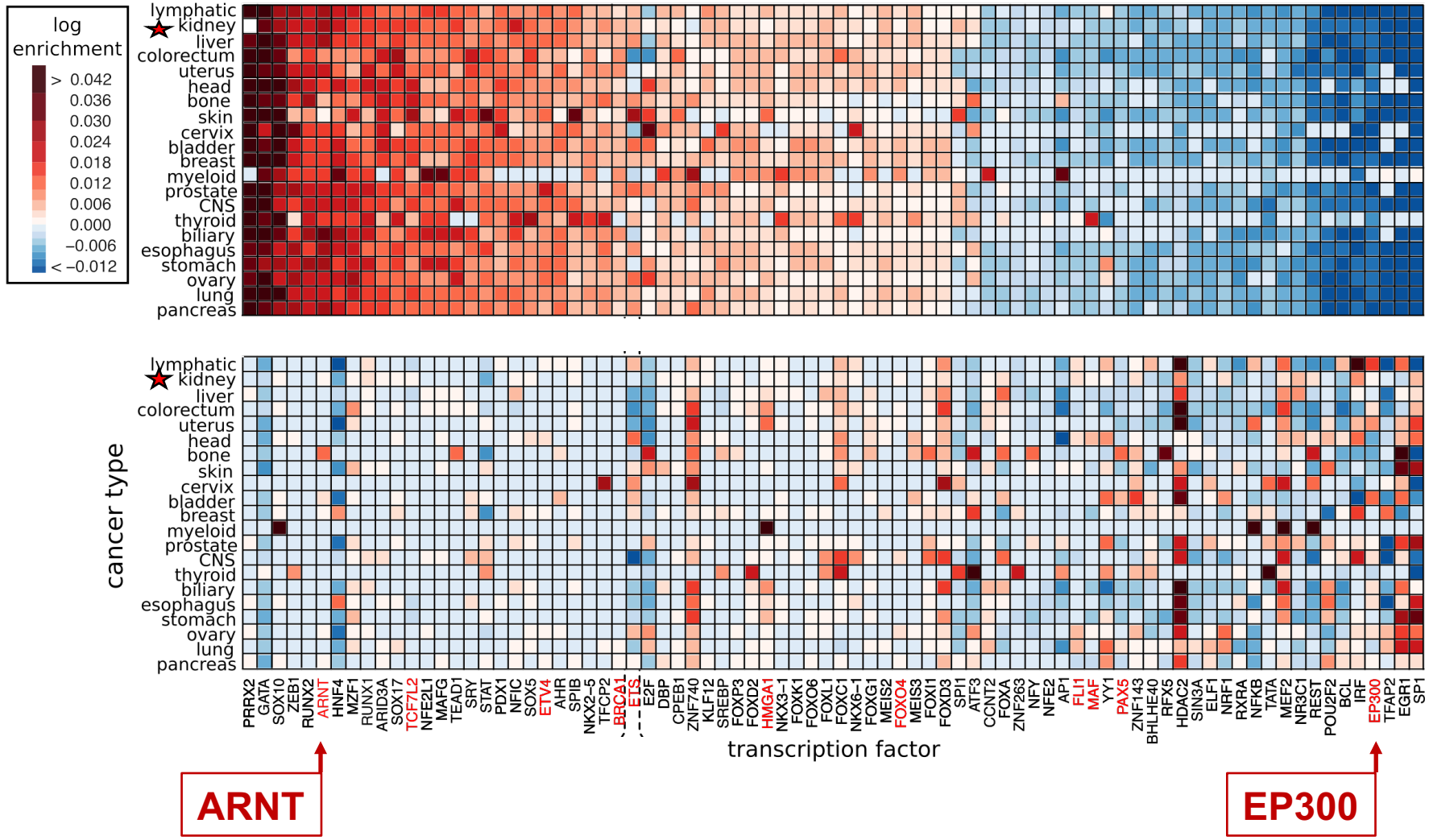
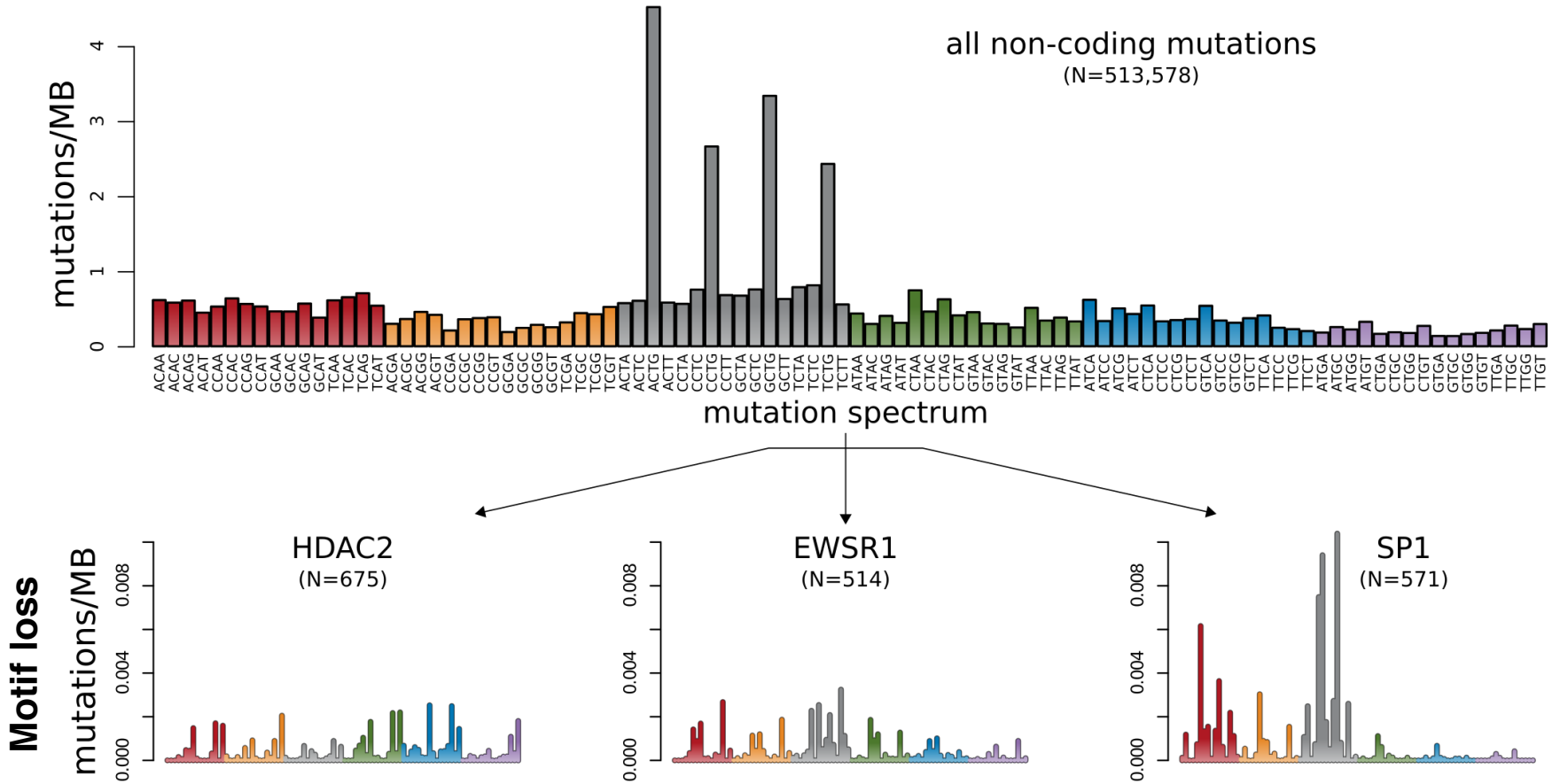


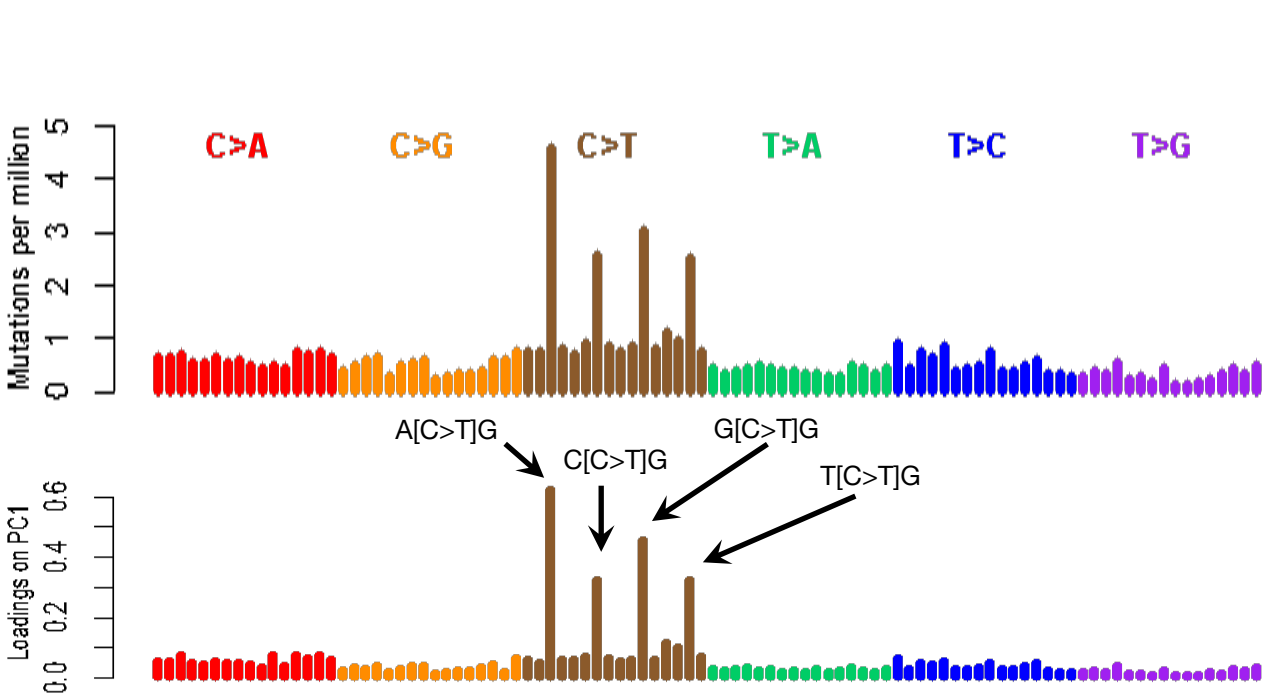
Khurana et. al., Nature Reviews Genetics ('16)

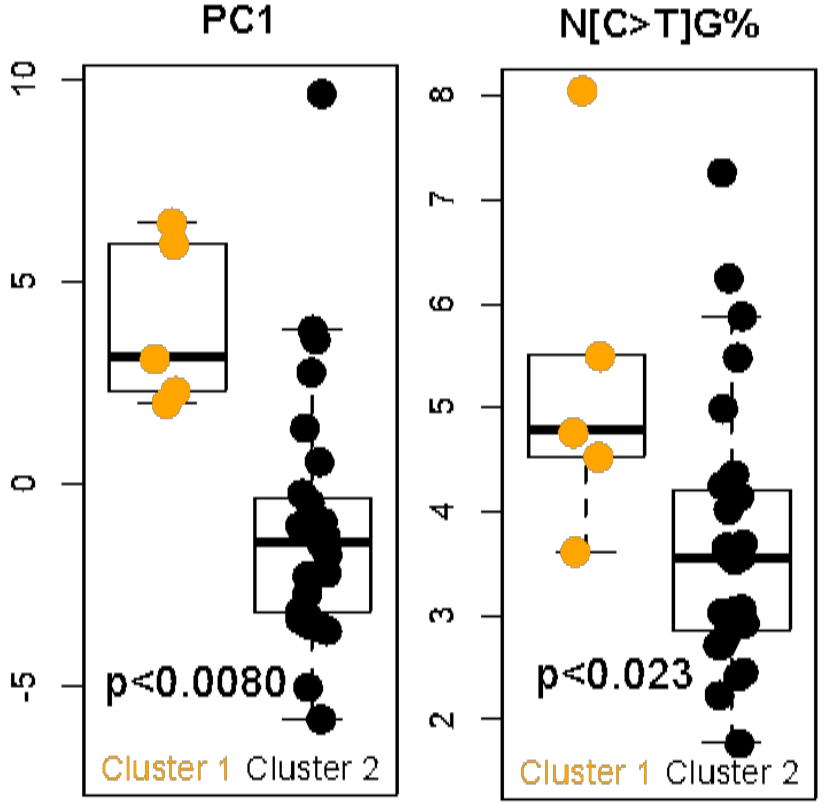
Kidney cancer as an example: differential TF burdening correlates with mutational spectrum



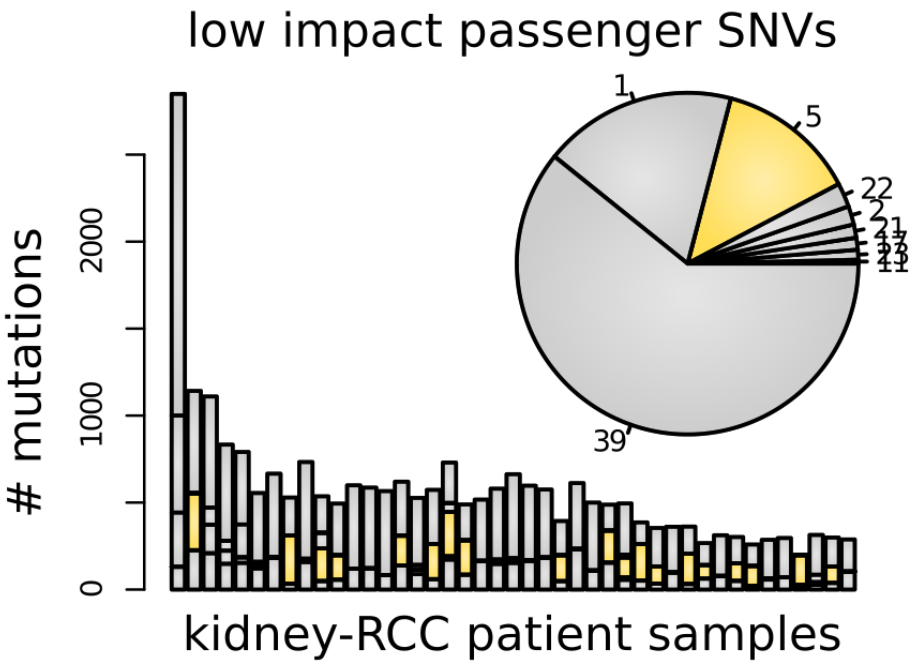
CpGs drive inter-patient variation in pRCC mutational spectra

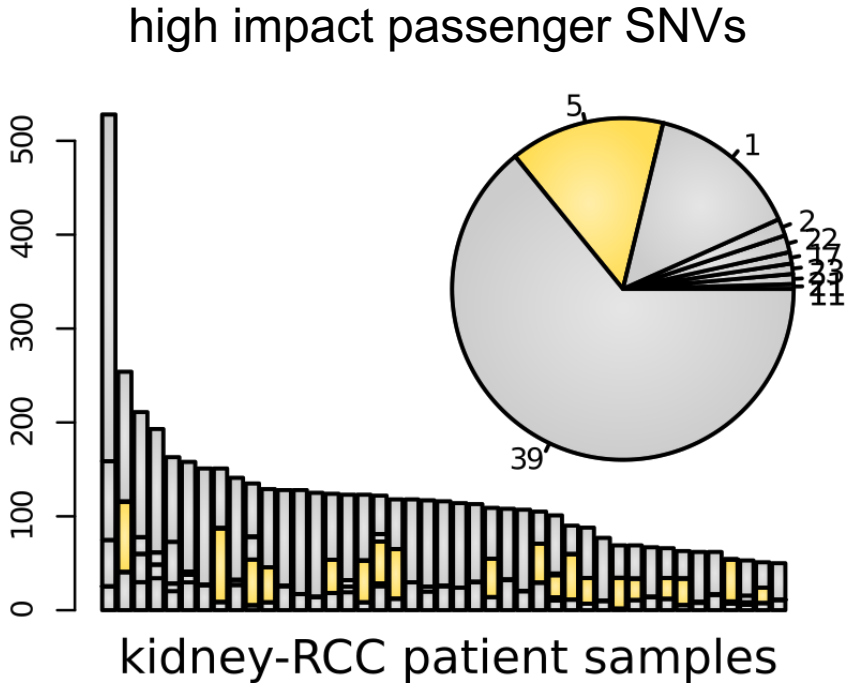
- The loadings on PC1 are mostly [C>T]G
- Confirmed by higher C>T% in CpGs in the hypermethylated group (cluster1)



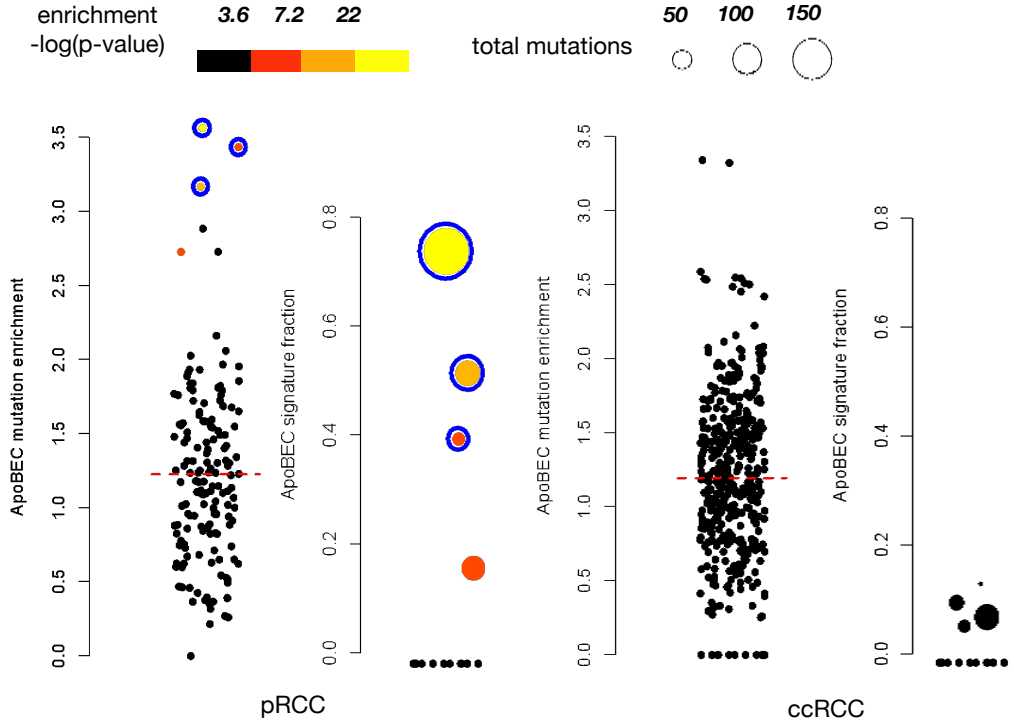


[S. Li, B. Shuch and M. Gerstein PLOS Genetics ('17)]



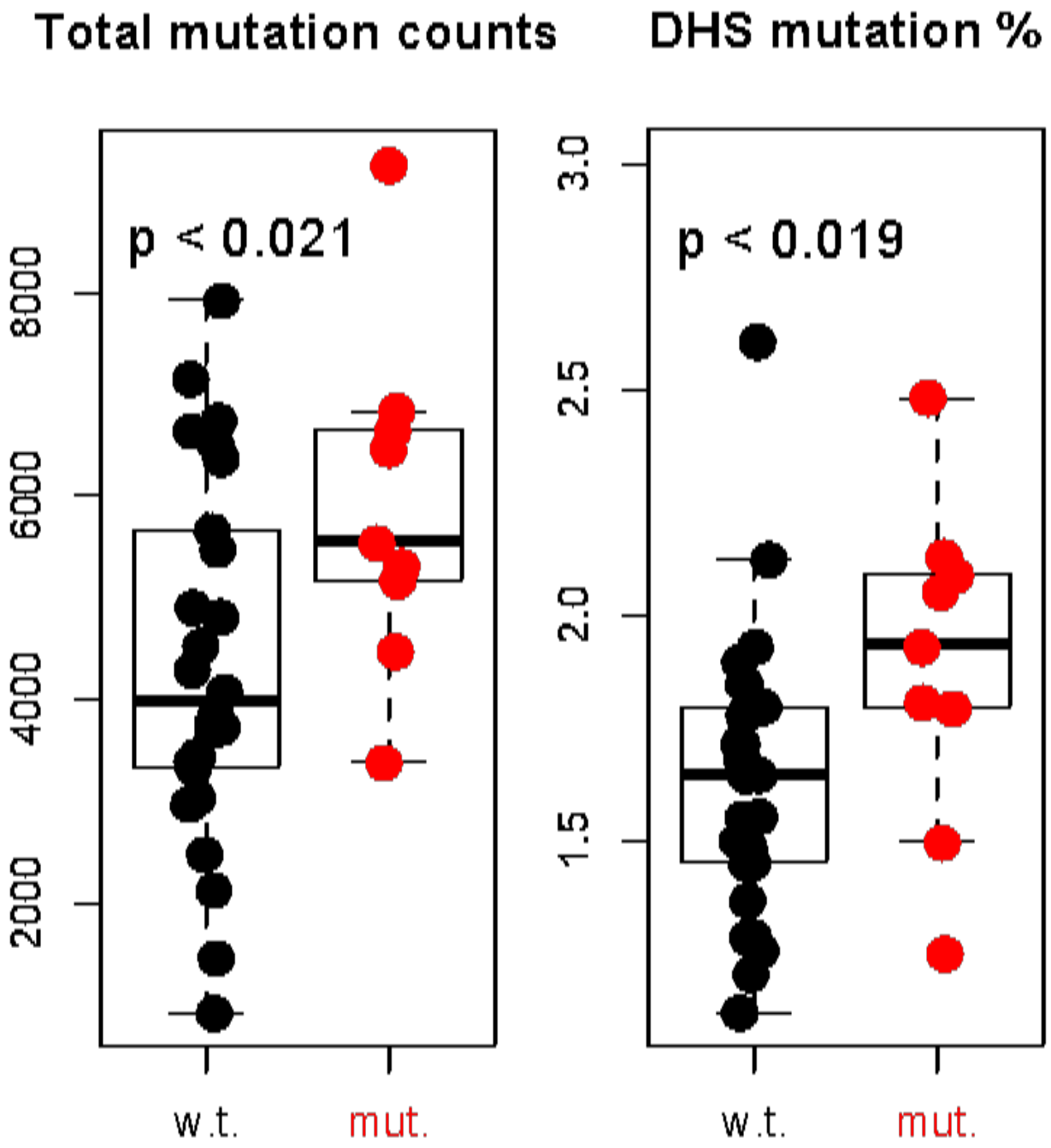


Signatures in pRCC



- Signatures burden the genome disproportionally
- We found 1 pRCC has ApoBEC signature, but nothing in a larger ccRCC cohort

[S. Li, B. Shuch and M. Gerstein PLOS Genetics ('17)]



Key mutation affects mutational landscape which, in turn, affects overall burden in pRCC

- Chromatin remodeling defect ("mut") leads to more mutations in open chromatin (raw number & fraction) in those pRCC cases w/ the mutation

[S. Li, B. Shuch and M. Gerstein PLOS Genetics ('17)]

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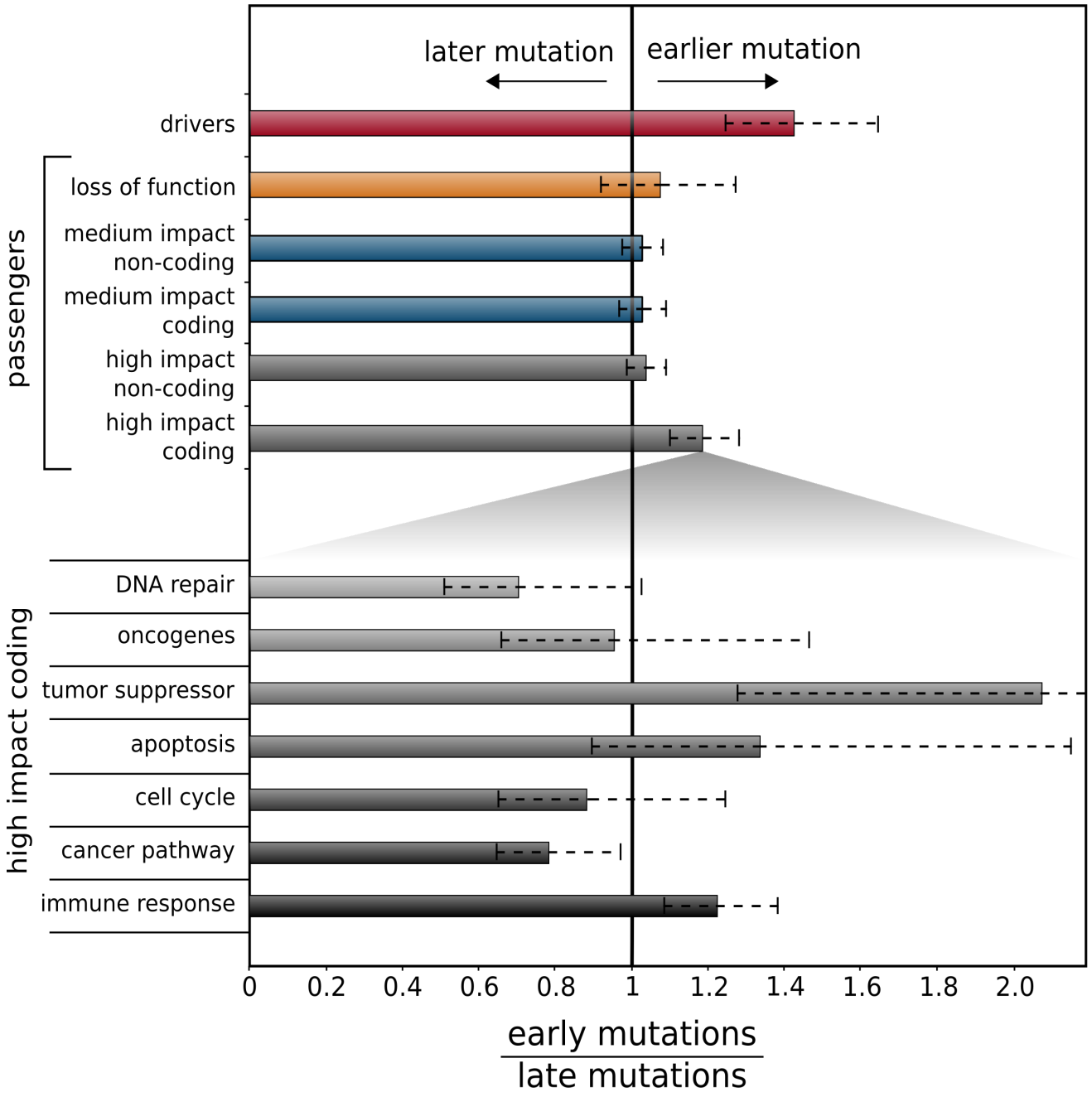
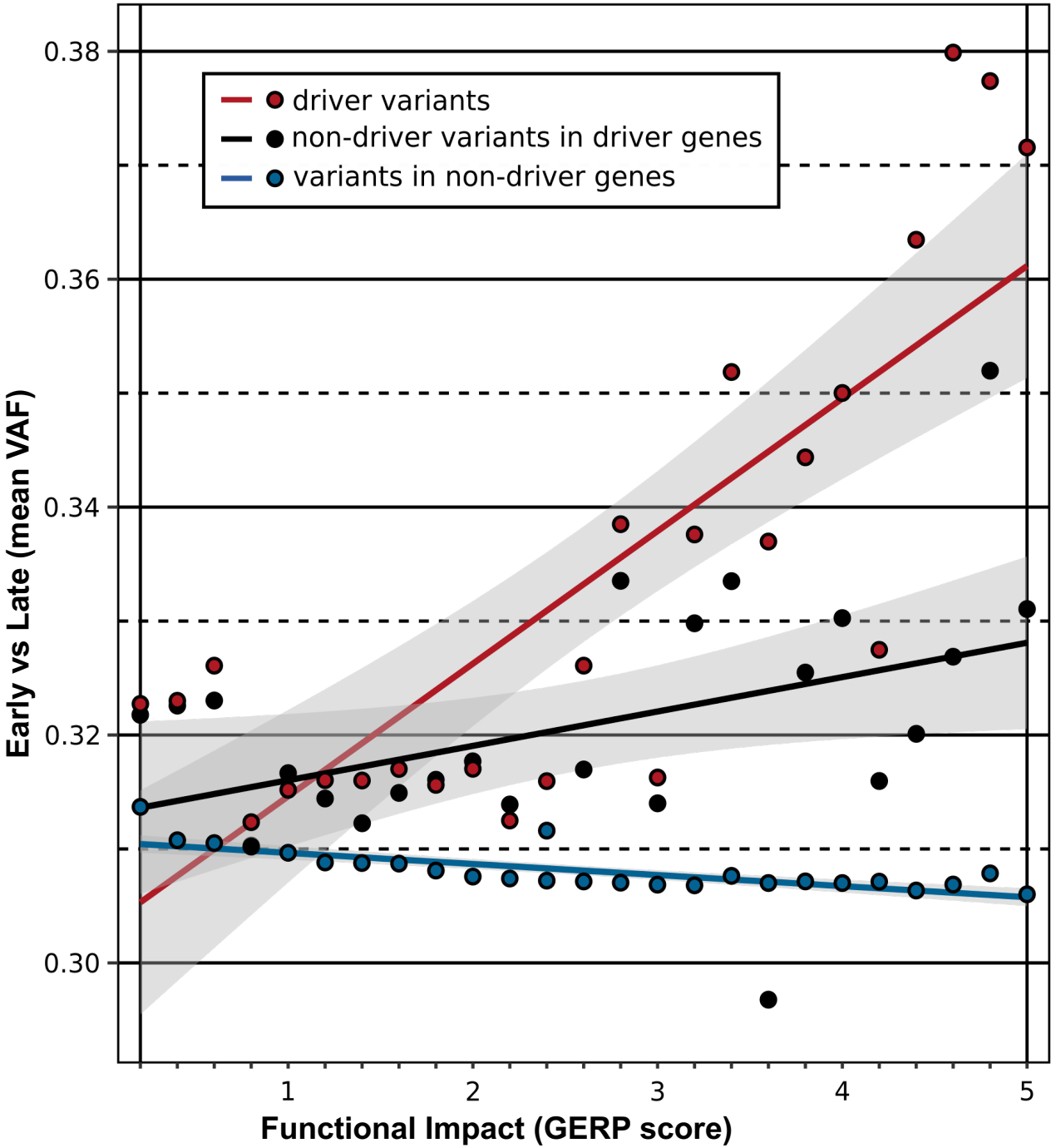


Sub-clonal architecture of mutations in PCAWG

As expected, drivers are enriched in earlier subclones. Overall, no such enrichment among passengers.

High impact passengers are slightly enriched among early subclones.

Particularly, passengers in tumor suppressor (in contrast to oncogenes, which require specific mutations).



Continuous correlation of functional impact & VAF

Among mutations in driver genes:
higher impact mutation
=> spreads to more cells.

Still true after removing all known driver variants from driver genes.
(Latent drivers?)

Outside driver genes:
higher impact mutation
=> spreads to fewer cells
(Deleterious passengers?)

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Functional impact in PCAWG (PanCancer.info)

S **Kumar,** J **Warrell**, W Meyerson, P McGillivary, L Salichos, S Li,
A Fundichely, E Khurana, C Chan, M Nielsen,C Herrman,
A Harmanci, L Lochovsky,Y Zhang, X Li,

PCAWG Drivers & Functional Interpretation Group, ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Network

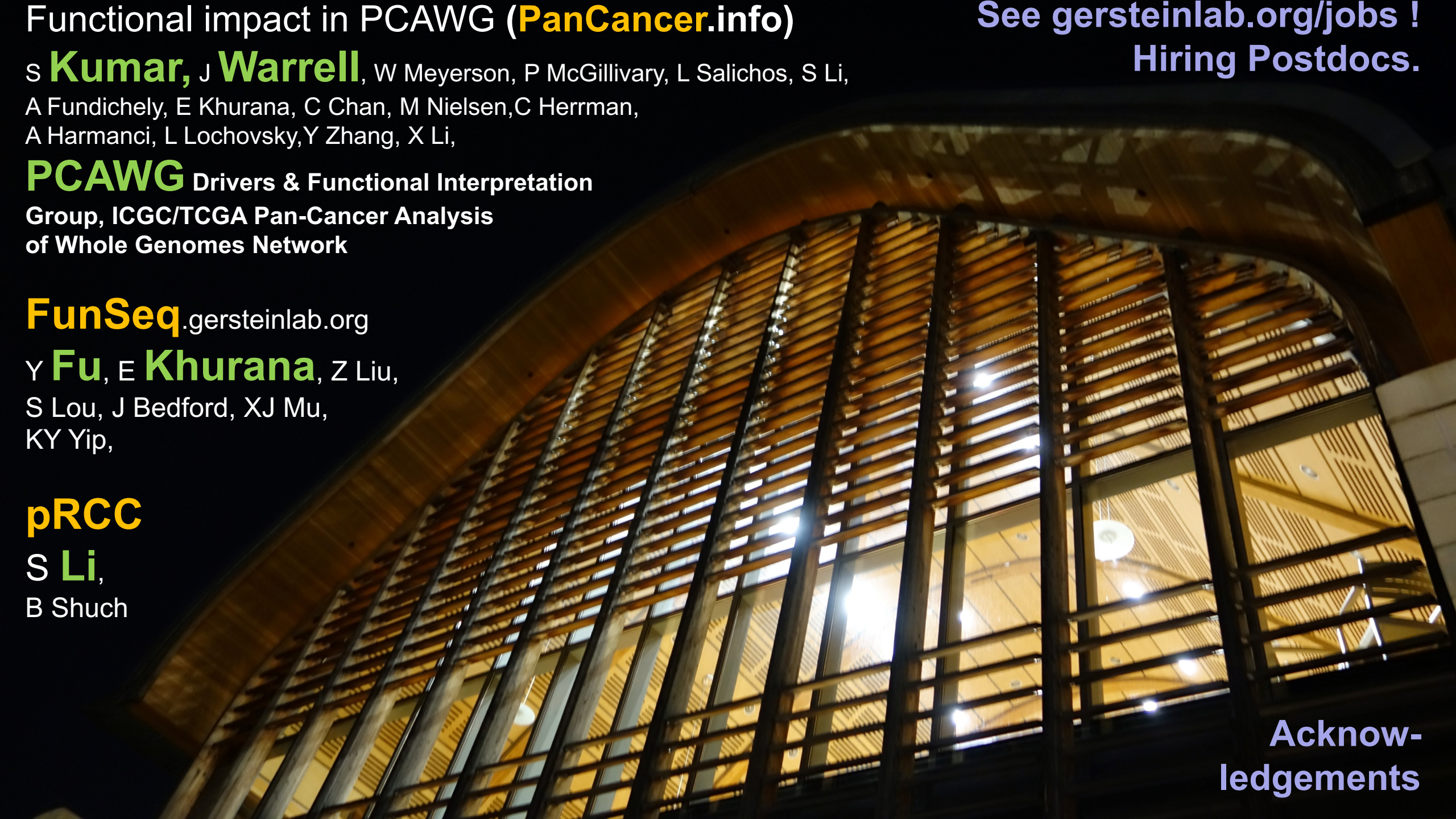
FunSeq.gersteinlab.org

Y **Fu**, E **Khurana**, Z Liu,
S Lou, J Bedford, XJ Mu,
KY Yip,

pRCC

S **Li**,
B Shuch

See gersteinlab.org/jobs !
Hiring Postdocs.



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