

The somatic molecular evolution of cancer

Pathology 681a

18 September 2020

Jeffrey Townsend

: @JeffTownsend

COI Disclosures:

Gilead

Agios

Black Diamond

Townsend, 2018, *Scientific American*

SMBE Satellite Meeting on The Molecular Biology and Evolution of Cancer

APRIL 12-13, 2019

Winslow Auditorium

Laboratory of Epidemiology and Public Health, 60 College St

YALE UNIVERSITY

NEW HAVEN, CT

Registration is free!

<https://smbe-cancerandevolution.org/>

Speakers include: Cheryl London, Heather Gardner, Amy Boddy, Gabriela Furukawa, Jacqui Shaw, Christine Desmedt, Marco Gerlinger, James DeGregori, Joao Xavier, Sheng Li, Vincent Cannataro, Jeff Chuang, Francesca Cicarelli, Anna Panchenko, Katherine Megquier

Sponsored by The Society for Molecular Biology & Evolution



Current challenges in understanding cancer

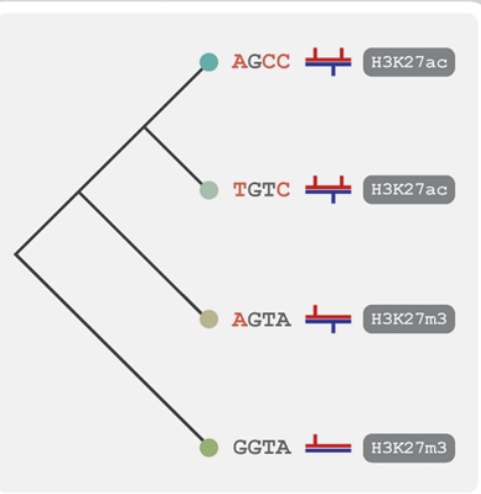
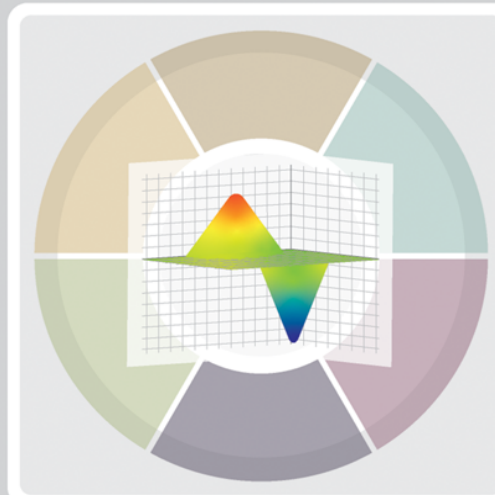
How can classical molecular evolutionary studies inform cancer discovery?

Study of genotype-by-environment interactions is well-established in evolutionary biology and can be applied to understand the molecular consequences of the cancer tissue microenvironment. Application of established evolutionary paradigms can elucidate the inheritance of cancer-predisposing alleles.



The Hallmarks of Cancer and Cancer Fitness Landscapes: how do they “add up”?

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Next steps: how do we bring our diverse areas together and keep communicating?

Molecular evolutionary paradigms should be a component of clinical treatment considerations: Evolutionary biologists and clinicians need continued venues for communication.



Consensus of attendees at the 2019 SMBE Satellite Conference on the Molecular Biology and Evolution of Cancer



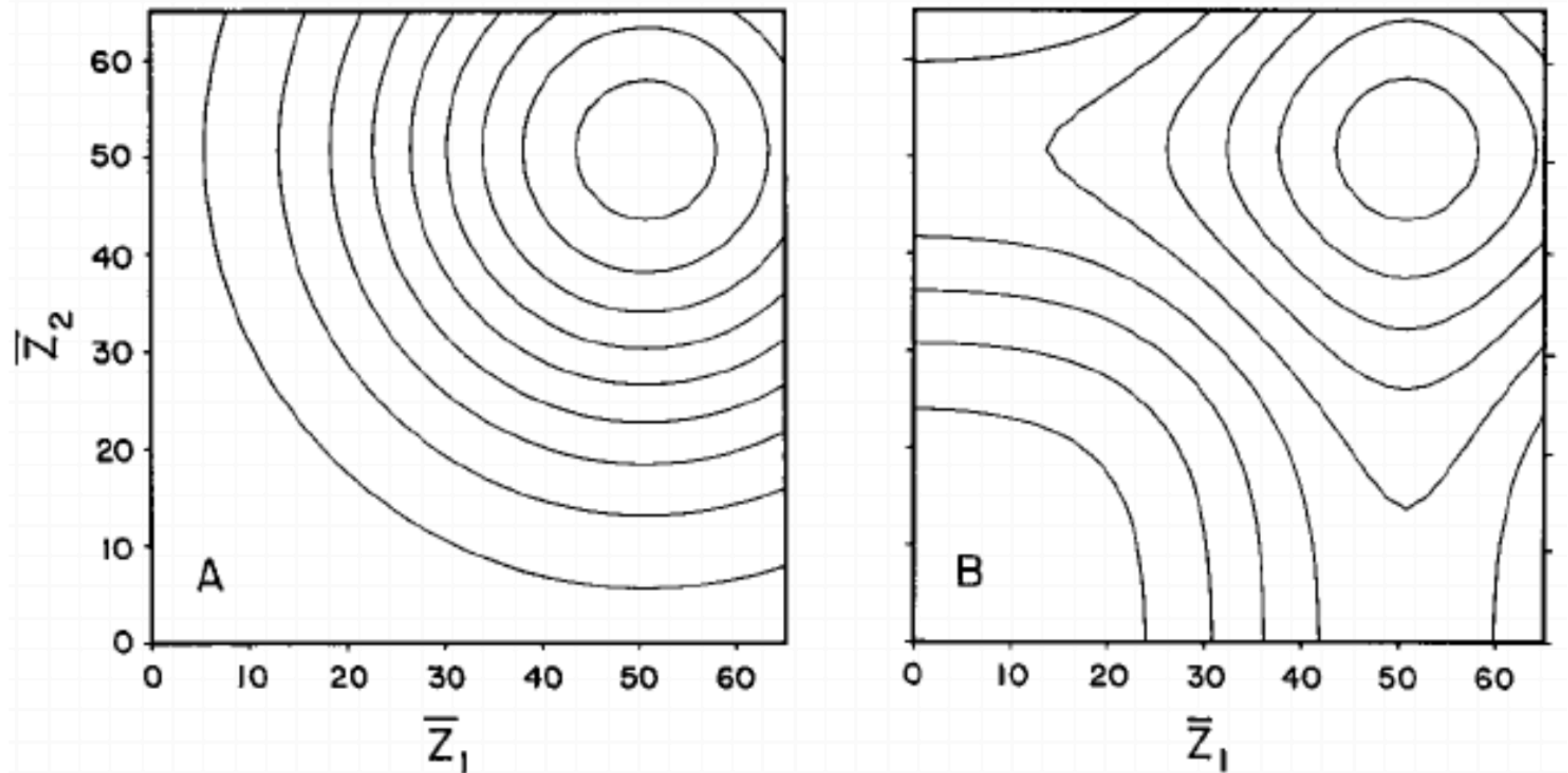
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Adaptive topographies for a character selected in two environments illustrate gene-by-environment interactions

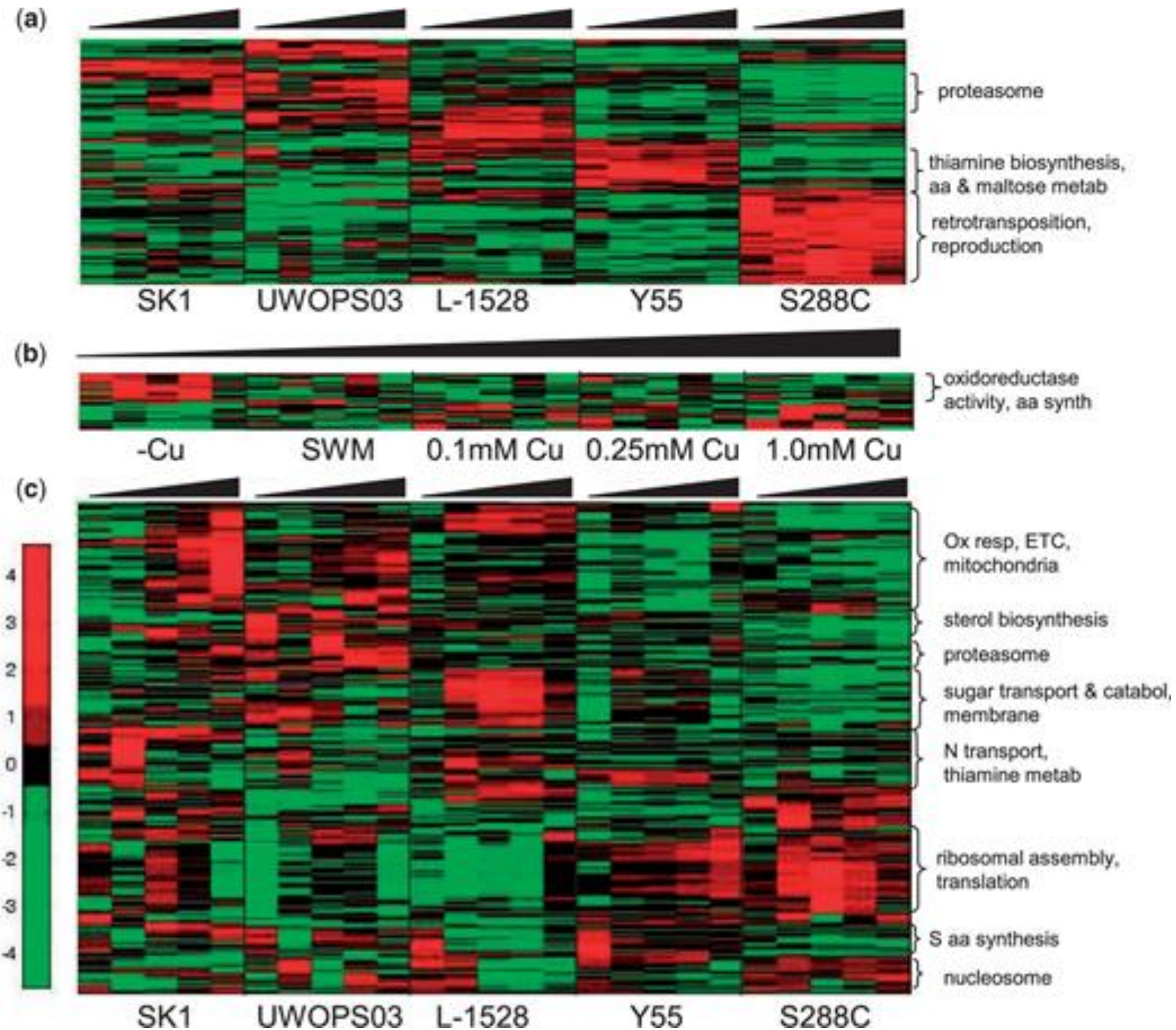


Gene-by-environment interactions are abundant in natural systems

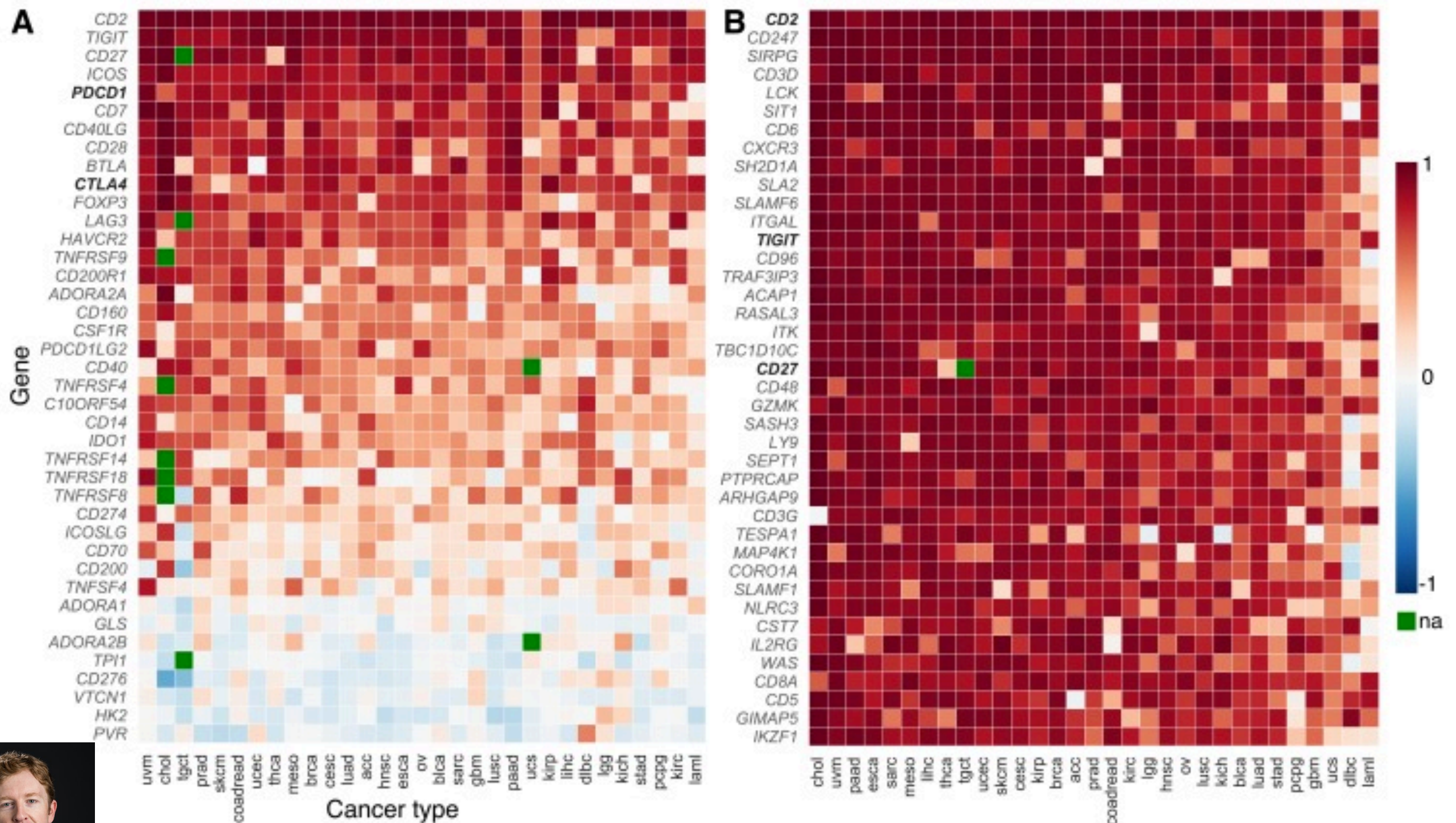
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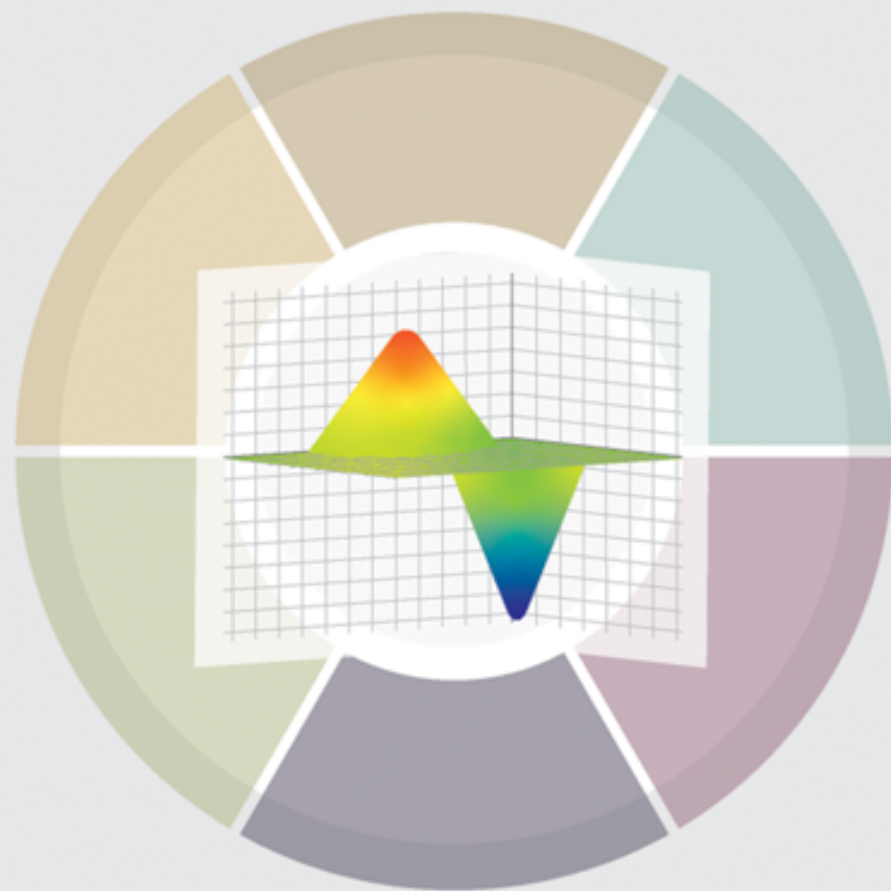
Gene expression in the tumor microenvironment dictates the landscape of targets for immunotherapy



Gaffney et al. 2019, *Oncotarget*



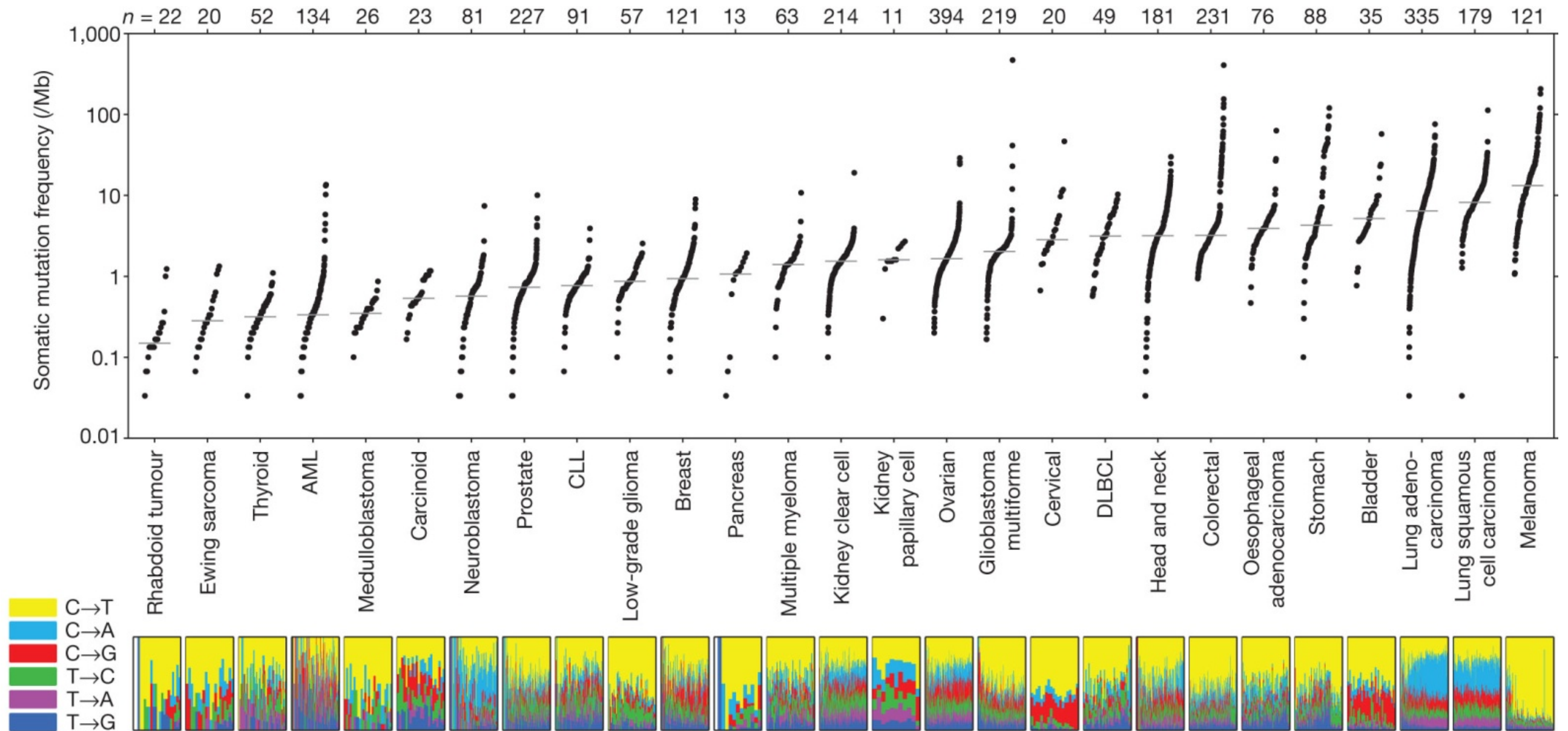
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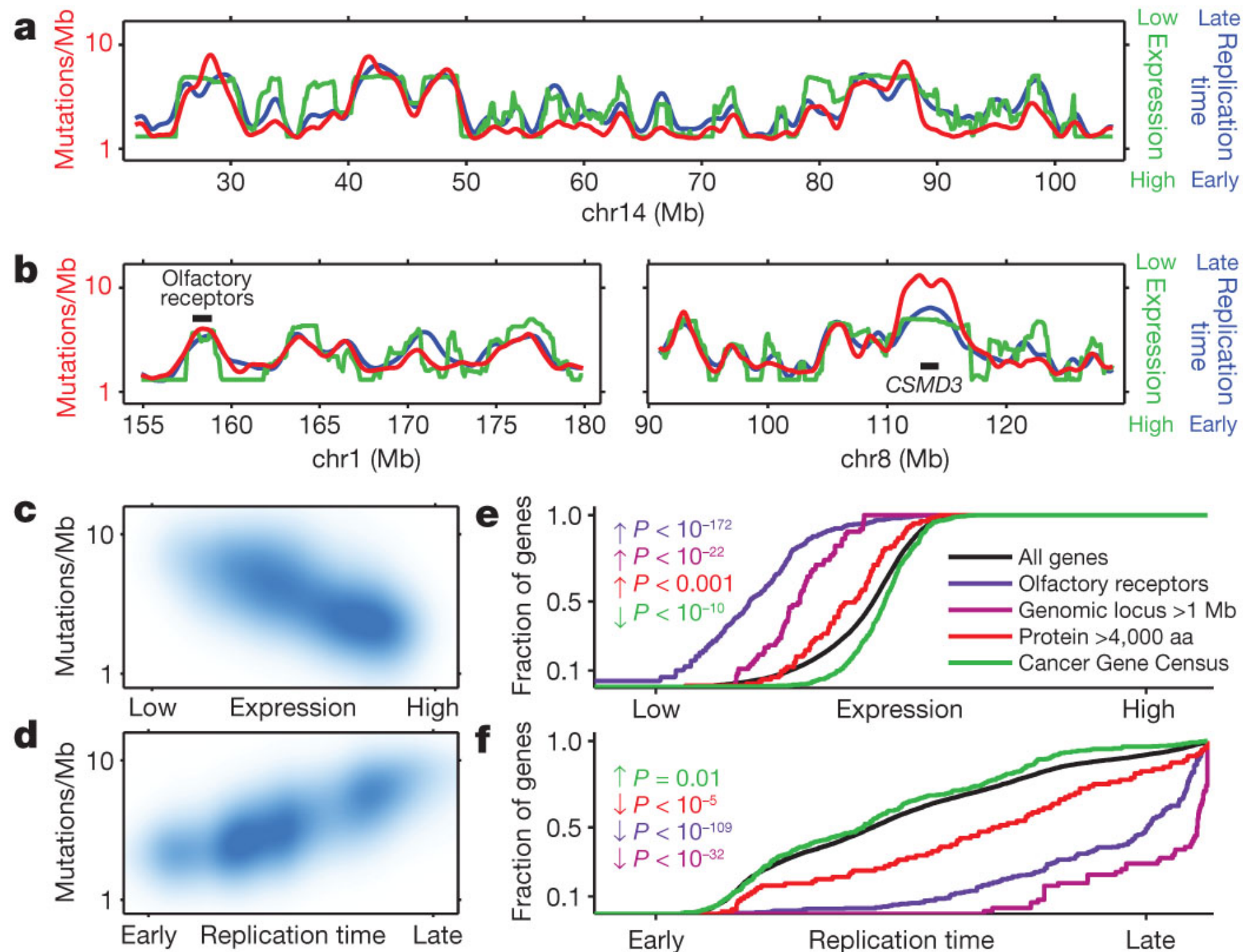
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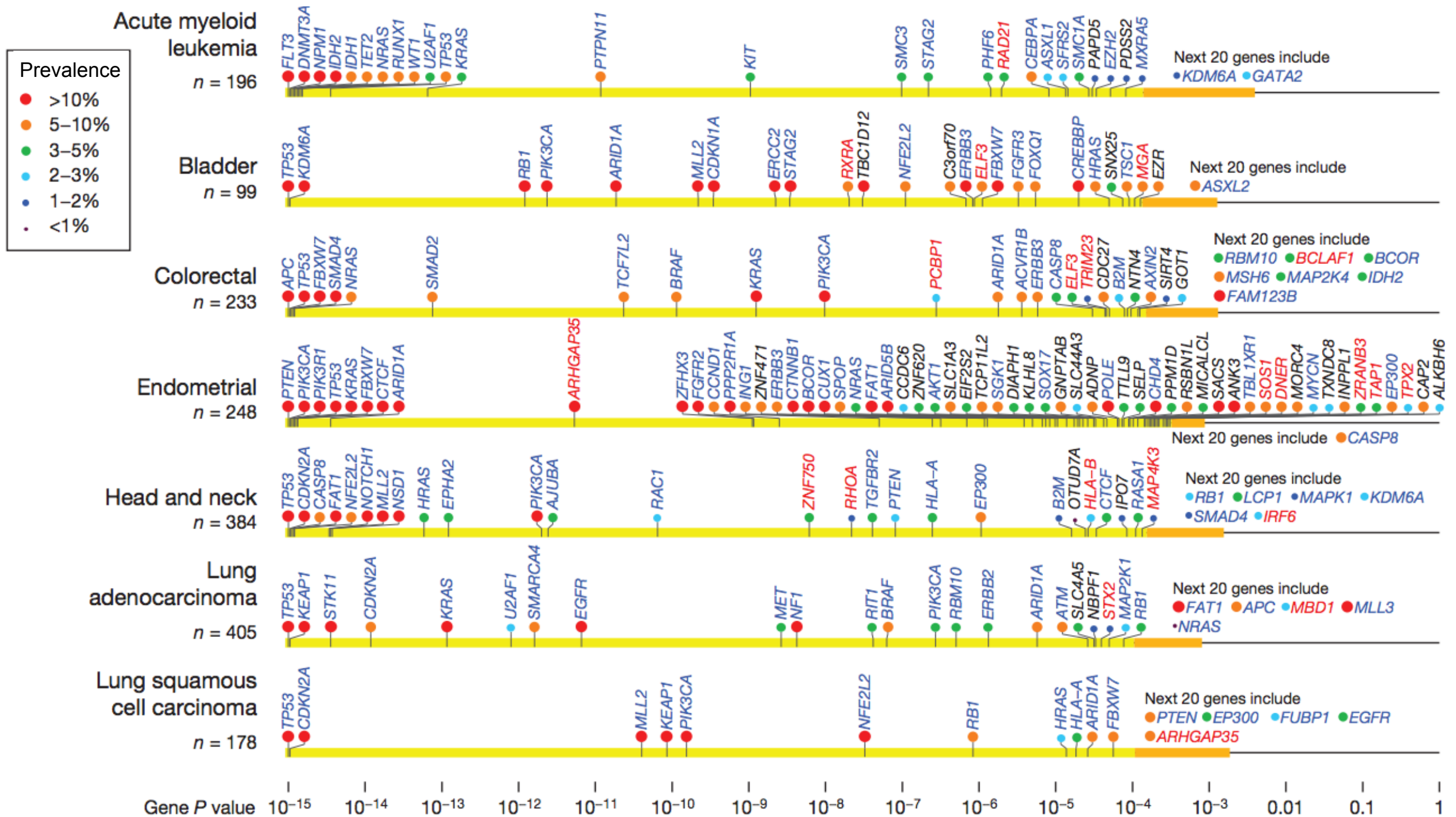
Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs



Mutation rate varies widely across the genome and correlates with DNA replication time and expression level

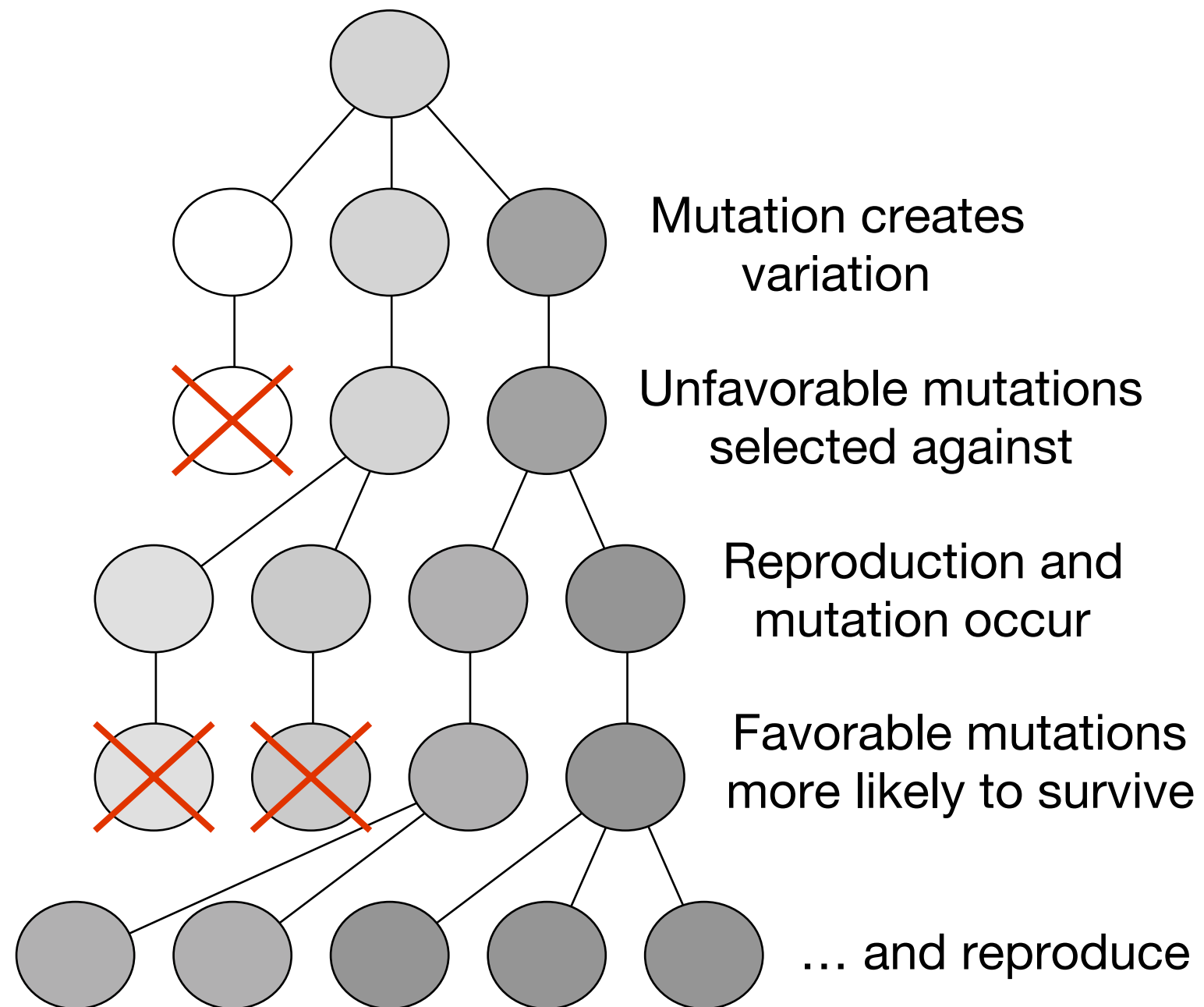


“Driver” genes in genomic analyses have been identified by their prevalence and P value

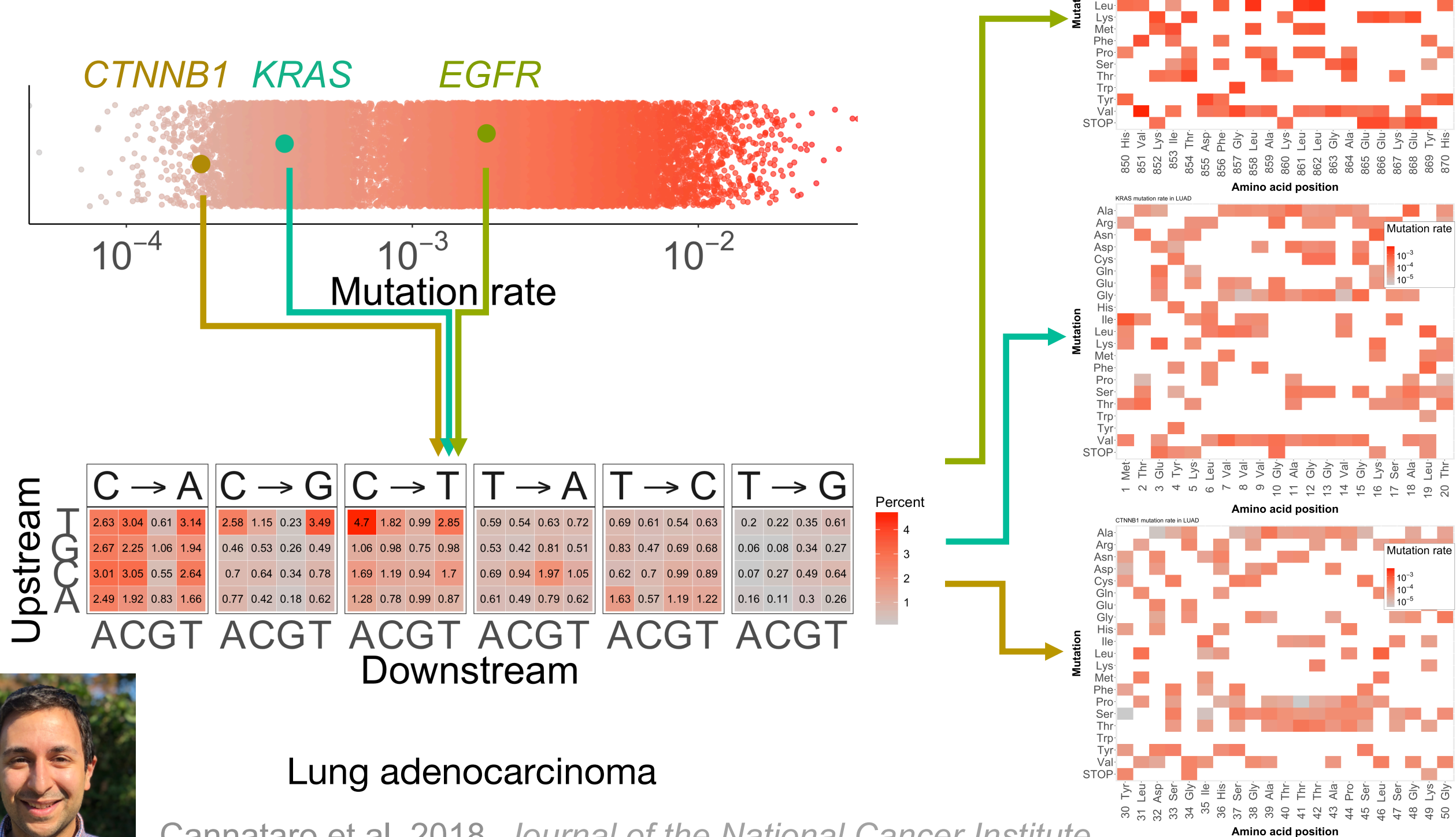


To quantify cancer effect size, prevalence must be deconvolved

into
the baseline
mutation rate
the degree of
selection for the
mutation in the cancer
lineage



Mutation rate at each site can be calculated by convolving gene-based rates from silent sites and covariates with trinucleotide context

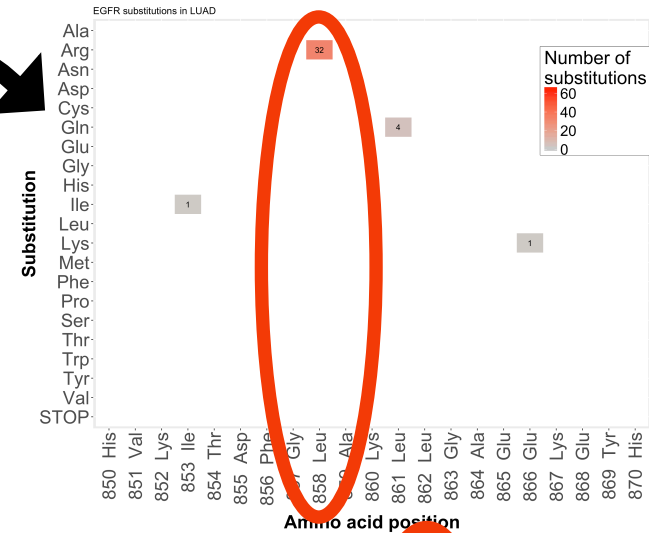
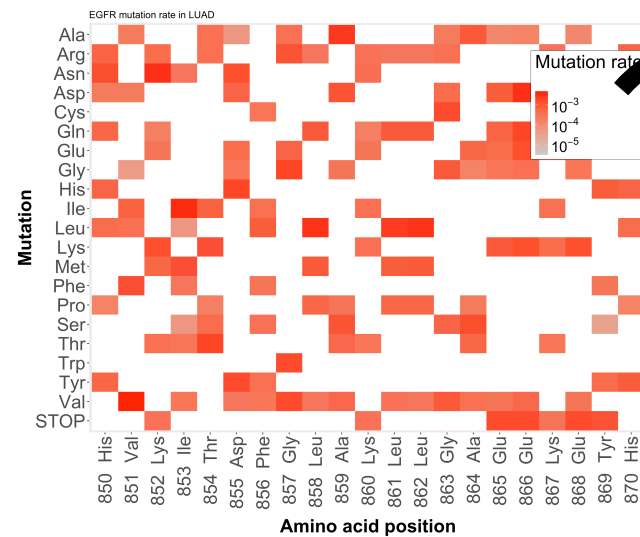


Lung adenocarcinoma

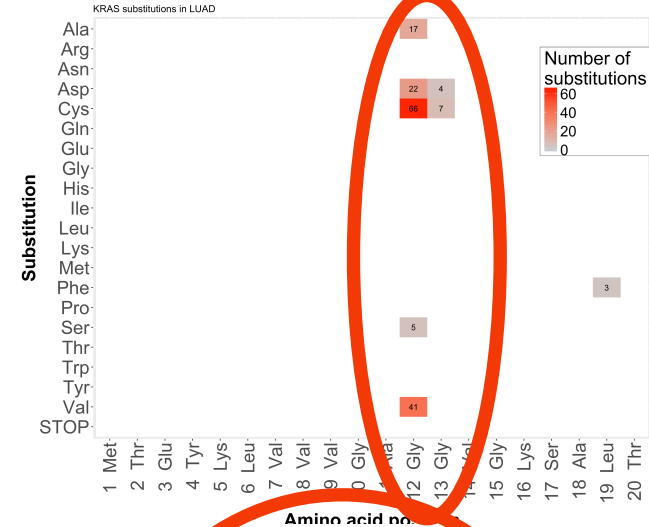
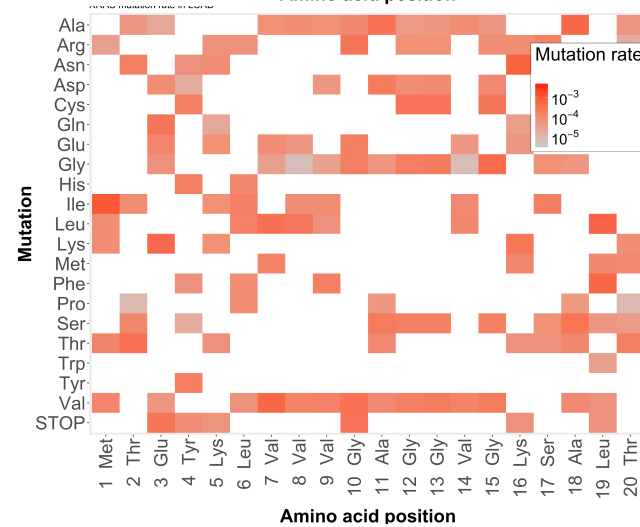
Cannataro et al. 2018, *Journal of the National Cancer Institute*

Variants that survive and persist within a tumor reflect the selective pressures within that tumor

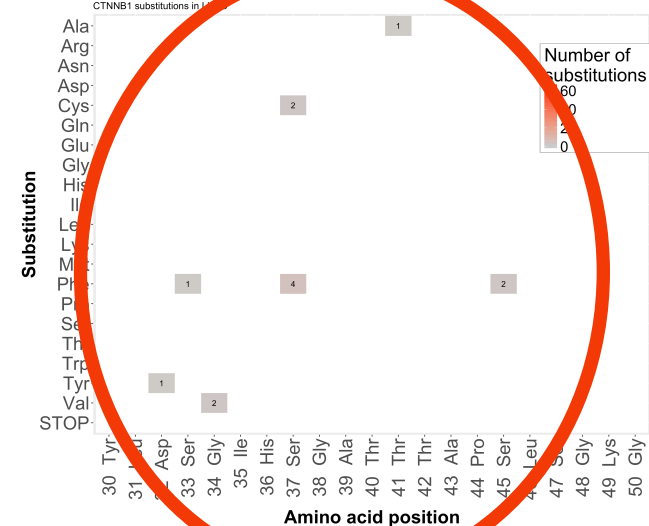
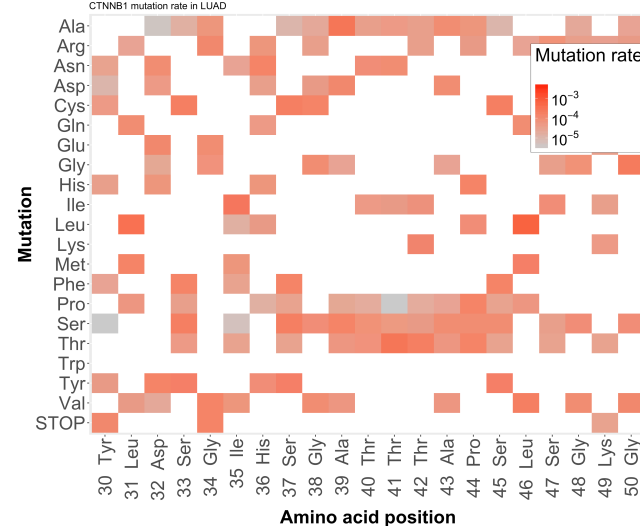
EGFR



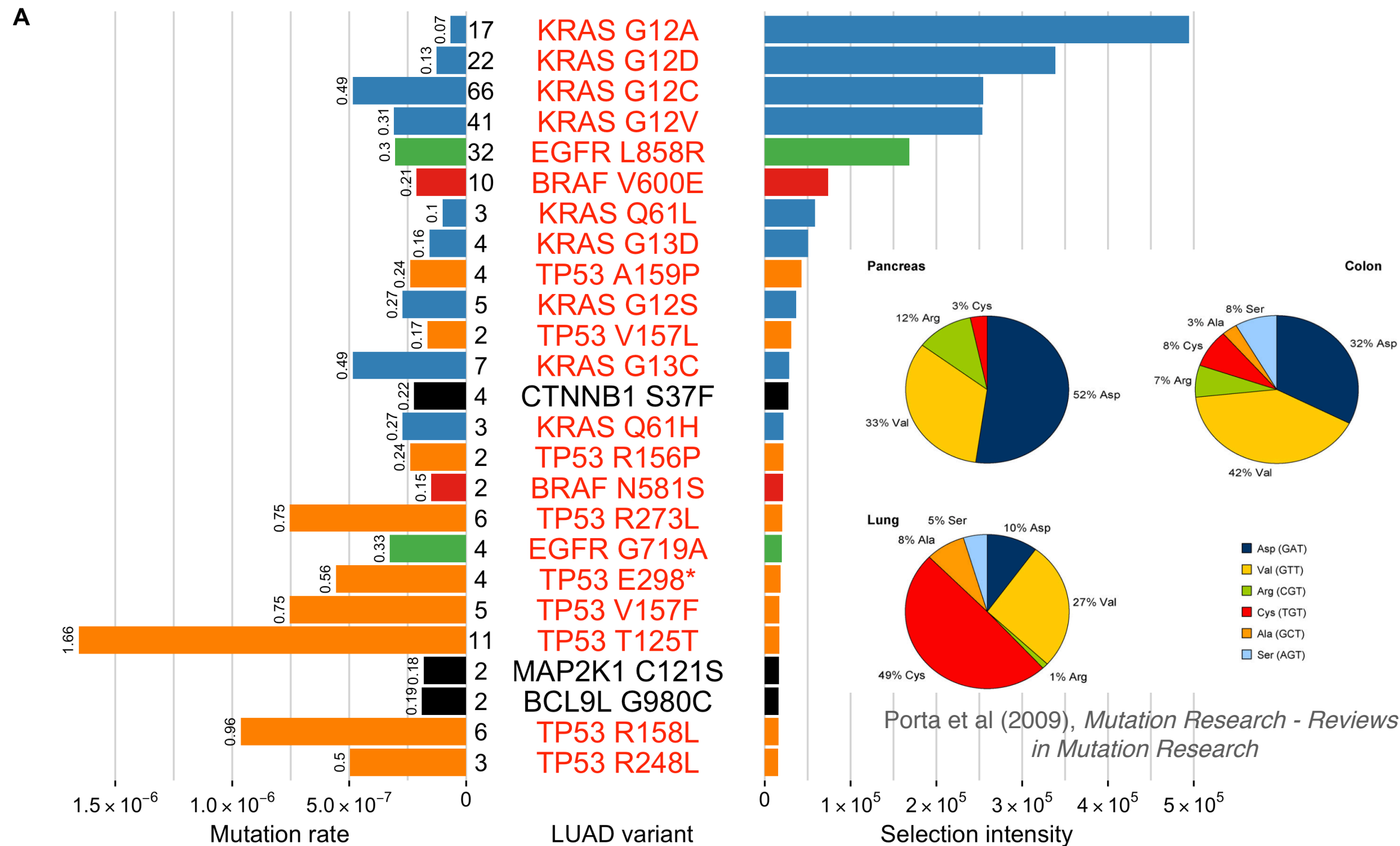
KRAS



CTNNB1

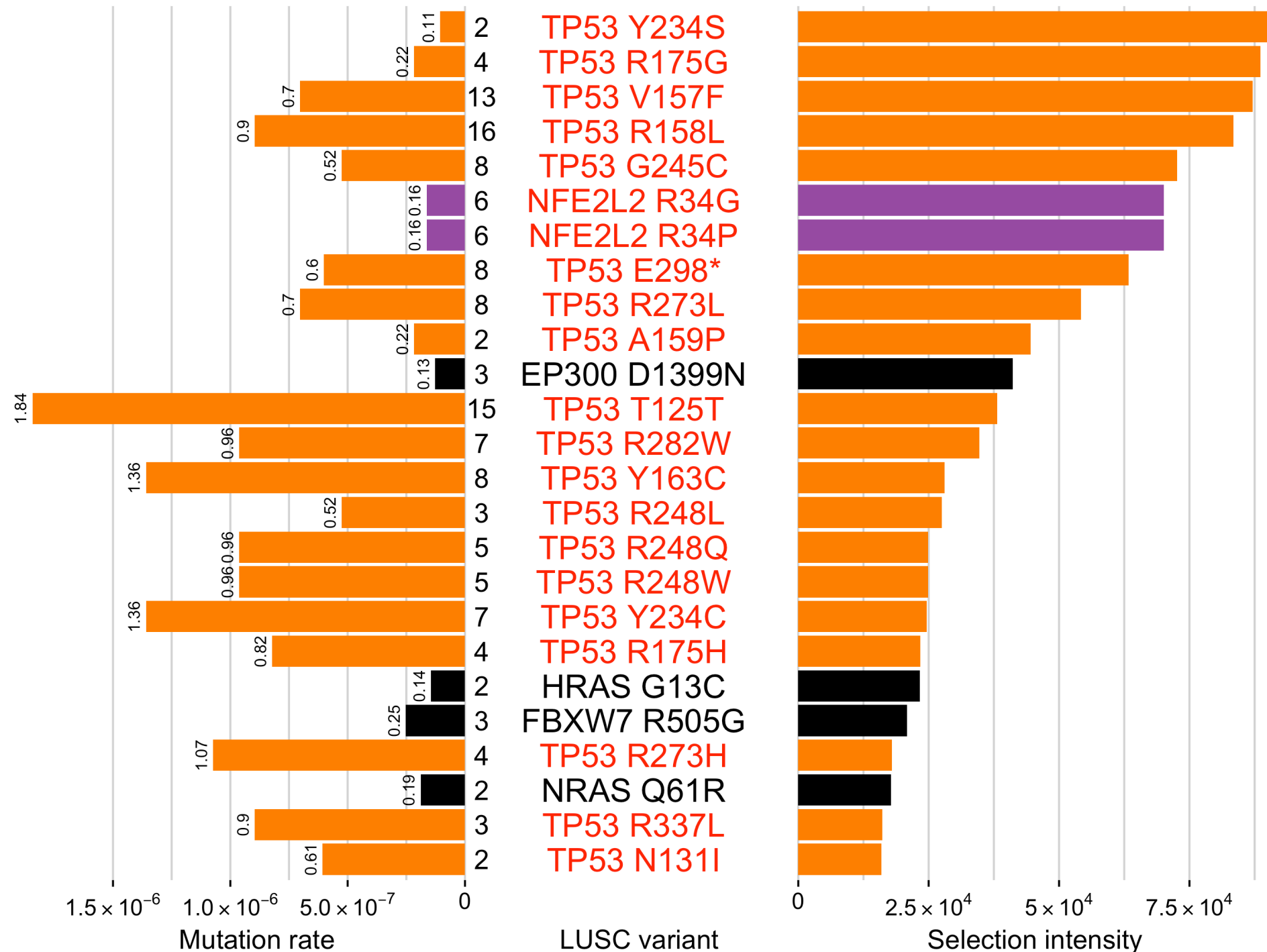


A number of low-frequency mutations exhibit high effect size in LUAD



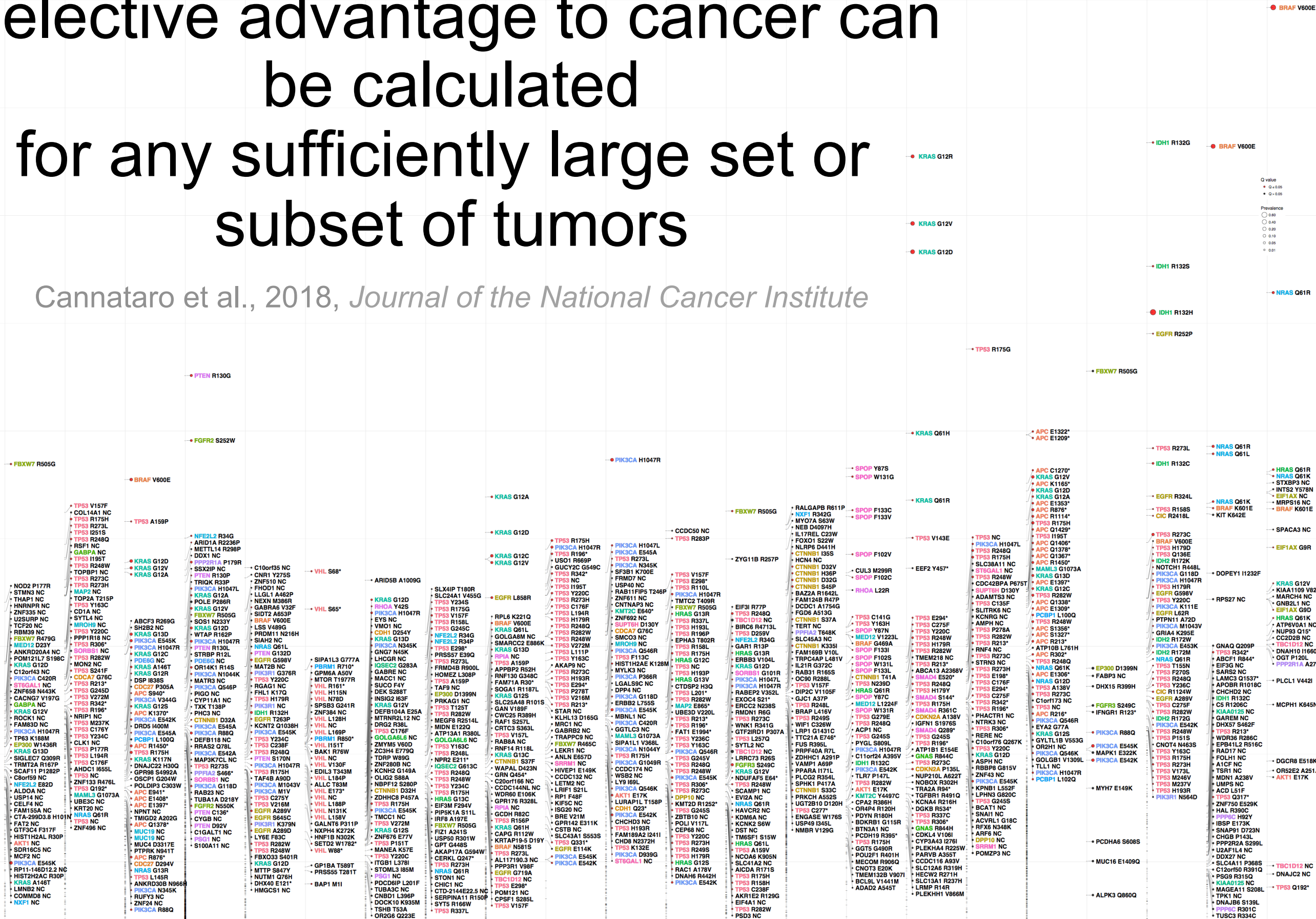
A very different distribution of effect sizes are characteristic of LUSC

B

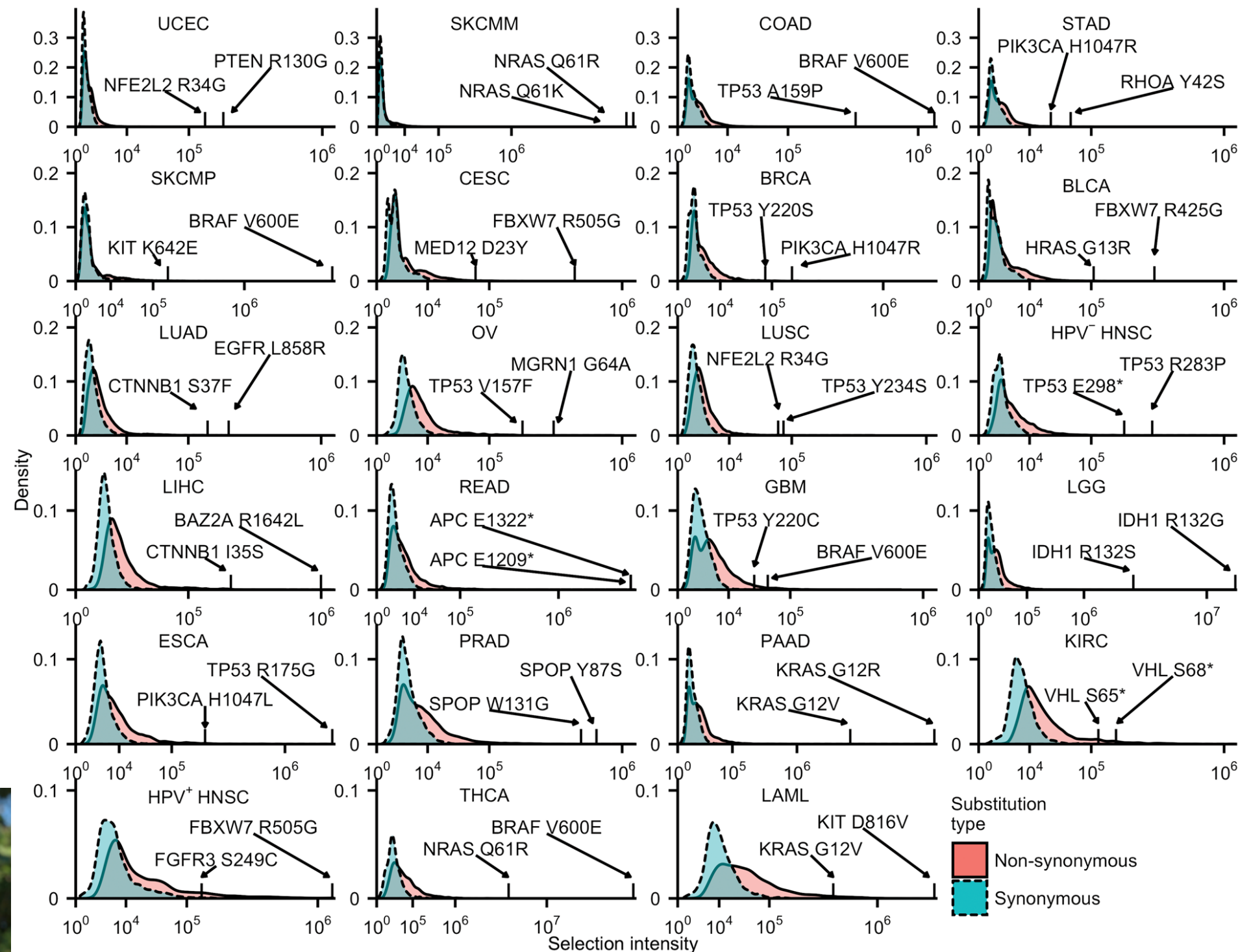


Selection intensity

CESC	OV	COAD	UCEC	GBM	KIRC	STAD	LUSC	LUAD	ER+ BRCA	ER+ BRCA	HPV+ HNSC	BLCA	LIHC	PRAD	PAAD	ESCA	READ	HPV+ HNSC	LGG	SKCM	THCA
Tumor type																					



This approach calculates the full distribution of scaled selection coefficients of *single-nucleotide mutations*



Cancer effect sizes are a key metric for the full range of basic and translational research

Basic research



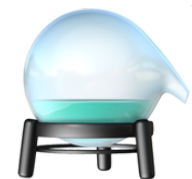
Precision medicine



The effect size of the genomic variants within cancers is of fundamental importance to oncology

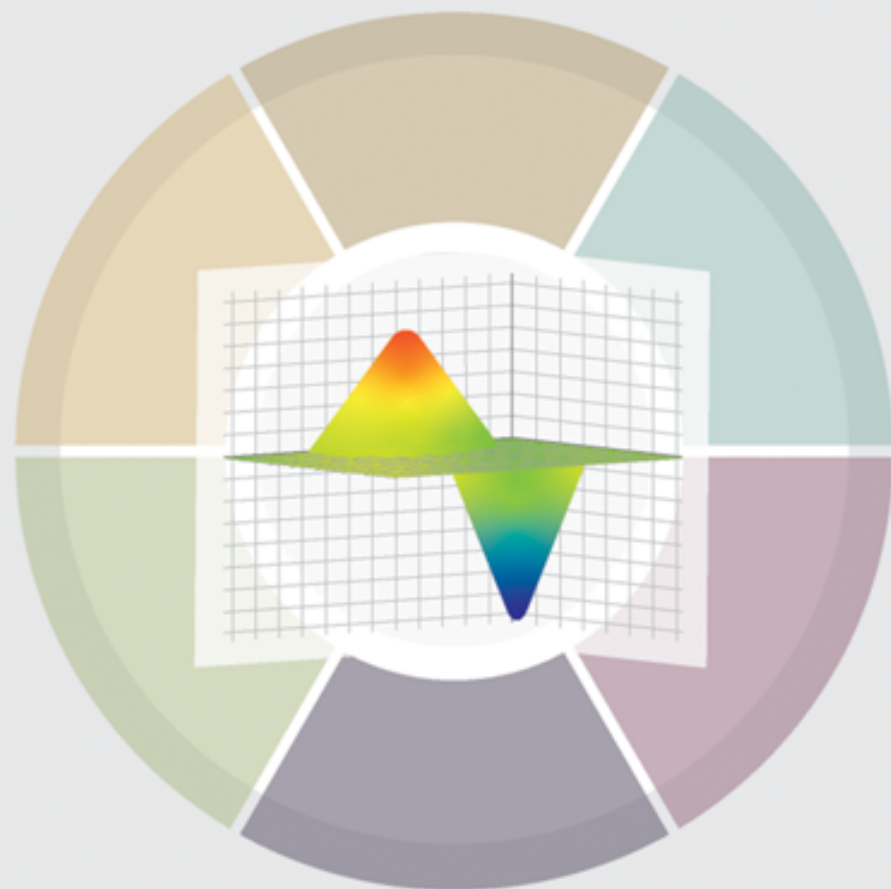


Clinical trials



Pharmaceutical development

Next steps include stage-specific and epistatic estimates of cancer effects on not just SNVs, but also diverse CNVs and epigenetic changes



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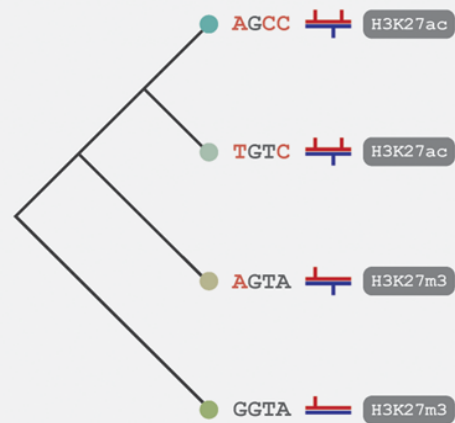
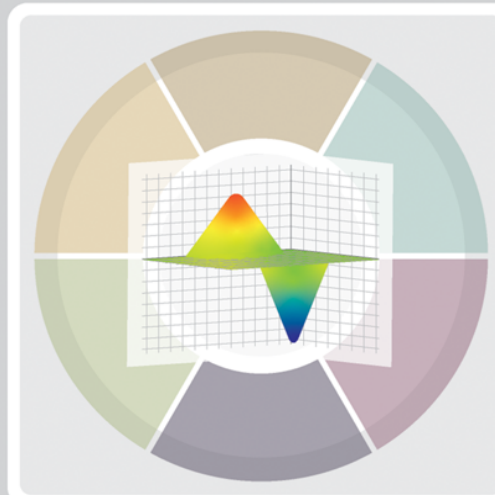
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How do we build molecular evolutionary models of cancer’s special characters?

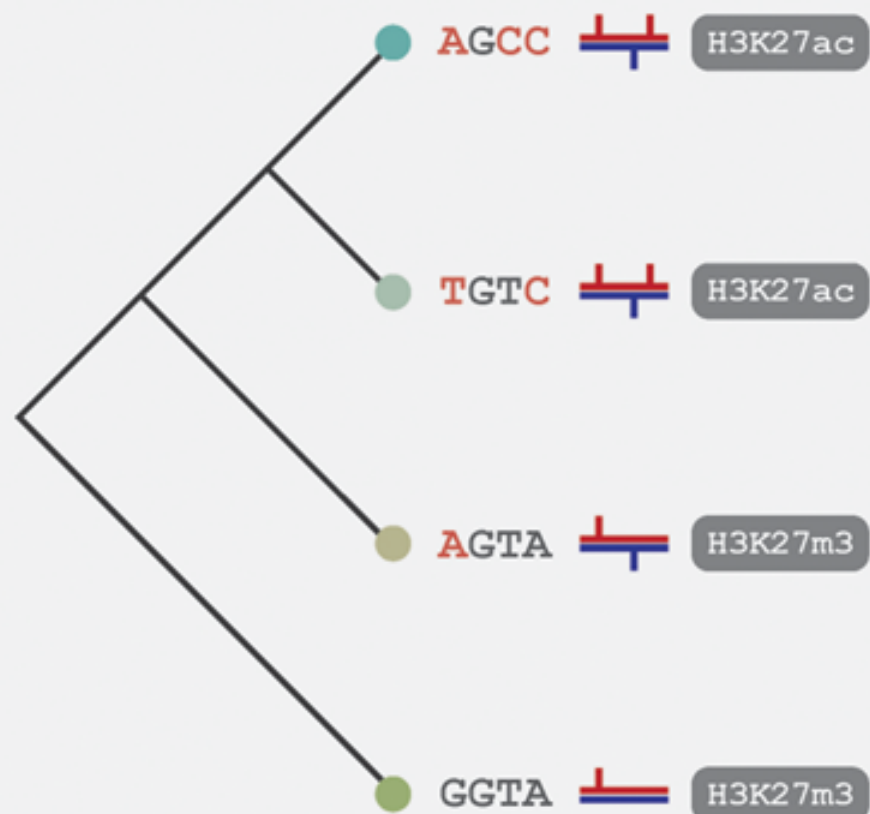
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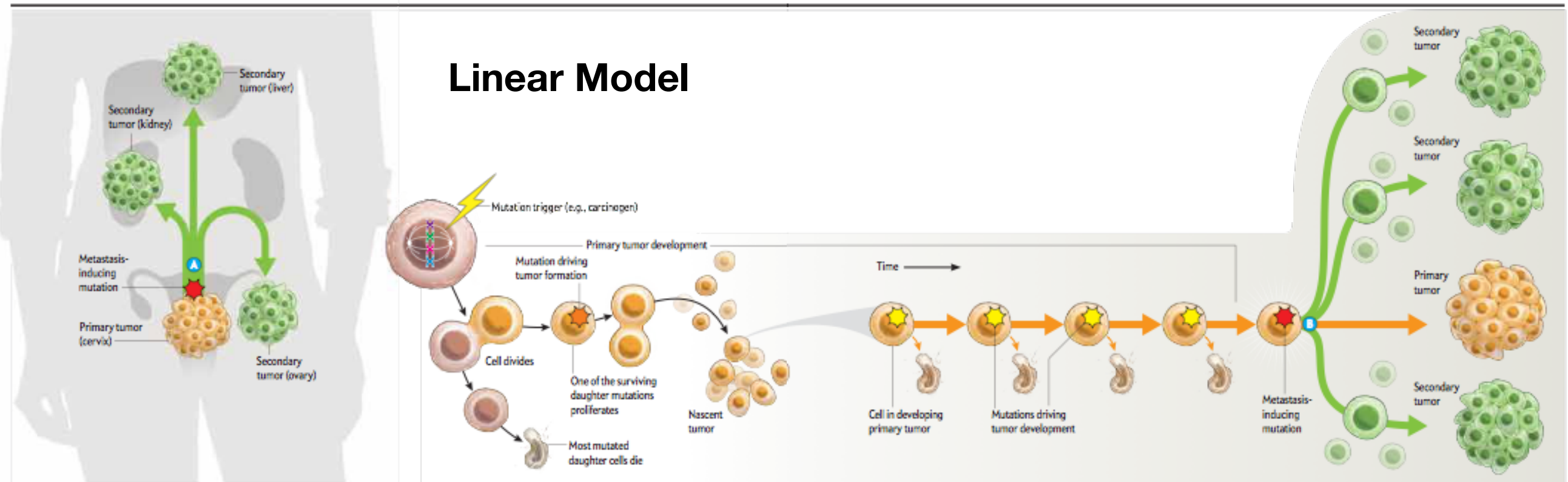


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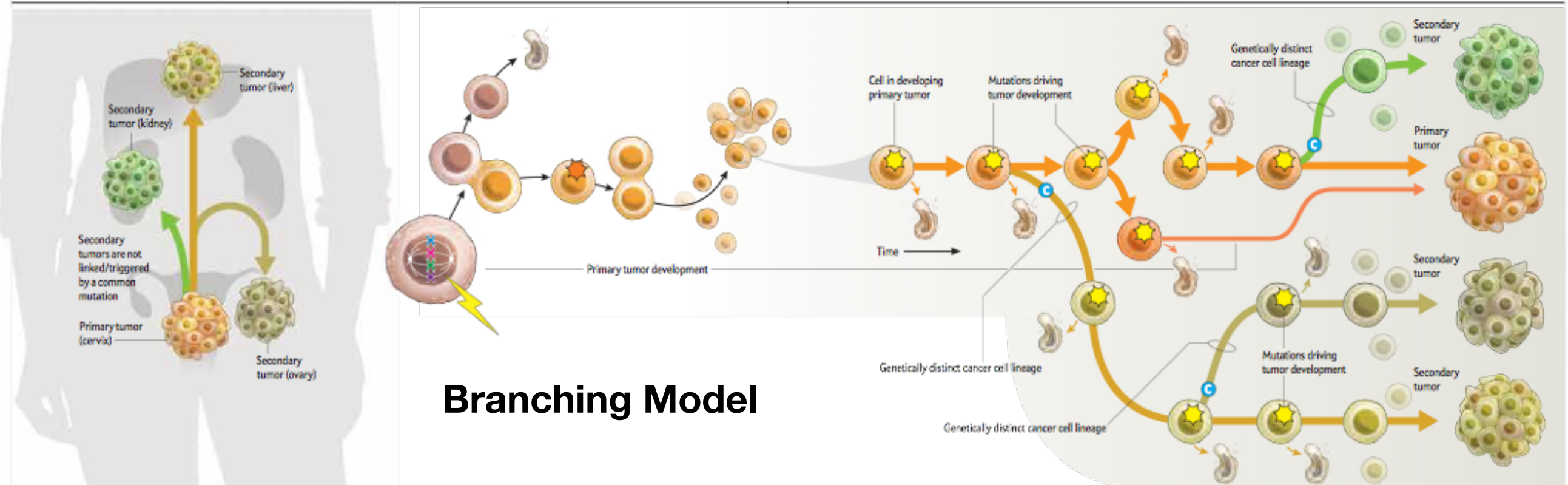
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Is the evolution of cancer “linear?”

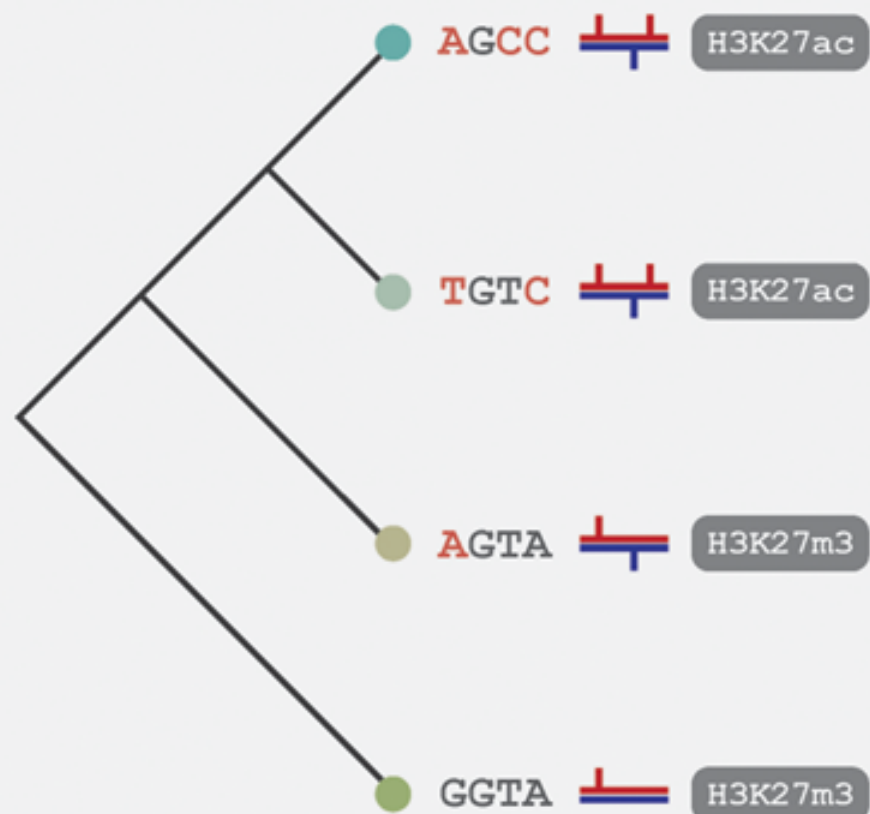
Linear Model



Branching Model



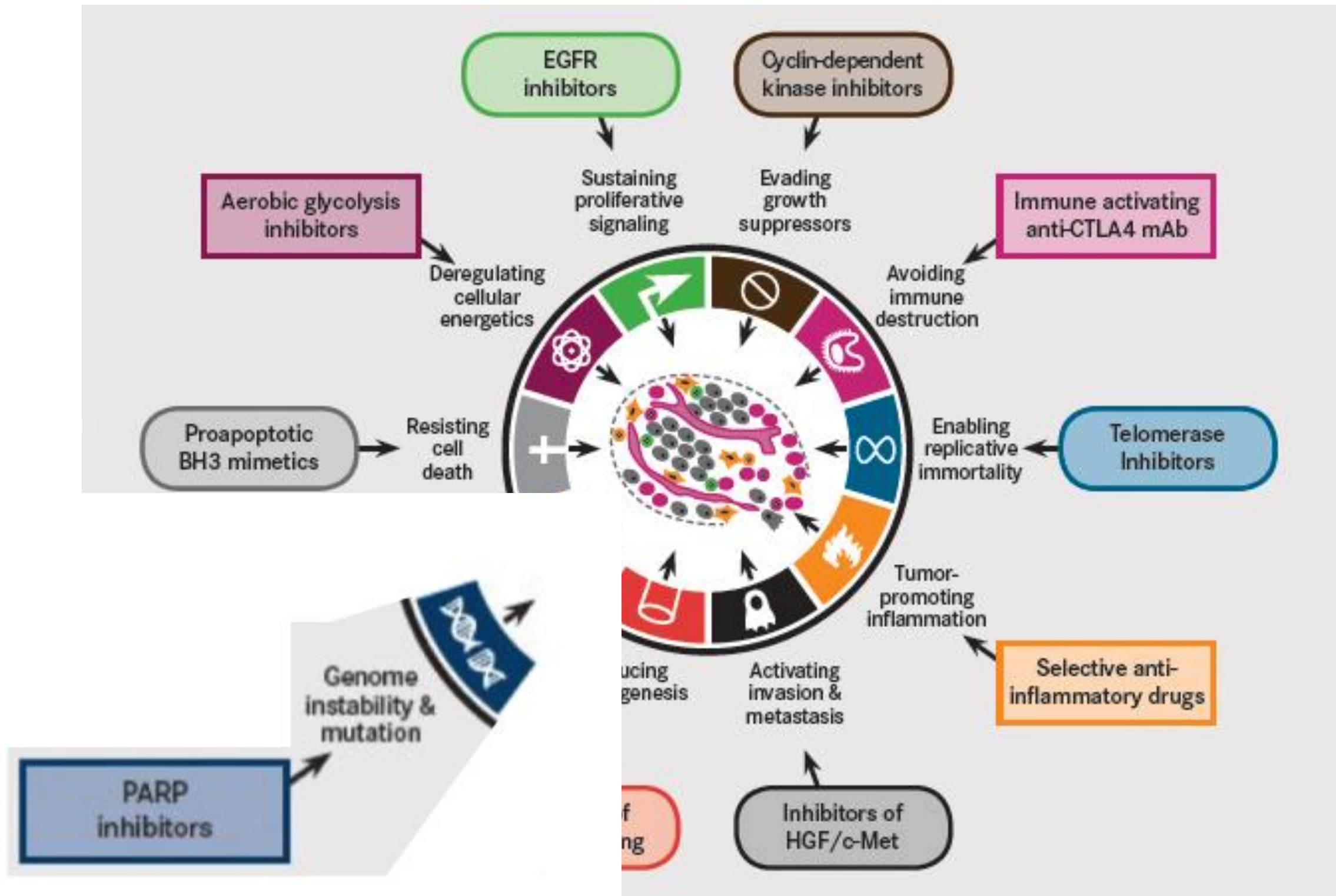
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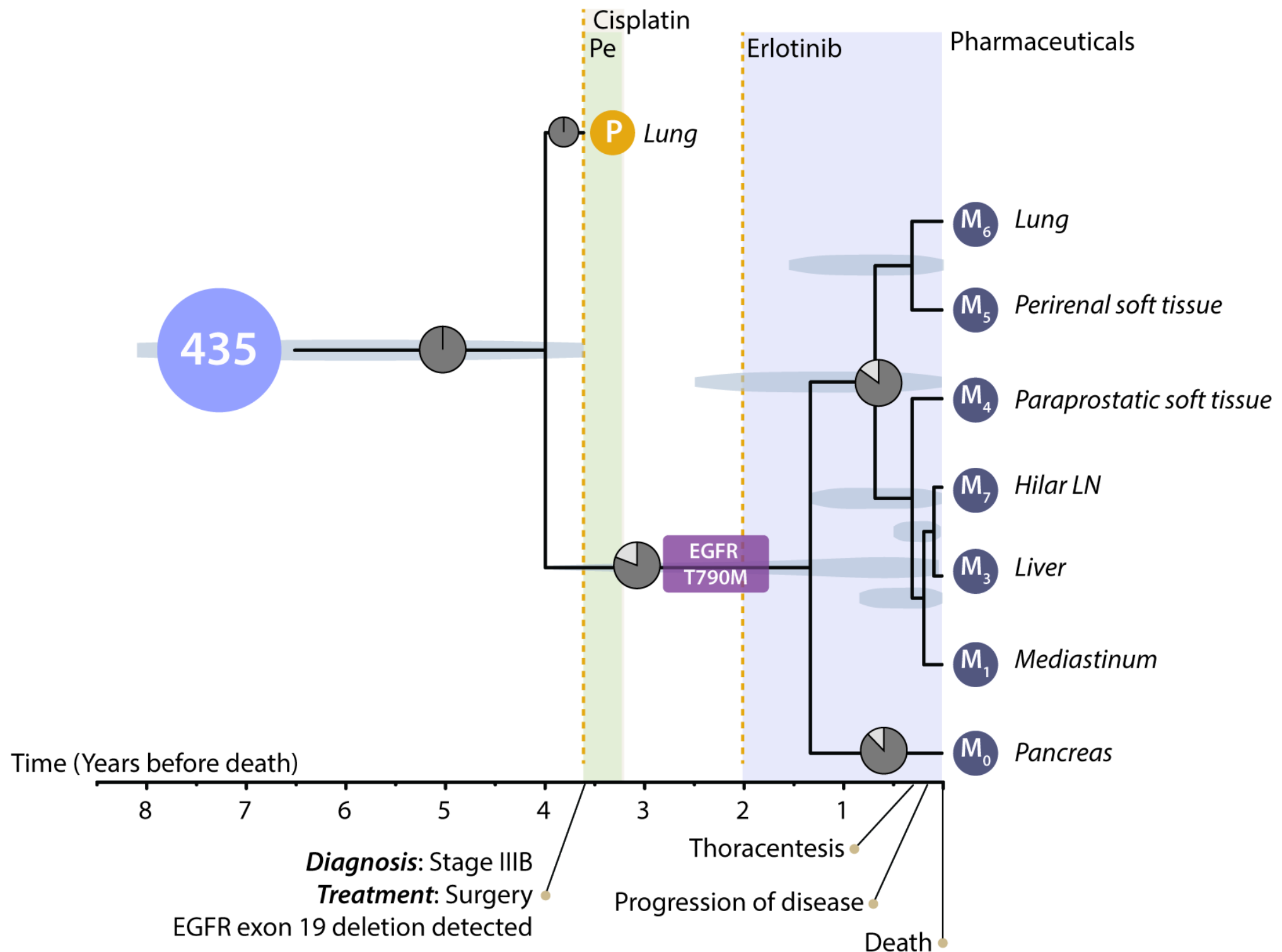
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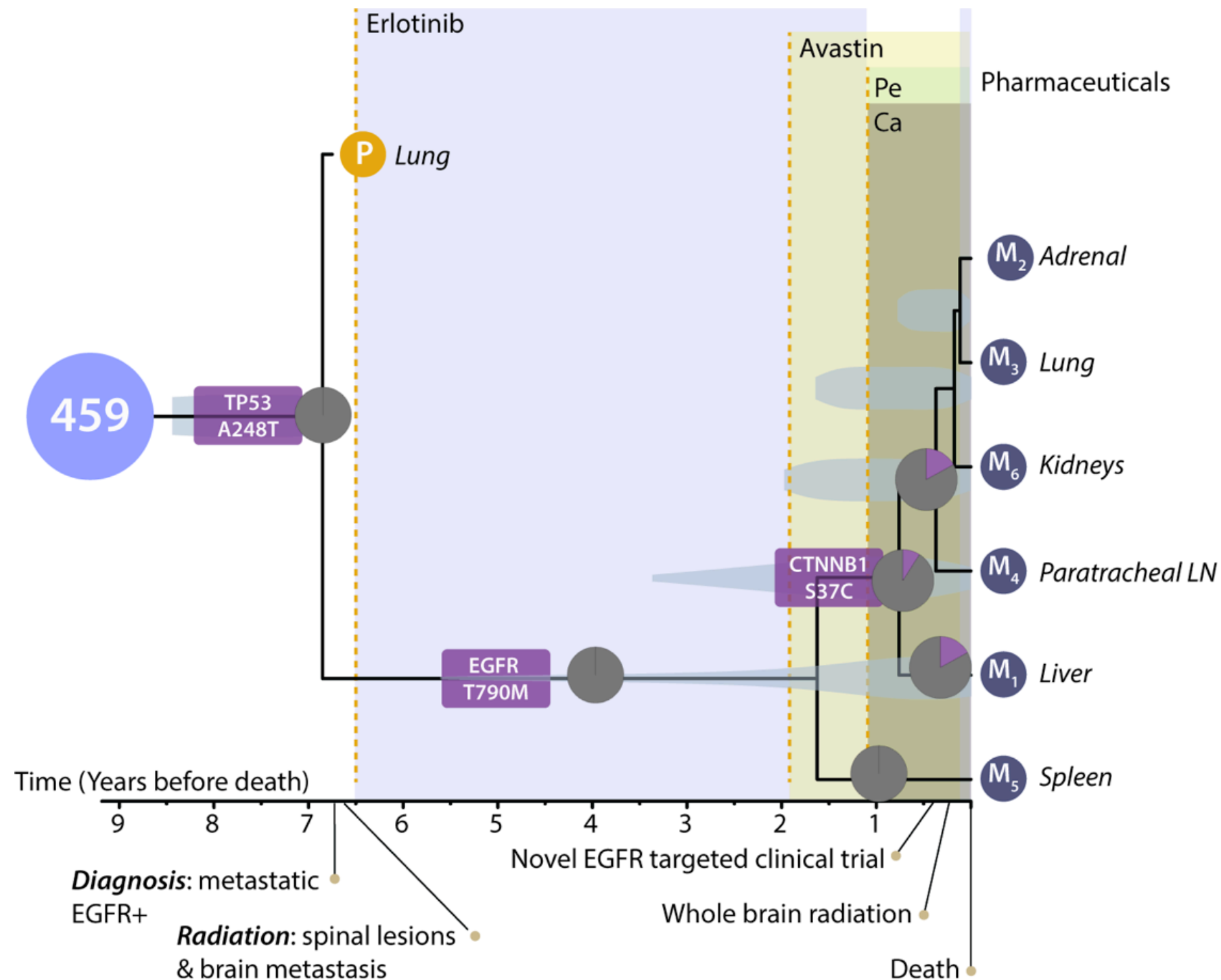
Hallmarks of cancer



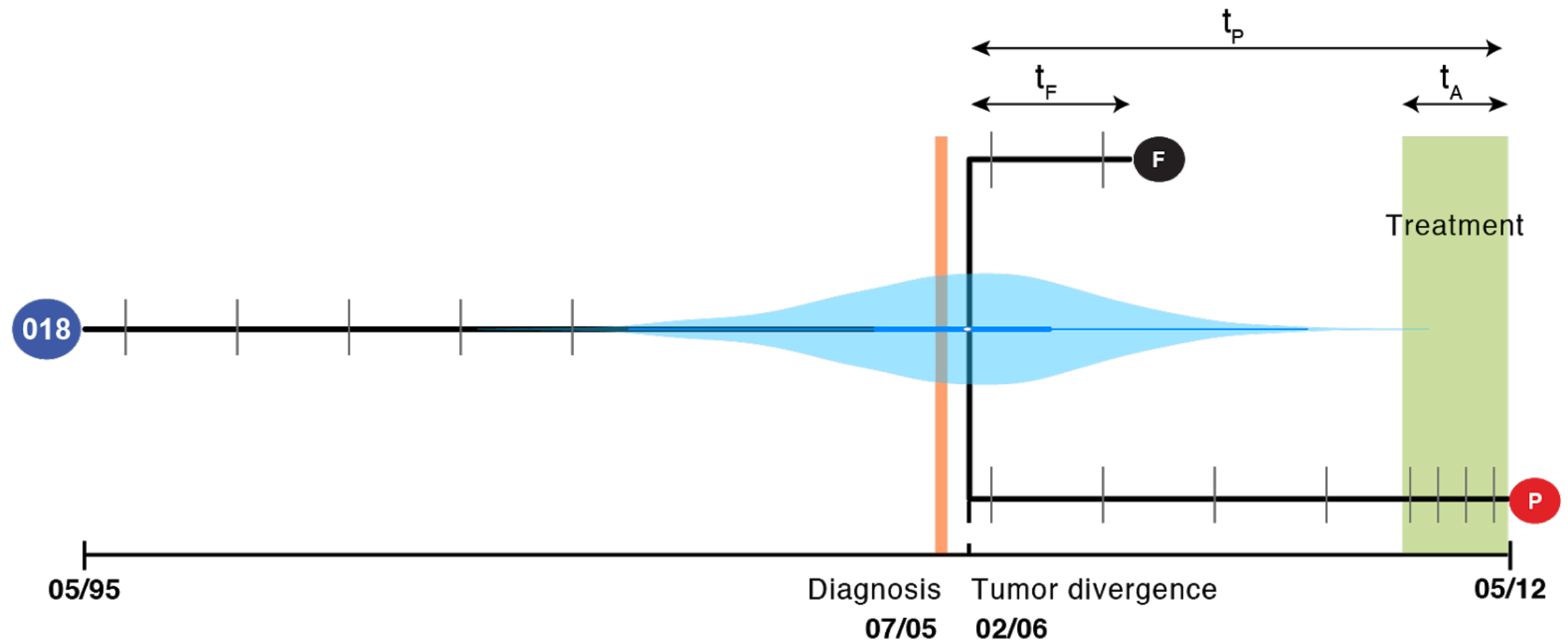
A cancer chronogram illuminates patient disease and treatment history



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Tumor trees will be essential to the evolution of therapeutic resistance



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