Somatic mutations in tumors and normal tissues

Nuria Lopez-Bigas
ICREA Research Professor
Institute for Research in Biomedicine (IRB) Barcelona

@nlbigas

ICREA

INSTITUTE FOR RESEARCH IN BIOMEDICINE
IRB BARCELONA

- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- Identifying Clonal Hematopoiesis Drivers
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

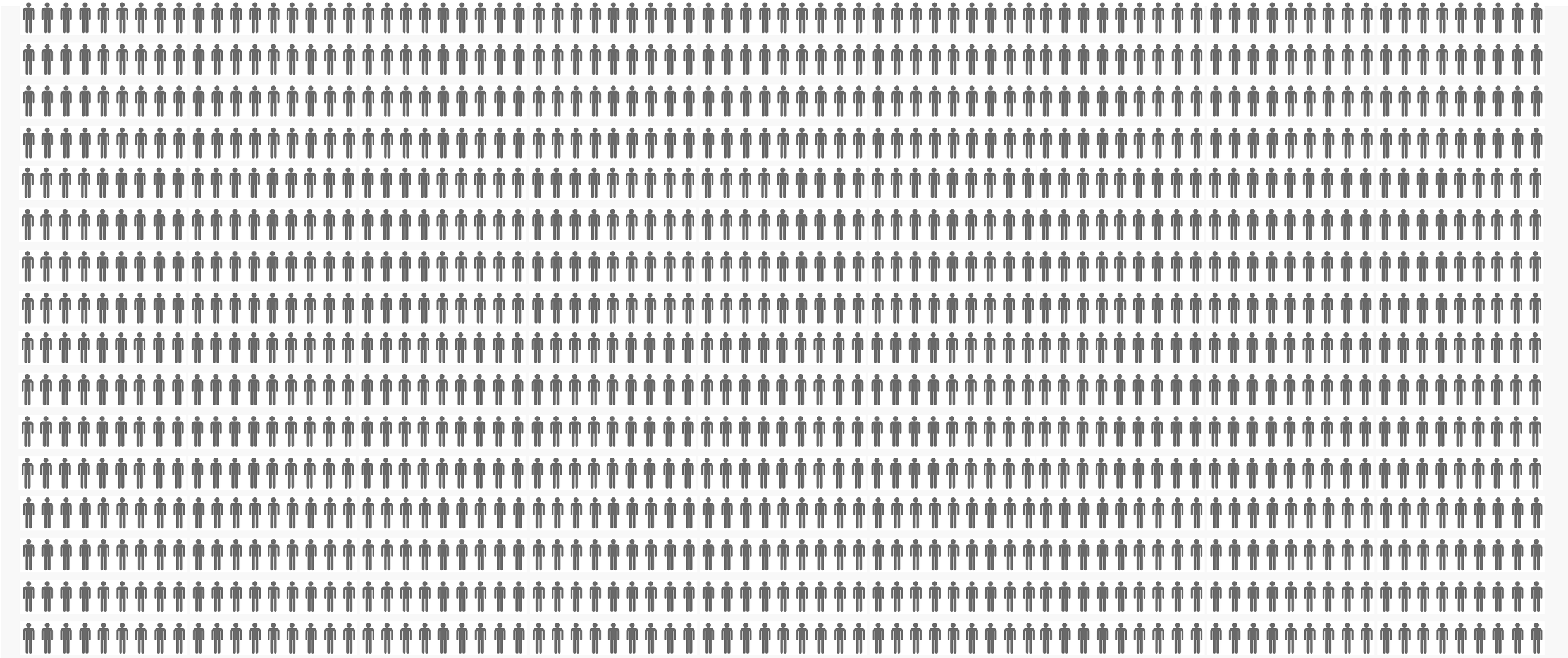
- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- Identifying Clonal Hematopoiesis Drivers
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

Which are the genes that drive tumorigenesis upon mutations?

Accumulated literature on cancer genes for decades

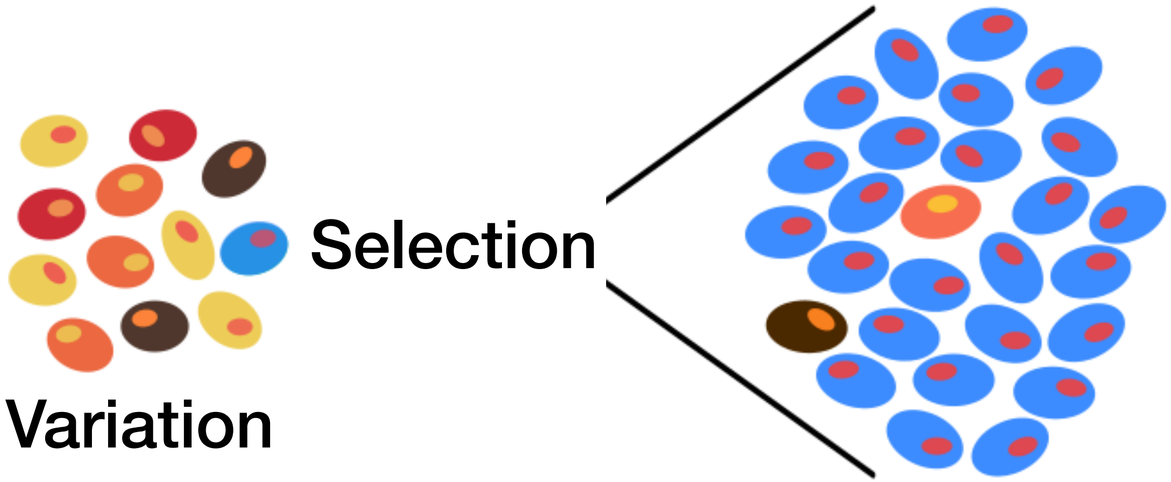
Montserrat monastery Library

Can we find cancer genes directly from tumors data?



Thousands of tumor genomes sequenced

Tumor development follows Darwinian Evolution

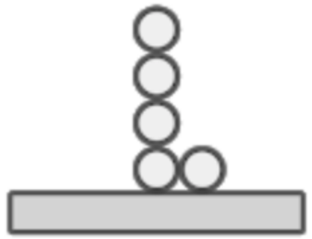


Drivers confer selective advantage to the cell

Identifying signals of positive selection is an effective way to find cancer drivers

R

Identify genes mutated more frequently than the background mutation rate



C

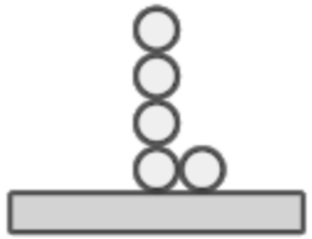
Identify genes with a significant regional clustering of mutations

FI

Identify genes with a bias towards high functional mutations (FM bias)

Identifying signals of positive selection is an effective way to find cancer drivers

R Identify genes mutated more frequently than the background mutation rate

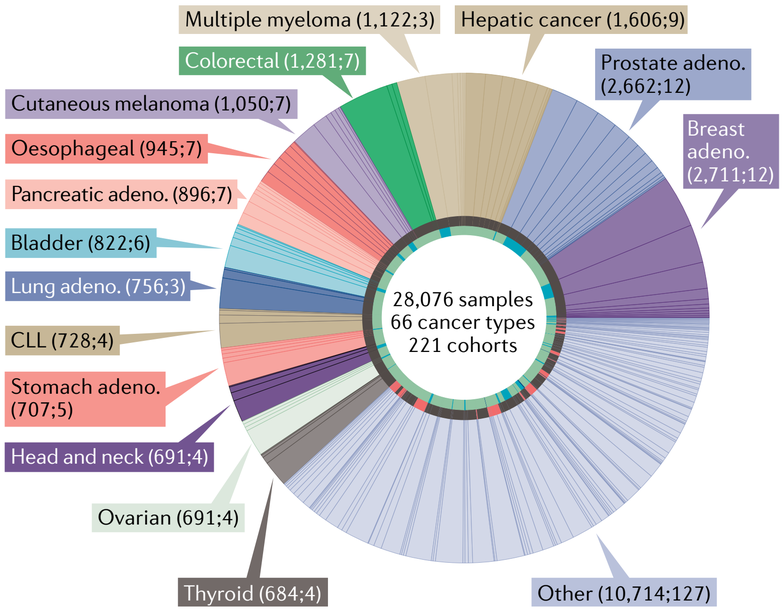


C Identify genes with a significant regional clustering of mutations

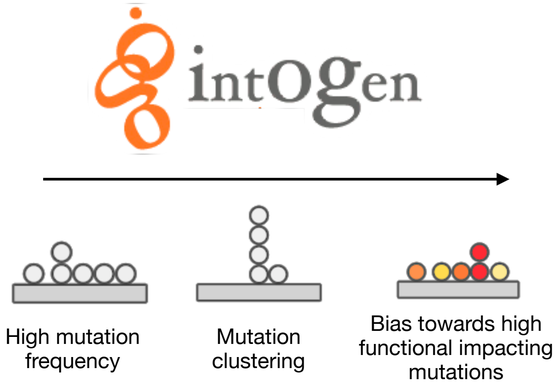
FI Identify genes with a bias towards high functional mutations (FM bias)

OncodriveFML - OncodriveCLUSTL - dNdSCV - cBase - Mutpanning - Hotmaps - SMregions

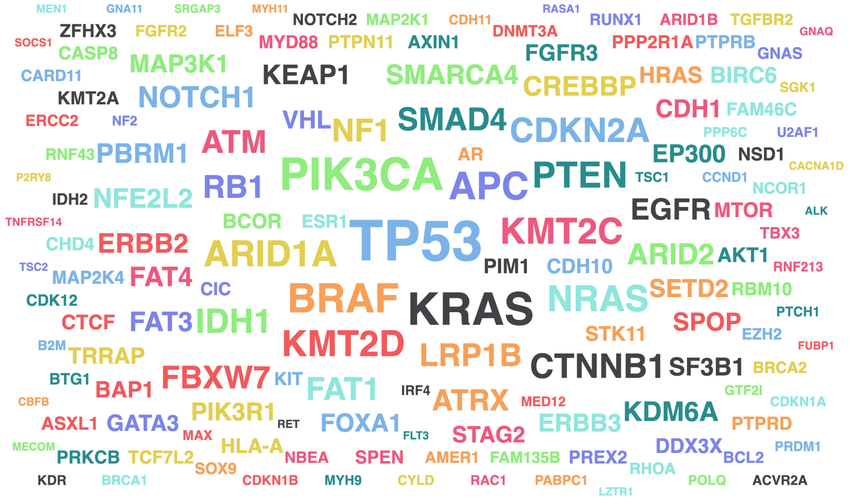
The Compendium of Mutational Cancer Driver Genes



28,076 Tumors · 221 cohorts · 66 Cancer Types · 203,003,747 Mutations



Mutation Pattern Analysis to identify Cancer Genes



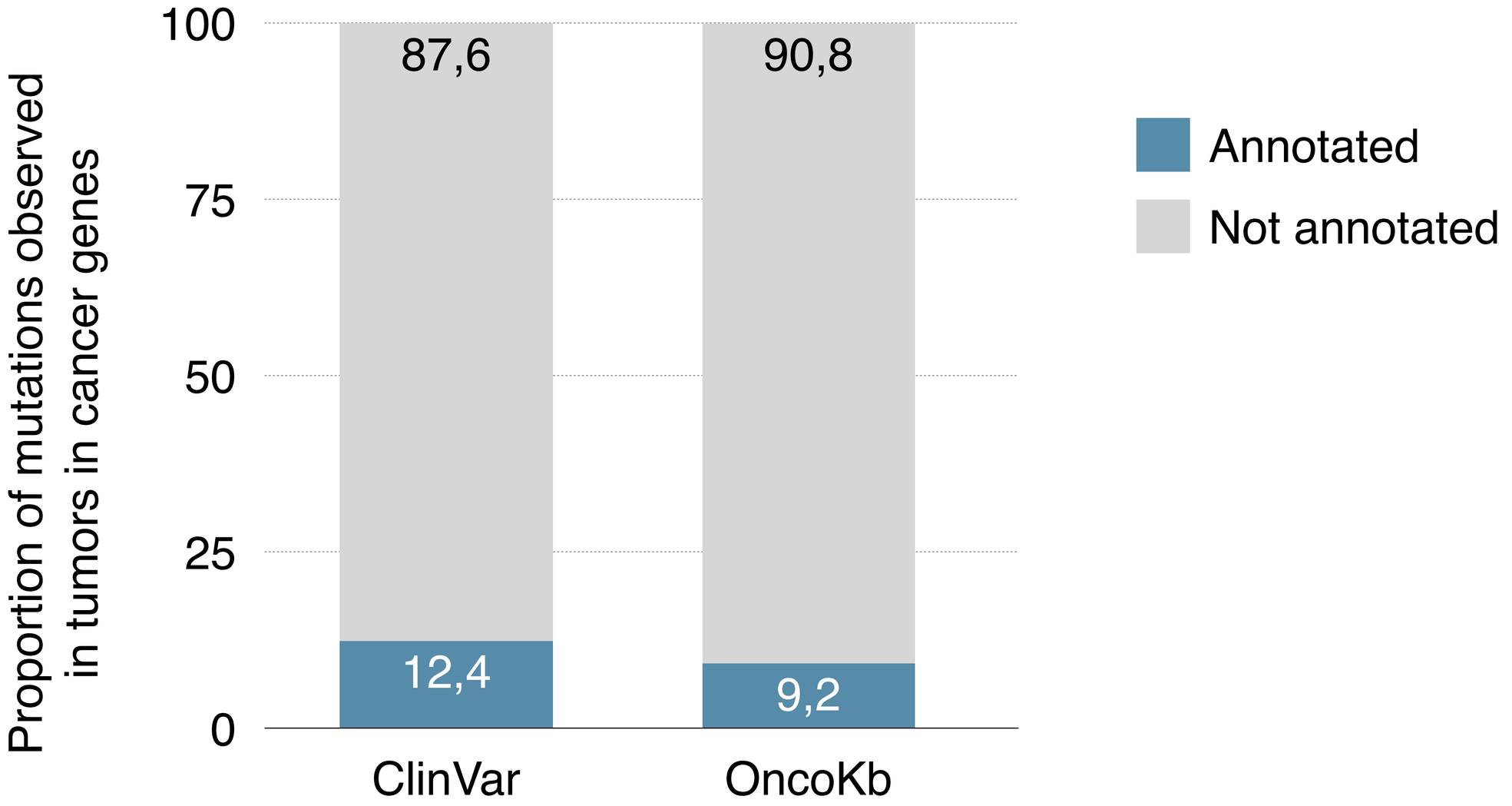
568 Cancer Genes across 66 Cancer Types

This approach recovers most known cancer genes and also identify new ones

http://www.intogen.org

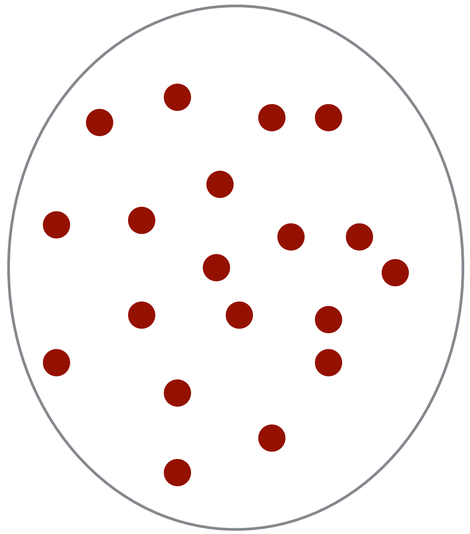
Martínez-Jimenez et al. Nature Reviews Cancer 2020

Most mutations in cancer genes are of uncertain significance

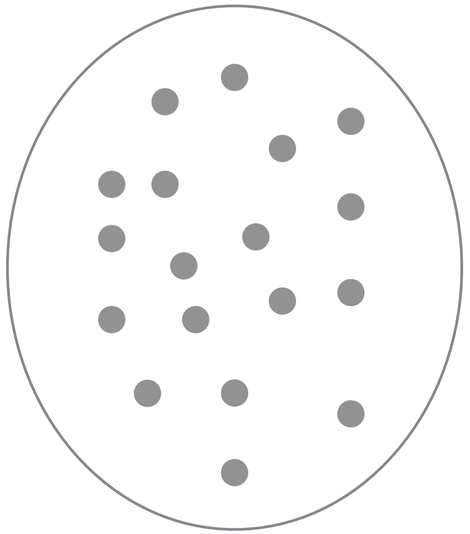


Which mutations in these cancer genes are capable of driving tumorigenesis?

BoostDM: Learns feature combinations that define driver mutations in each gene/tumor type



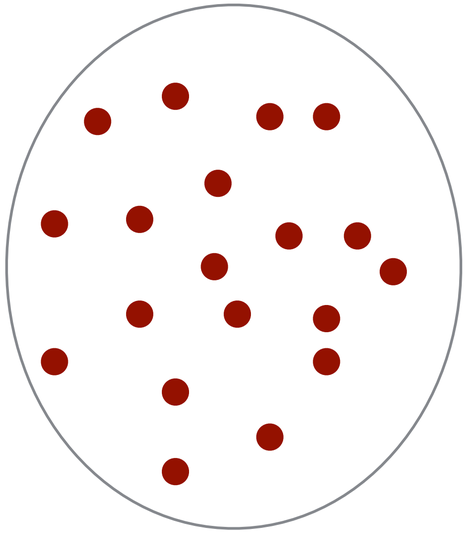
Driver mutations



Passenger mutations

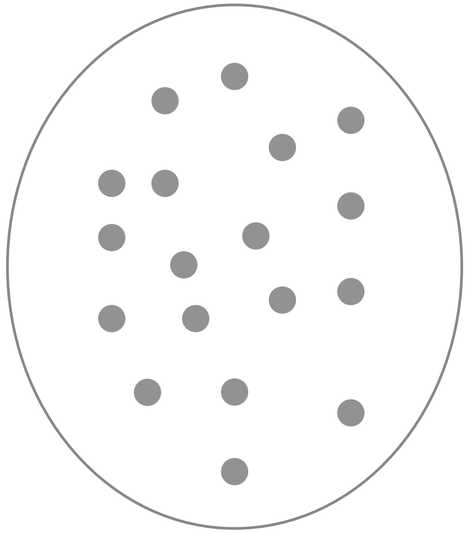
Muiños, Martínez-Jimenez et al Nature 2021

BoostDM: Learns feature combinations that define driver mutations in each gene/tumor type



Driver mutations

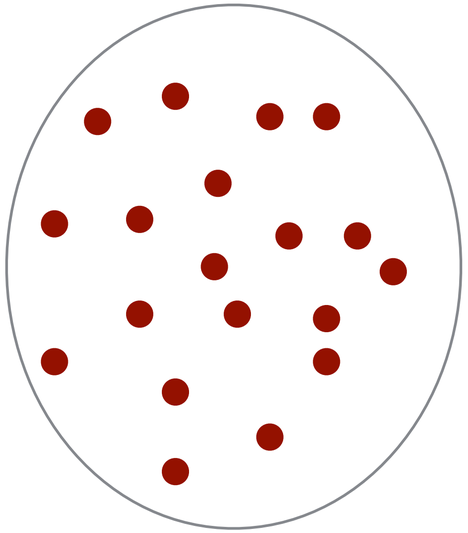
Mutations observed in cancer genes in human tumors are enriched for drivers



Passenger mutations

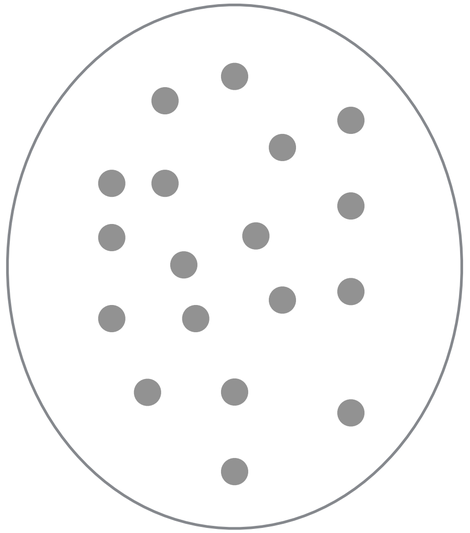
Muiños, Martínez-Jimenez et al Nature 2021

BoostDM: Learns feature combinations that define driver mutations in each gene/tumor type



Driver mutations

Mutations observed in cancer genes in human tumors are enriched for drivers



Passenger mutations

Simulate neutral mutagenesis to create mutations enriched for passengers

Muiños, Martínez-Jimenez et al Nature 2021

BoostDM: Learns feature combinations that define driver mutations in each gene/tumor type

28,076 Tumors · 221 cohorts · 66 Cancer Types · 203,003,747 Somatic Mutations

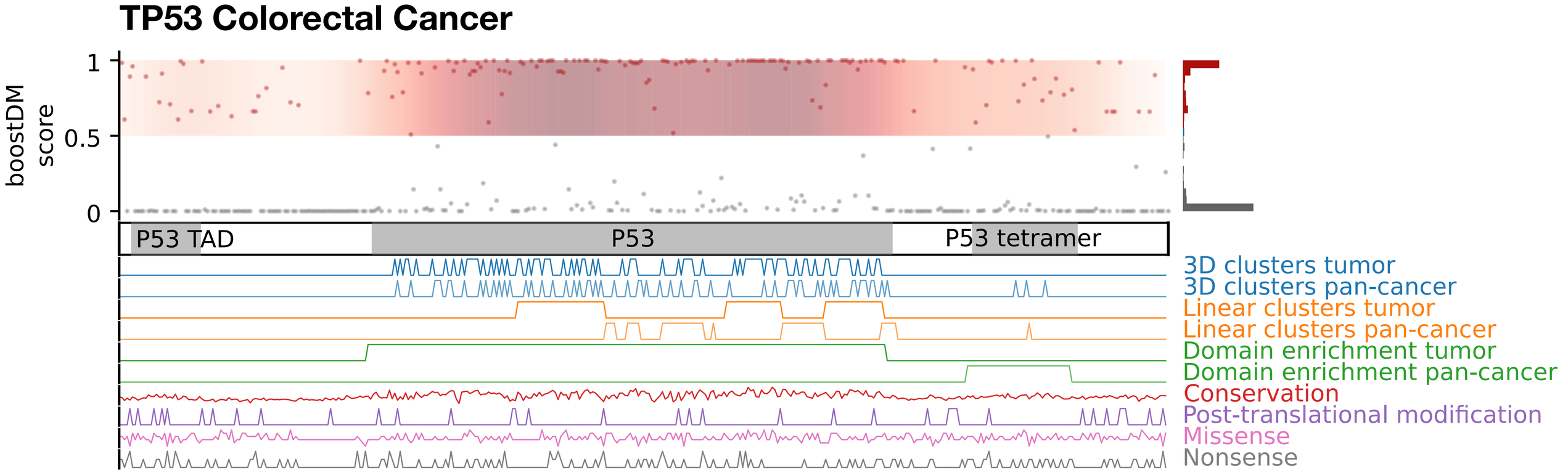
- Gene-tissue specific models
- Interpretable models

185 high quality models

BoostDM

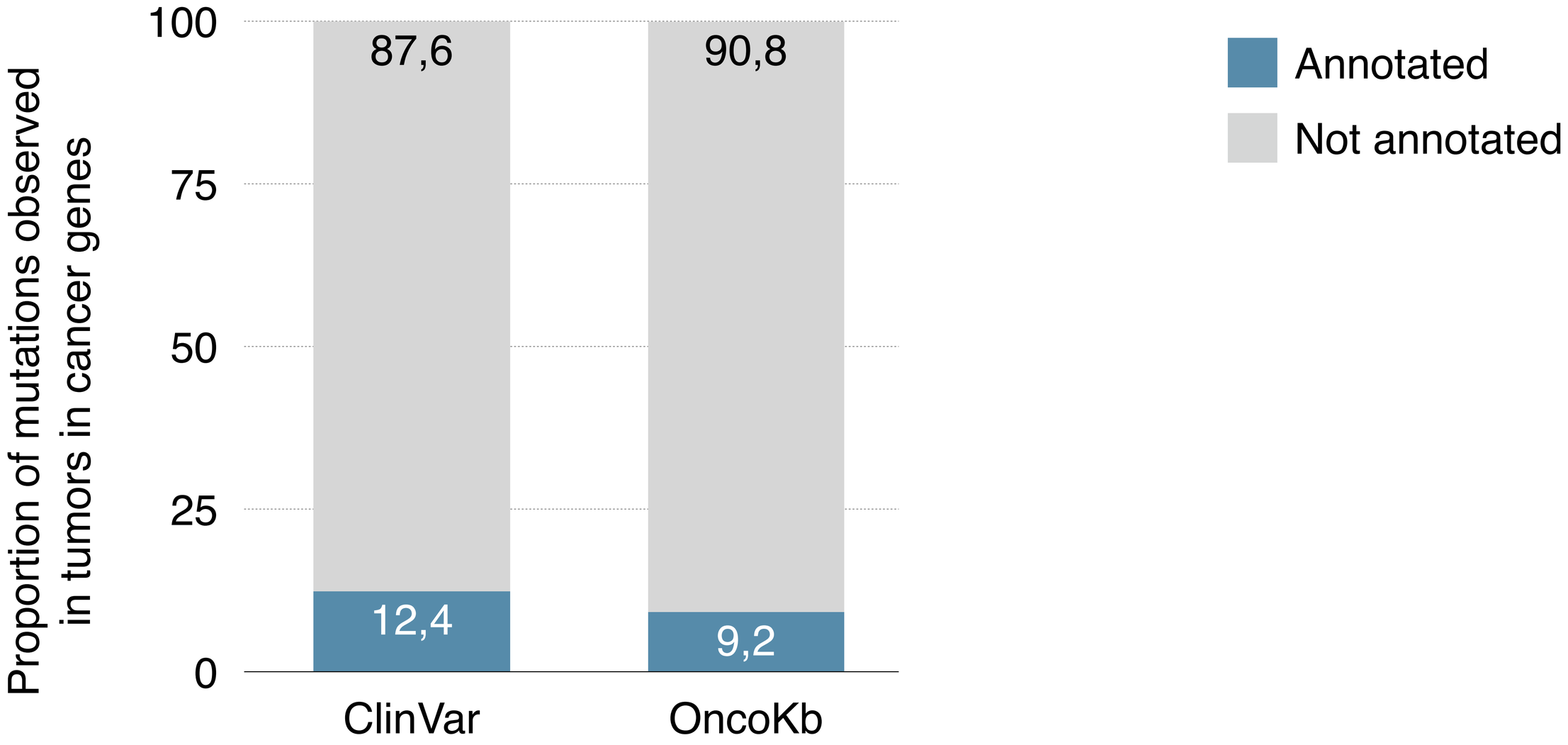
Muiños, Martínez-Jimenez et al Nature 2021

In Silico Saturation Mutagenesis of Cancer Genes

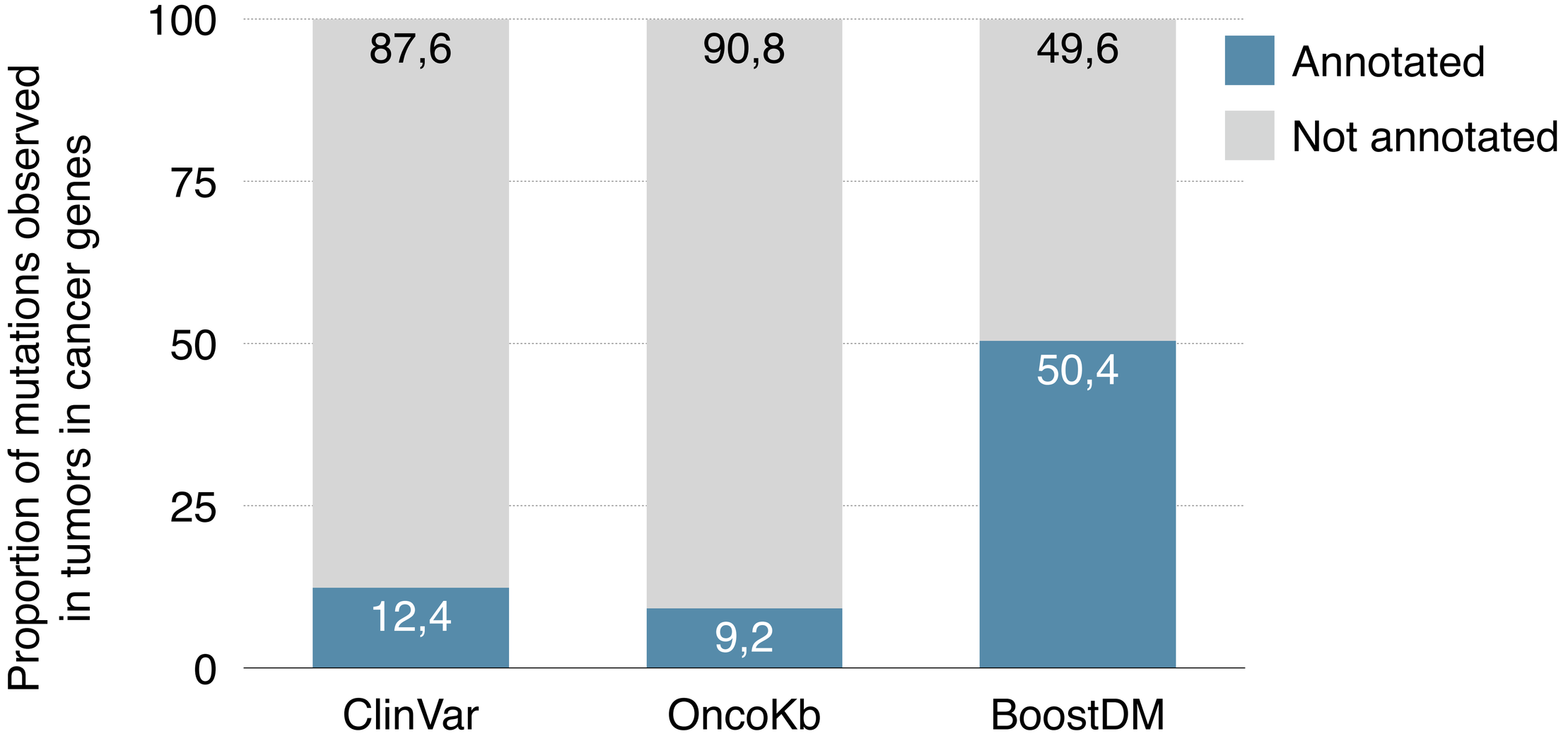


More blueprints at **http://intogen.org/boostdm**

Most mutations in cancer genes are of uncertain significance



Most mutations in cancer genes are of uncertain significance



CANCER GENOME INTERPRETER

http://www.cancergenomeinterpreter.org

- ✔ Identifies potentially oncogenomic alterations
- ✔ Flags genomic biomarkers of drug response with different levels of clinical relevance

ALTERATIONS | PRESCRIPTIONS

Mutations

Show entries with: ☑ Mutations identified as **drivers** ☑ Mutations with oncogenic **annotations** ☑ **Other** mutations

Sample ID	Gene	Protein Change	Oncogenicity	Mutation	Consequence	Oncog
Search here...						
TCGA-49-4494-01A-01D-	EGFR	T790M	driver	chr7:55249071 C>T	missense variant	
TCGA-49-4494-01A-01D-	EGFR	L858R	driver	chr7:55259515 T>G	missense variant	
TCGA-49-4494-01A-01D-	MGA	E2115*	driver	chr15:42042148 G>T	stop gained	
TCGA-49-4494-01A-01D-	LRP1B	R851P	driver	chr2:141751656 C>G	missense variant	
TCGA-49-4494-01A-01D-	LRPPRC	splice acceptor variant	driver	chr2:44204416 C>A	splice acceptor variant	
TCGA-49-4494-01A-01D-	RBM10	splice donor variant	driver	chrX:47034492 G>T	splice donor variant	
TCGA-49-4494-01A-01D-	ARHGAP21	E724*	passenger	chr10:24908654 C>A	stop gained	

Clinical Implementation

CGI-Clinics
Cancer Genome Interpreter

Data-driven cancer genome interpretation
for personalized cancer treatment

https://www.cgiclinics.eu/

HORIZON-HLTH-2021-CARE-05
5 years EU project, started November 2022

CGI-Clinics is an international multidisciplinary project with 17 partners involving biologists, bioinformaticians, oncologists, patients,...

CGI-Clinics
Cancer Genome Interpreter

4 EU Countries
5 years
10 M€

www.cgiclinics.eu

Clinical partners and Healthcare payers

VHIO Vall d'Hebron Institute of Oncology
althaia Xarxa Assistencial Universitària Manresa
Gustave Roussy Cancer Campus Grand Paris
Centre de Lutte contre le Cancer Léon Bérard
ICO Institut Català d'Oncologia
dIBGi Institut d'Investigació Biomèdica de Girona Dr. Josep Trueta
Servicio Andaluz de Salud Consejería de Salud
Junta de Andalucía Consejería de Salud y Consumo
UNIKLINIK RWTH AACHEN
UNIKLINIK KÖLN
MANCHESTER CANCER RESEARCH CENTRE

Technical Development and Data Sharing

IRB Barcelona
Institute for Research in Biomedicine
cnag
CRG Centre for Genomic Regulation

Patient associations and Policy makers

European Cancer Patient Coalition
aecc Contra el Cáncer

Health economics, Regulatory, Patient engagement

AliraHealth

Communication and Dissemination

EACR European Association for Cancer Research

9 Hospitals + 3 collaborators

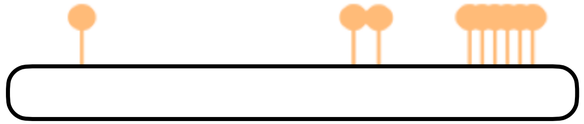
30 hospitals in implementation phase (from 2026)

- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- Identifying Clonal Hematopoiesis Drivers
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

Modeling neutral mutagenesis

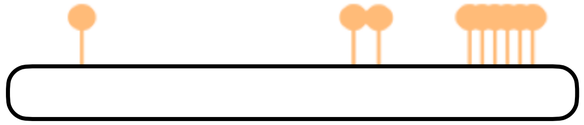
Modeling neutral mutagenesis

- Variable mutation rate along the genome

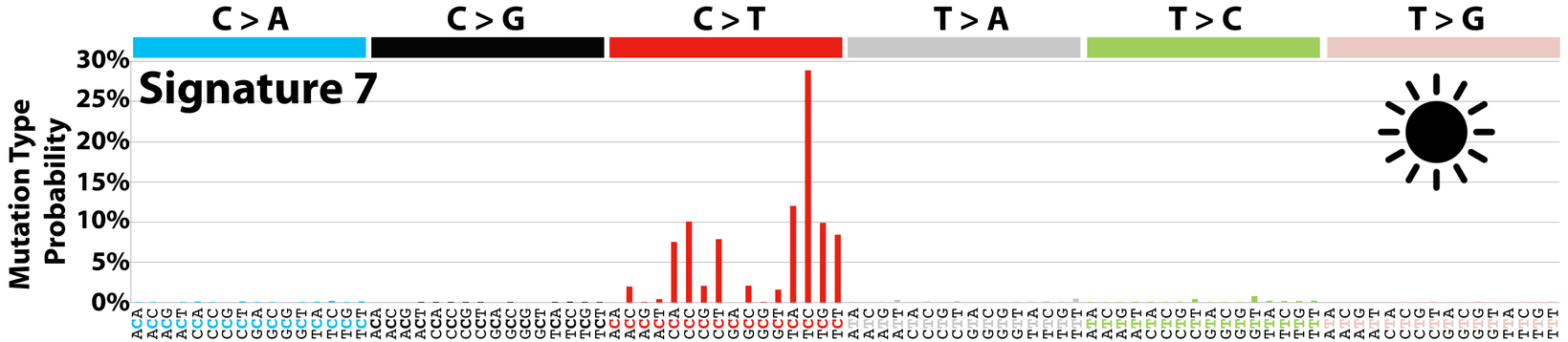


Modeling neutral mutagenesis

- Variable mutation rate along the genome



- Different probability for different sequence context (mutational signatures)

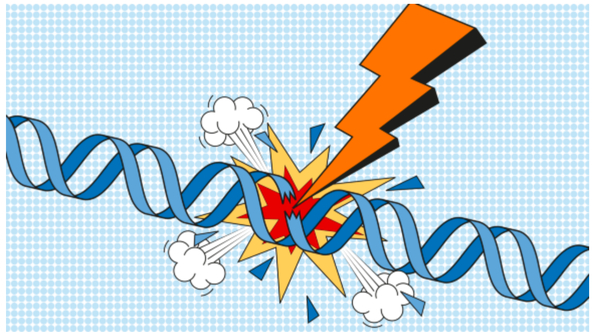


Mutational signatures of cancer treatments

DNA damaging agent

Chemotherapy

e.g. alkylating agents



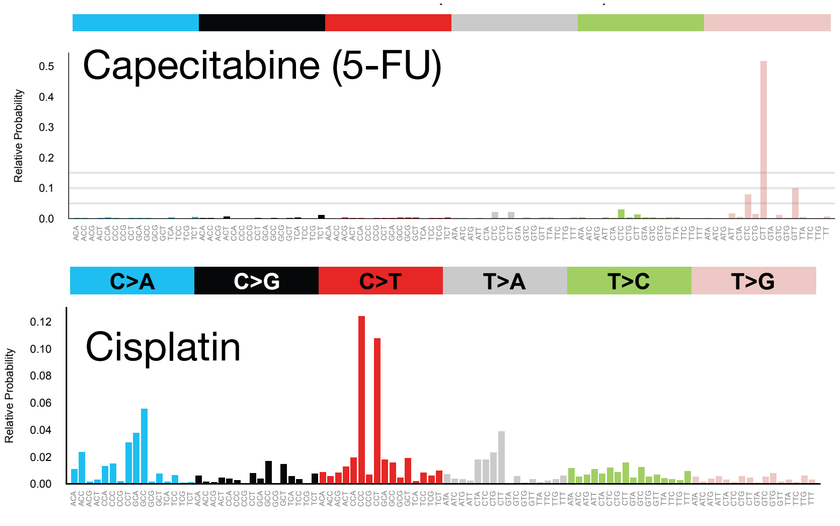
Mutational signatures of cancer treatments

DNA damaging agent

Chemotherapy

e.g. alkylating agents

Mutational signatures of cancer treatments



Pich et al., Nature Genetics 2019

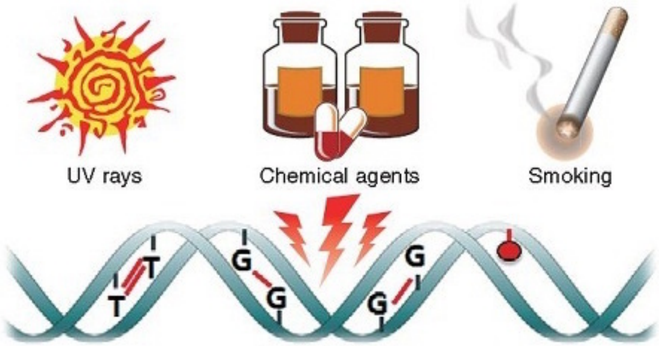
Oriol Pich

Abel Gonzalez-Perez

Ferran Muiños

Interplay between DNA damage and DNA repair

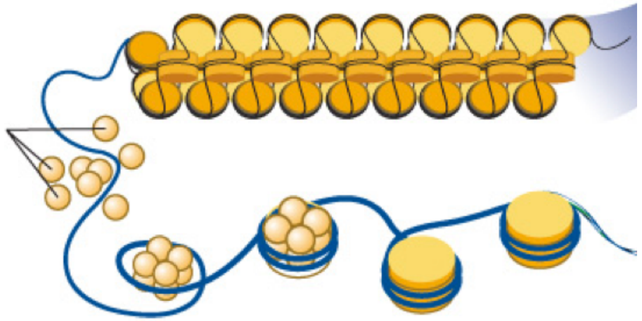
DNA damage and replication errors



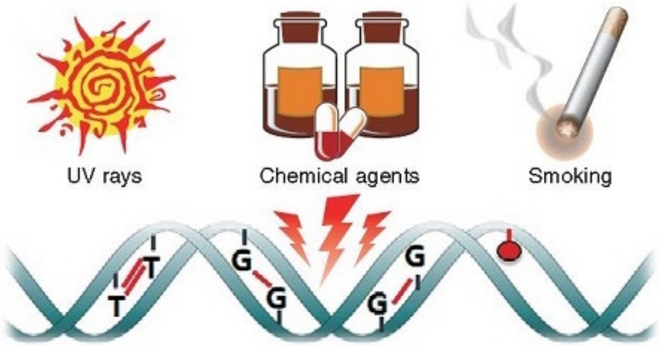
DNA repair

Interplay between DNA damage and DNA repair and chromatin

Chromatin conformation

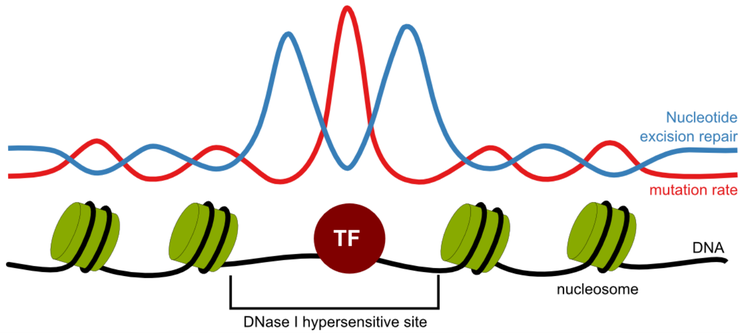


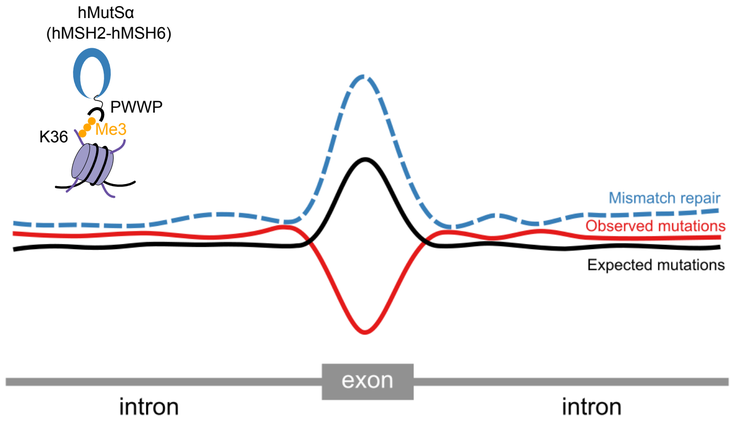
DNA damage and replication errors

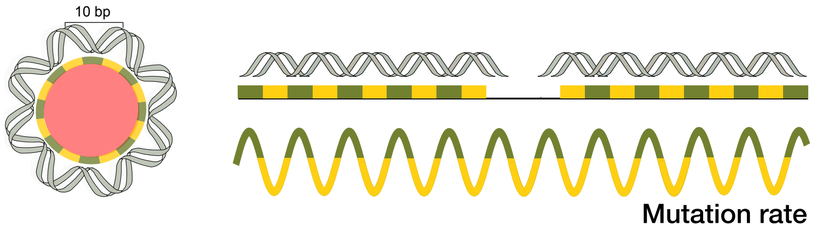


DNA repair

Mutation rate variability at local scale







High mutation rate in TFBS due to impaired Nucleotide Excision Repair

Sabarinathan et al., Nature 2016

Differential mismatch repair leads to reduced mutation rate in exons

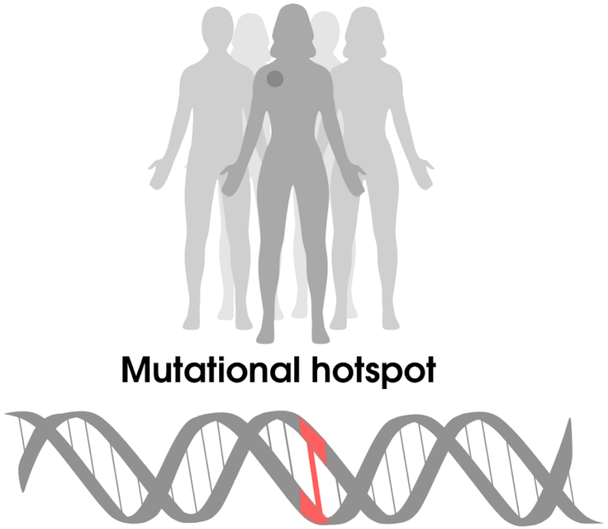
Frigola et al., Nature Genetics 2017

10-bp mutation rate peridicity in nucleosome covered DNA

Pich et al., Cell 2018

Reviewed in Gonzalez-Perez, Sabarinathan and Lopez-Bigas. Cell 2019

How well do we estimate mutation rate at single-nucleotide resolution?



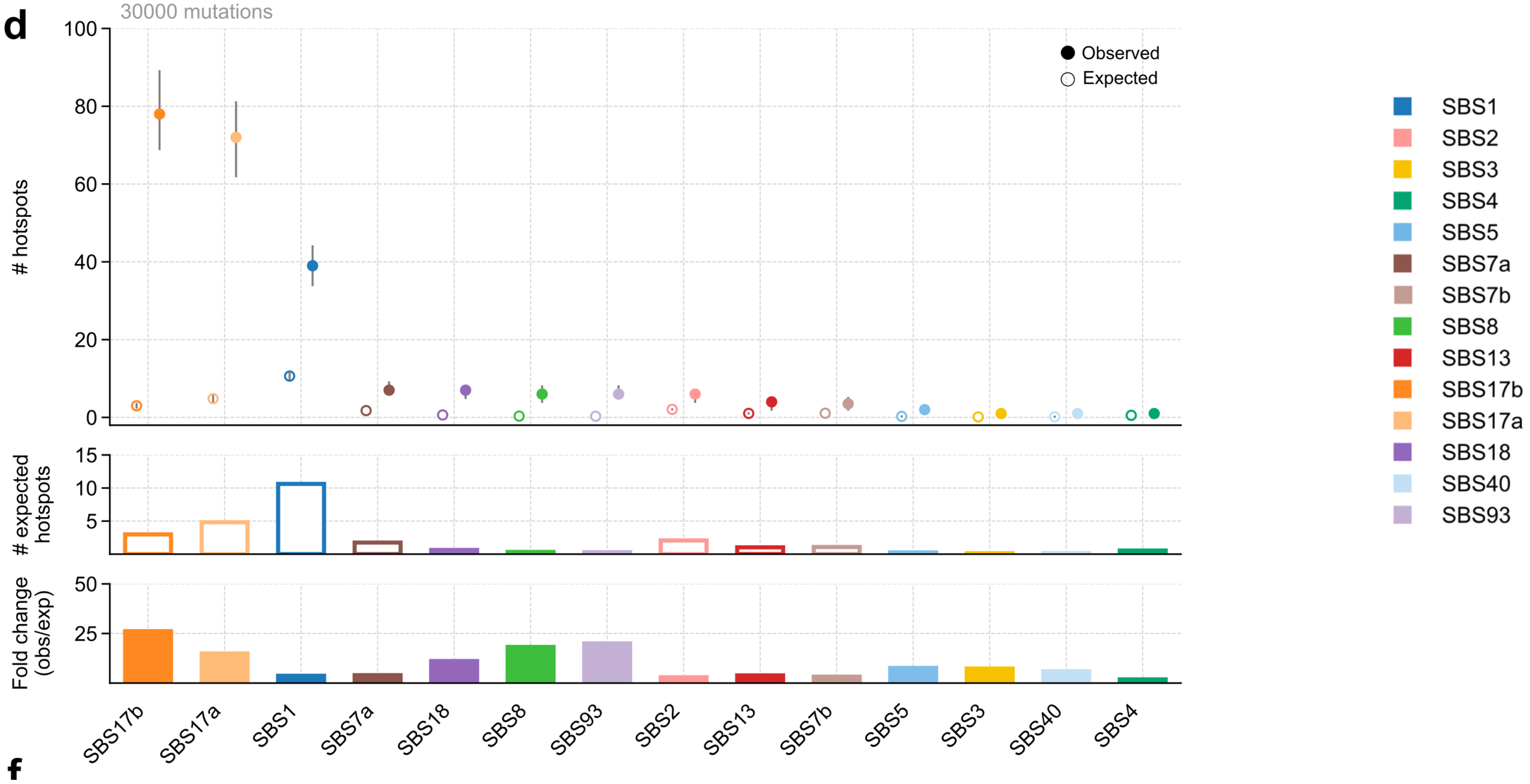
Identification of somatic mutation hotspots across 7,507 whole genomes

Which processes create hotspots? Can we predict those with current models?

Claudia Arnedo

Arnedo et al., BioRxiv 2022 (under review)

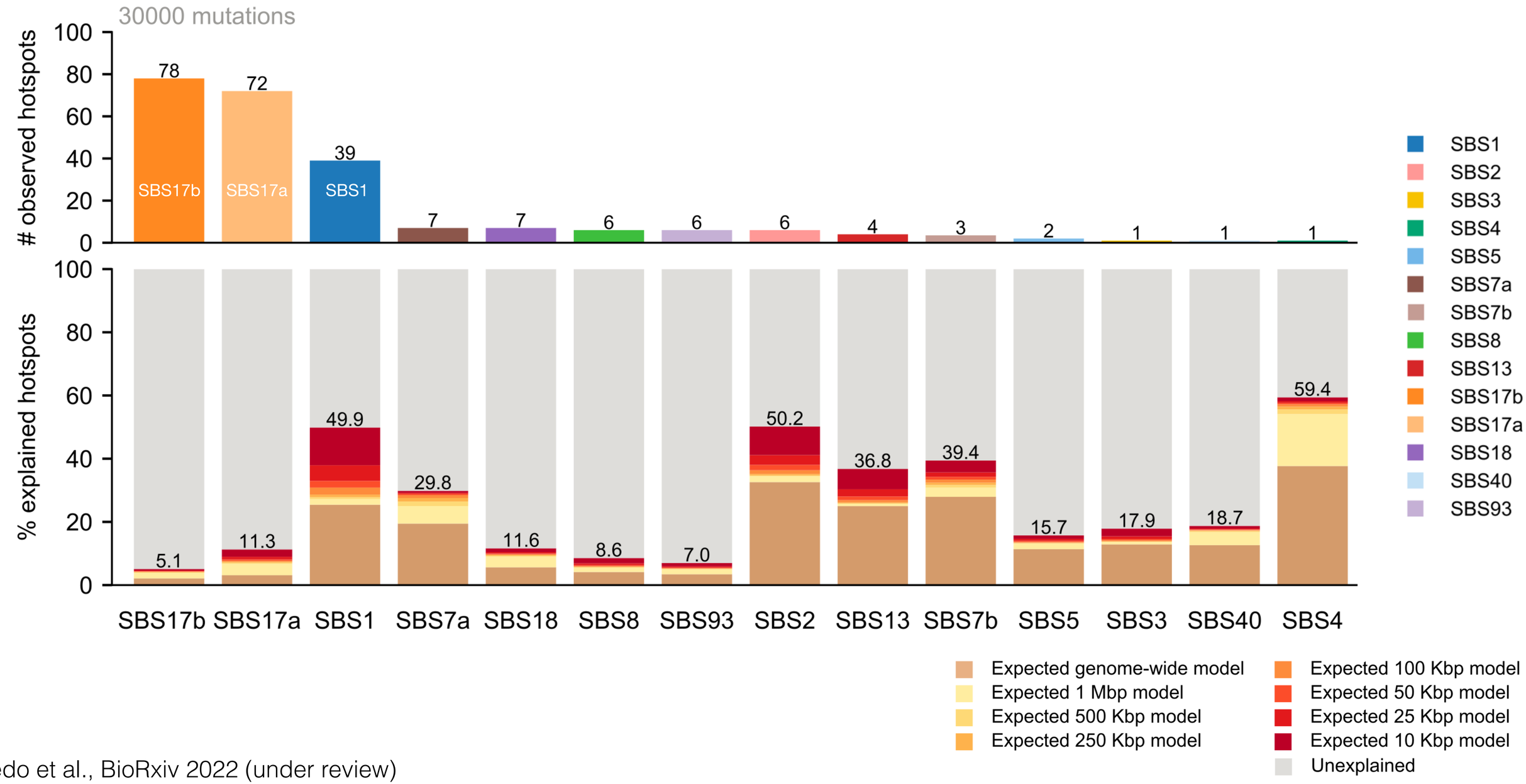
SBS1 and SBS17a, b have the highest propensity to hotspot formation



Hotspot = 2 o more samples with the same mutation

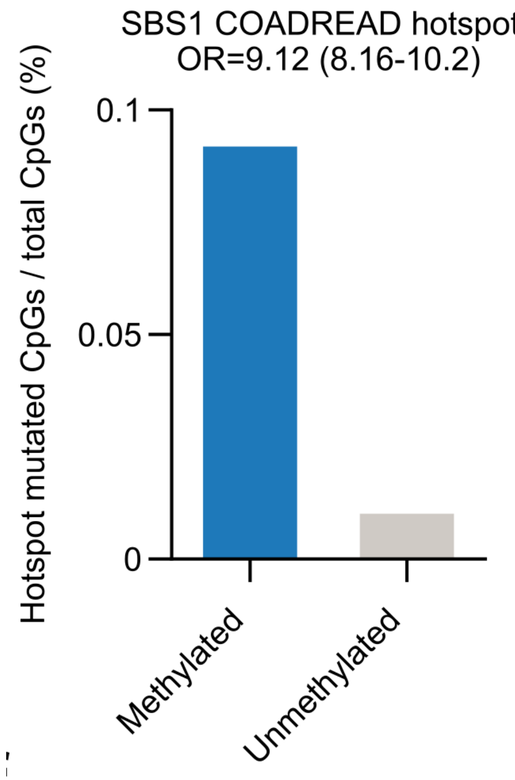
Arnedo et al., BioRxiv 2022 (under review)

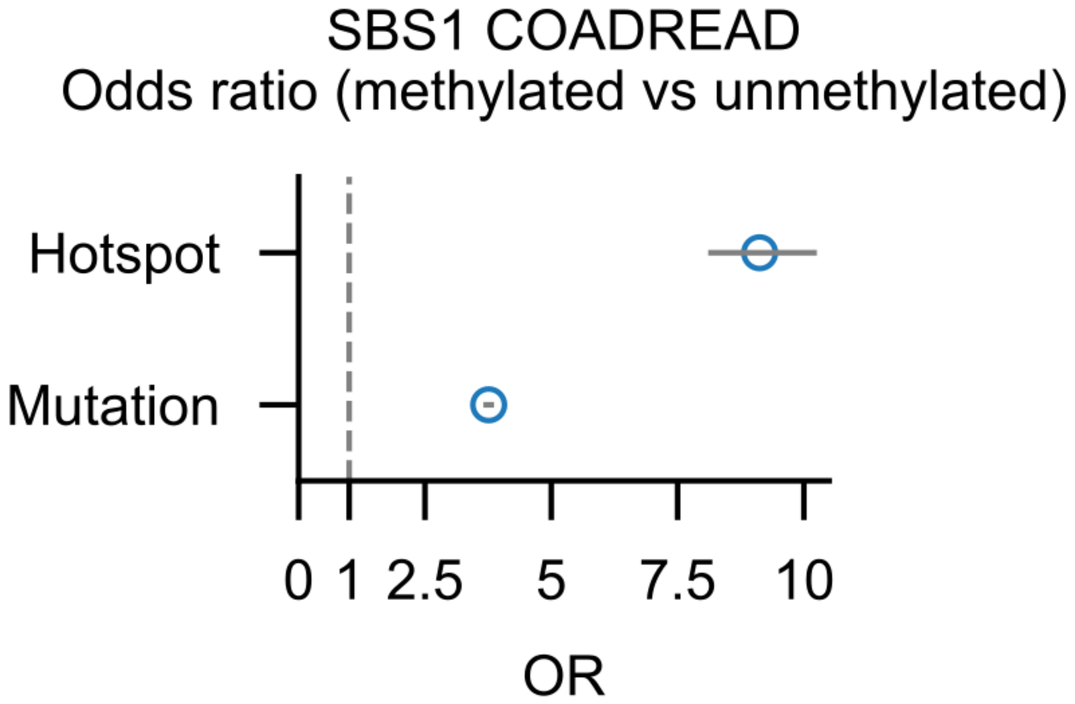
Large proportion of hotspots remain unexplained



Arnedo et al., BioRxiv 2022 (under review)

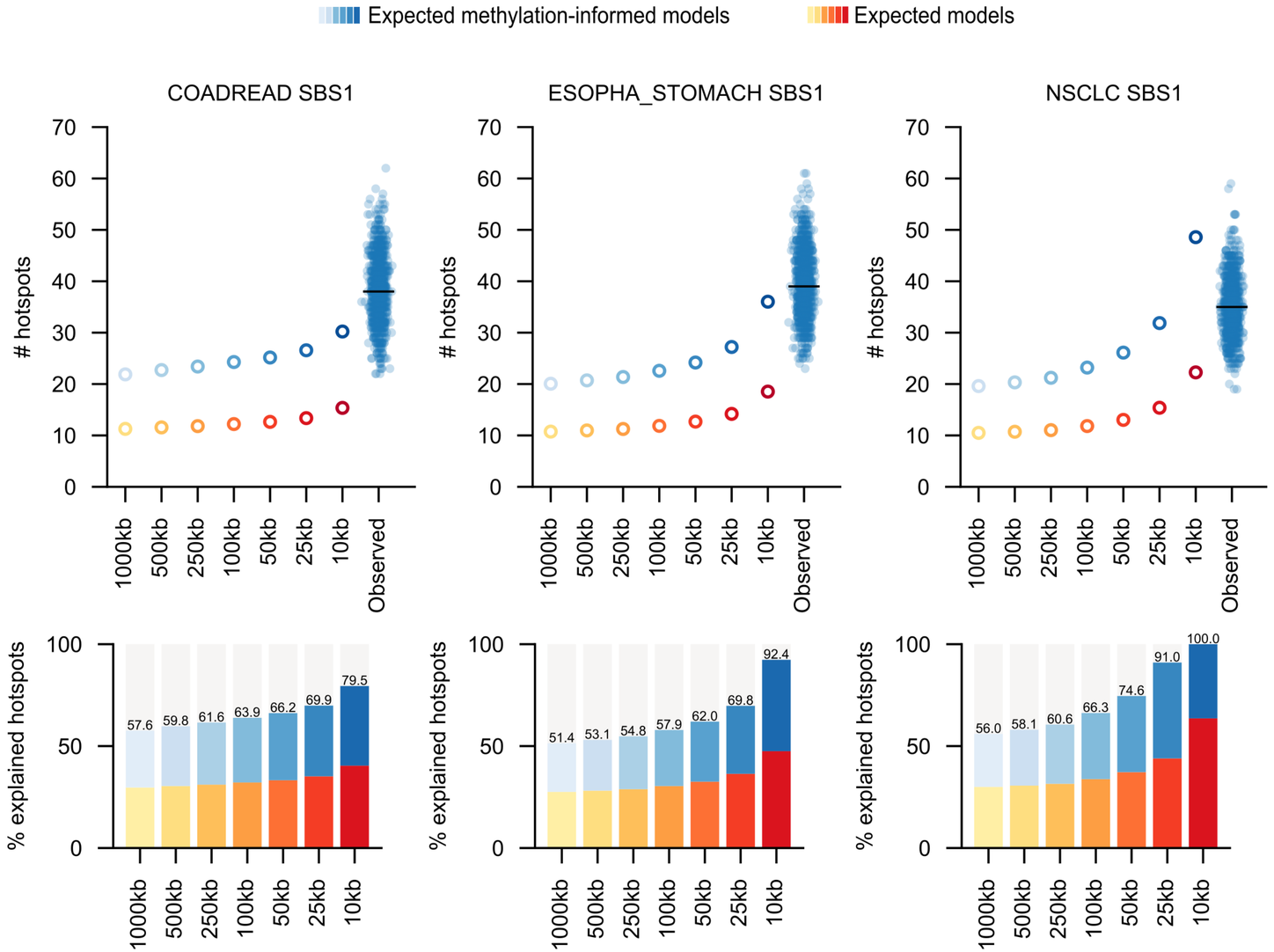
High proportion of hotspots in methylated CpGs





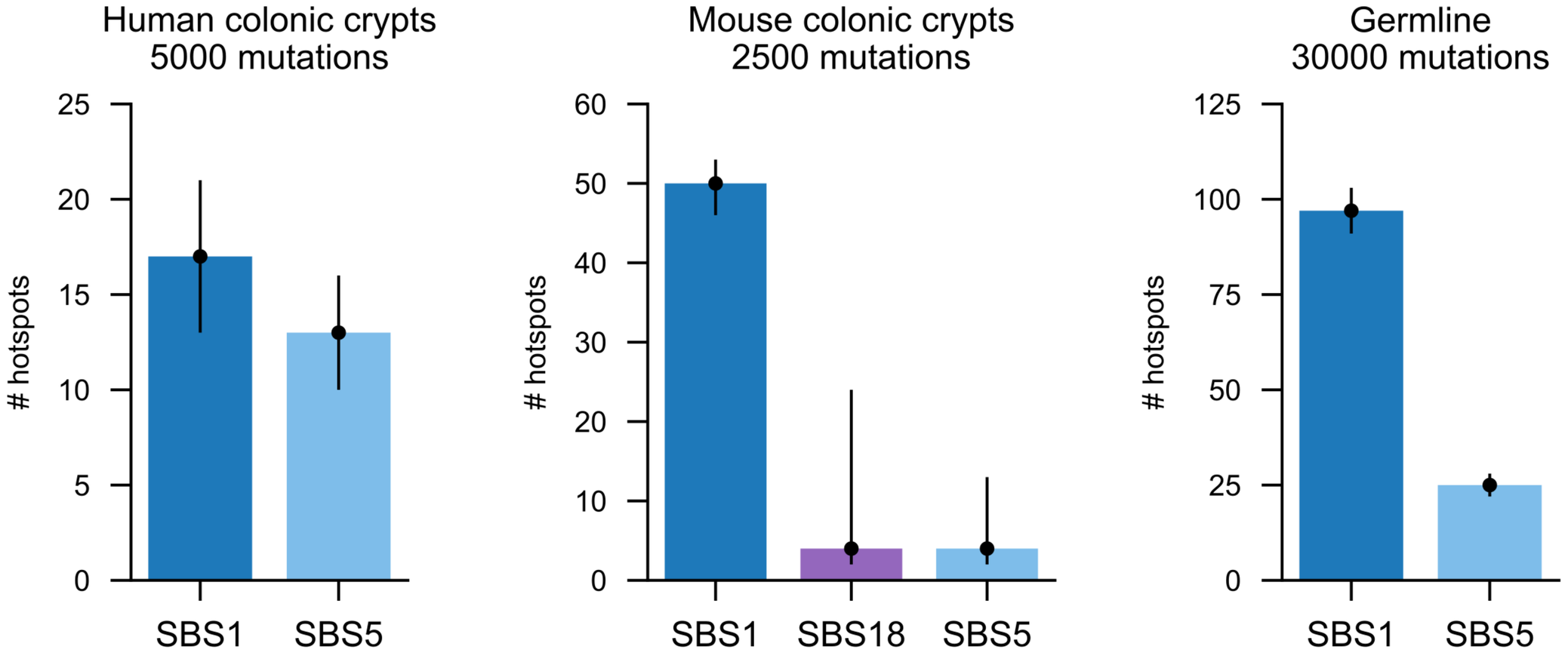
Arnedo et al., BioRxiv 2022 (under review)

Genome-wide distribution of methylated CpGs sites can explain most of SBS1 hotspot propensity



Arnedo et al., BioRxiv 2022 (under review)

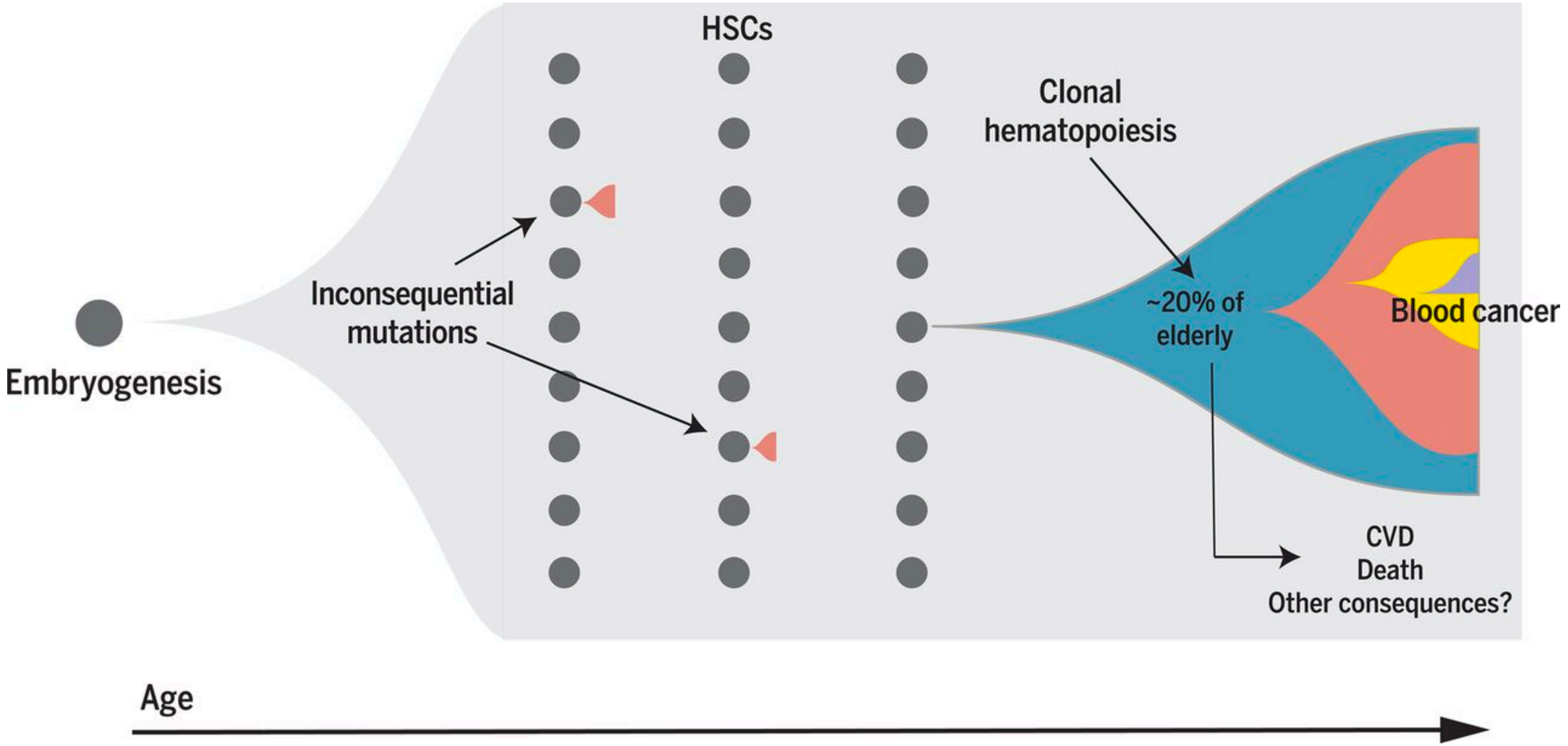
Beyond cancer: high SBS1 hotspot propensity in normal tissues and germline variants



Arnedo et al., BioRxiv 2022 (under review)

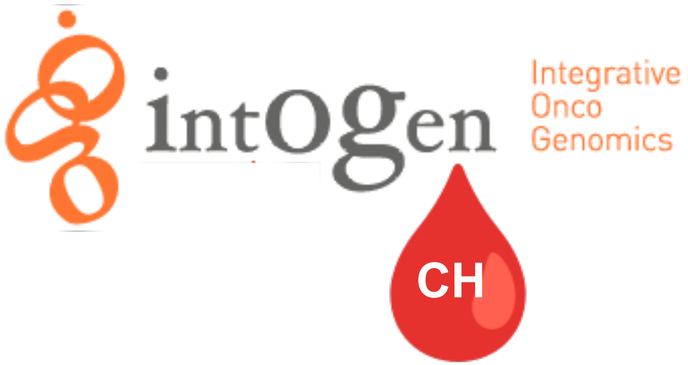
- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- **Identifying Clonal Hematopoiesis Drivers**
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

Clonal expansions in normal tissue



Jaiswal and Ebert Science 2019

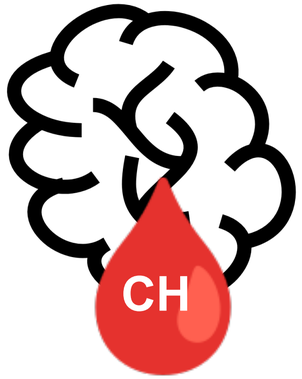
Identification of clonal hematopoiesis driver genes and driver mutations



https://www.intogen.org/ch/

CH driver genes

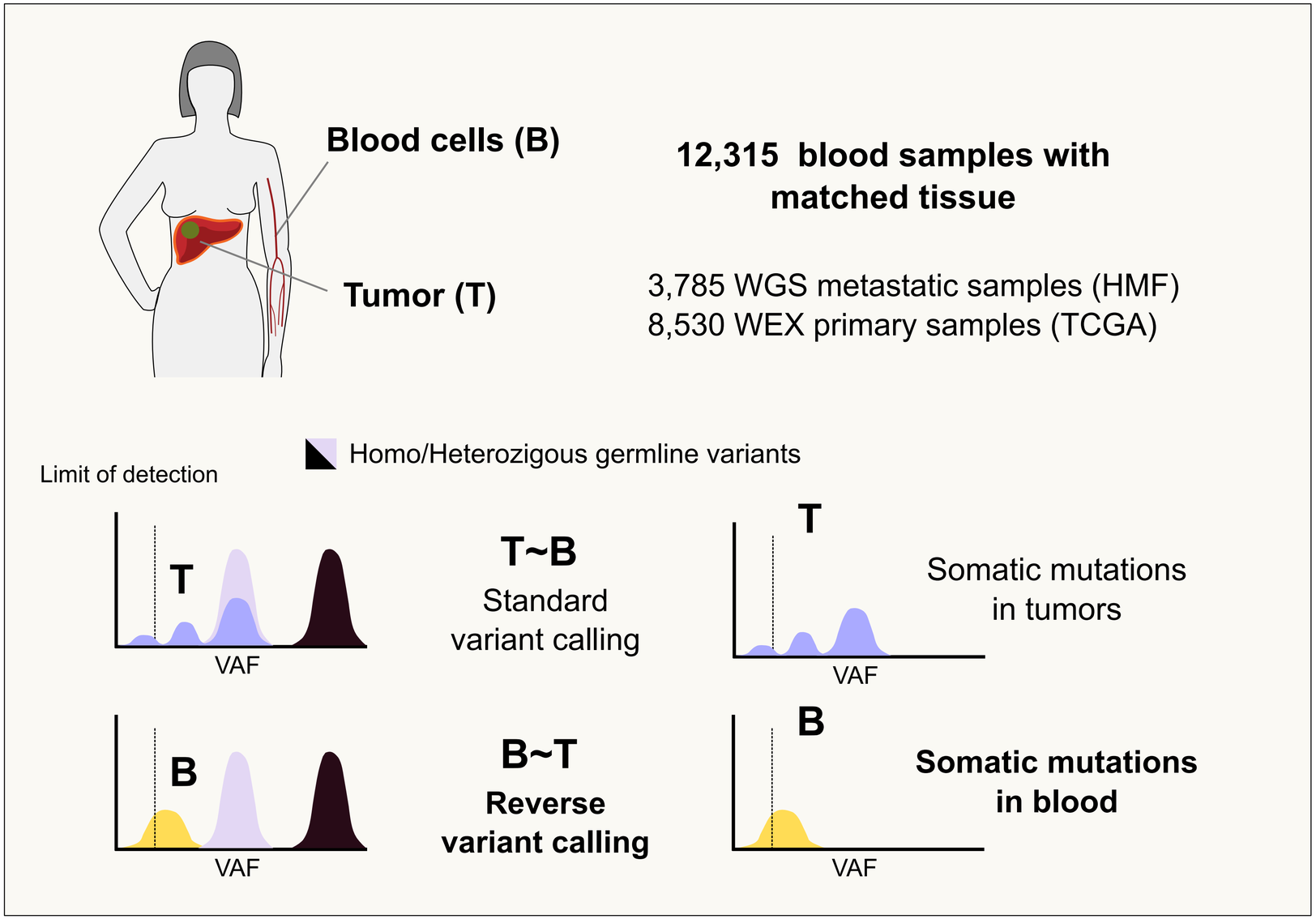
BoostDM



CH driver mutations

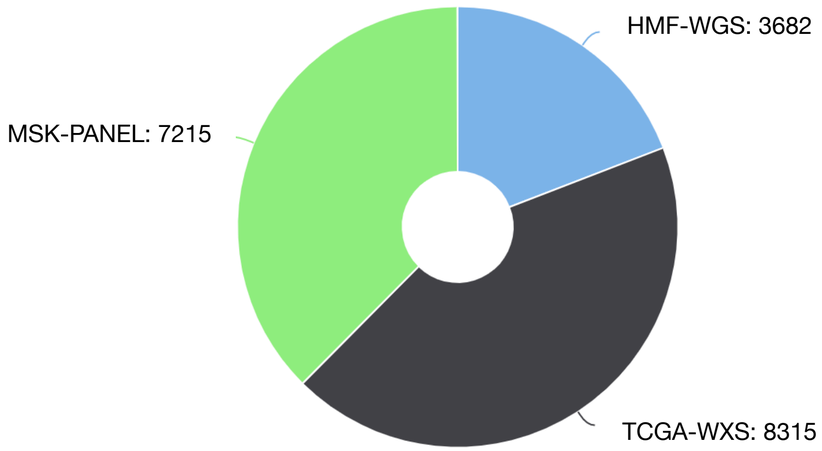
Clinical interpretation of CH mutations

Exploiting cancer genomics data to identify blood somatic mutations

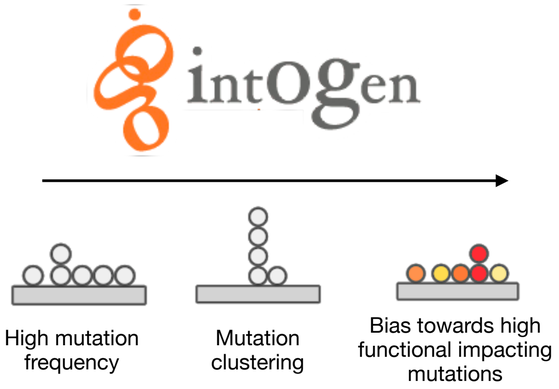


Pich et al., Nature Comms 2022

Discovering Clonal Hematopoiesis Driver Genes



19,202 Tumors · 3 cohorts



Mutation Pattern Analysis
to identify Cancer Genes

64 Clonal Hematopoiesis Driver Genes
(All known + new candidates)

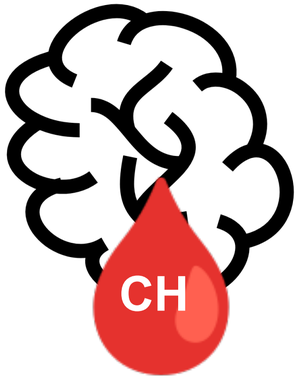
intOgen Integrative Onco Genomics
CH

Pich et al., Nat Comms 2022

http://www.intogen.org/ch

Identification of Clonal Hematopoiesis Driver Mutations through In Silico Saturation Mutagenesis

BoostDM



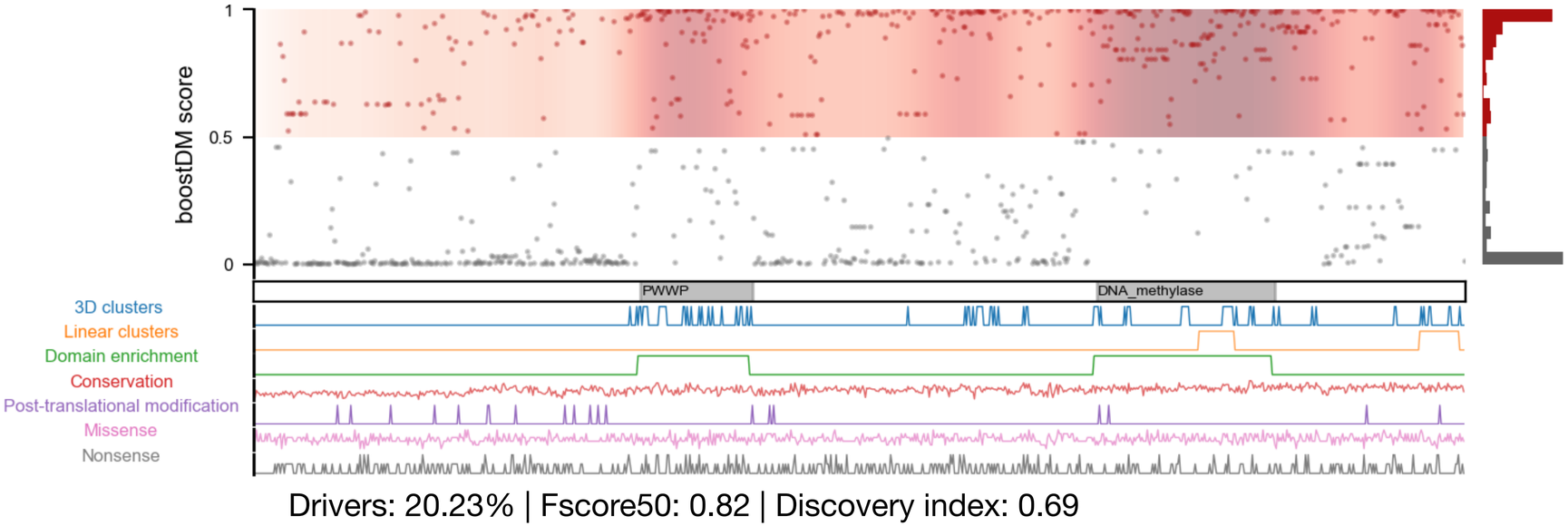
Santi Demajo

Joan Enric Ramis

Abel Gonzalez-Perez

Ferran Muiños

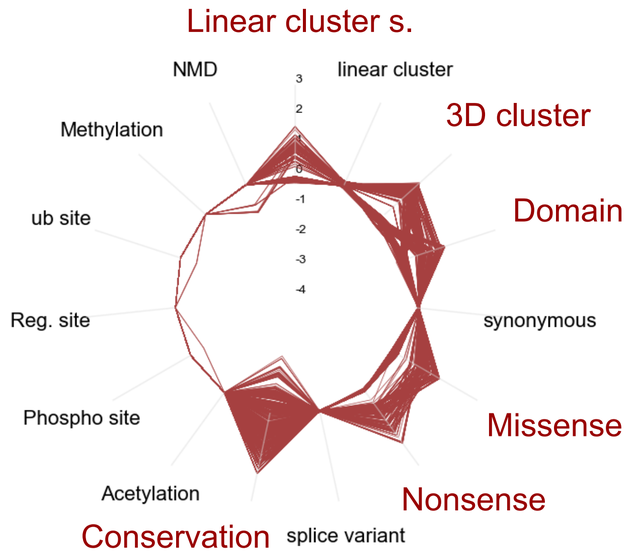
In silico saturation mutagenesis of **DNMT3A**



Drivers: 20.23% | Fscore50: 0.82 | Discovery index: 0.69

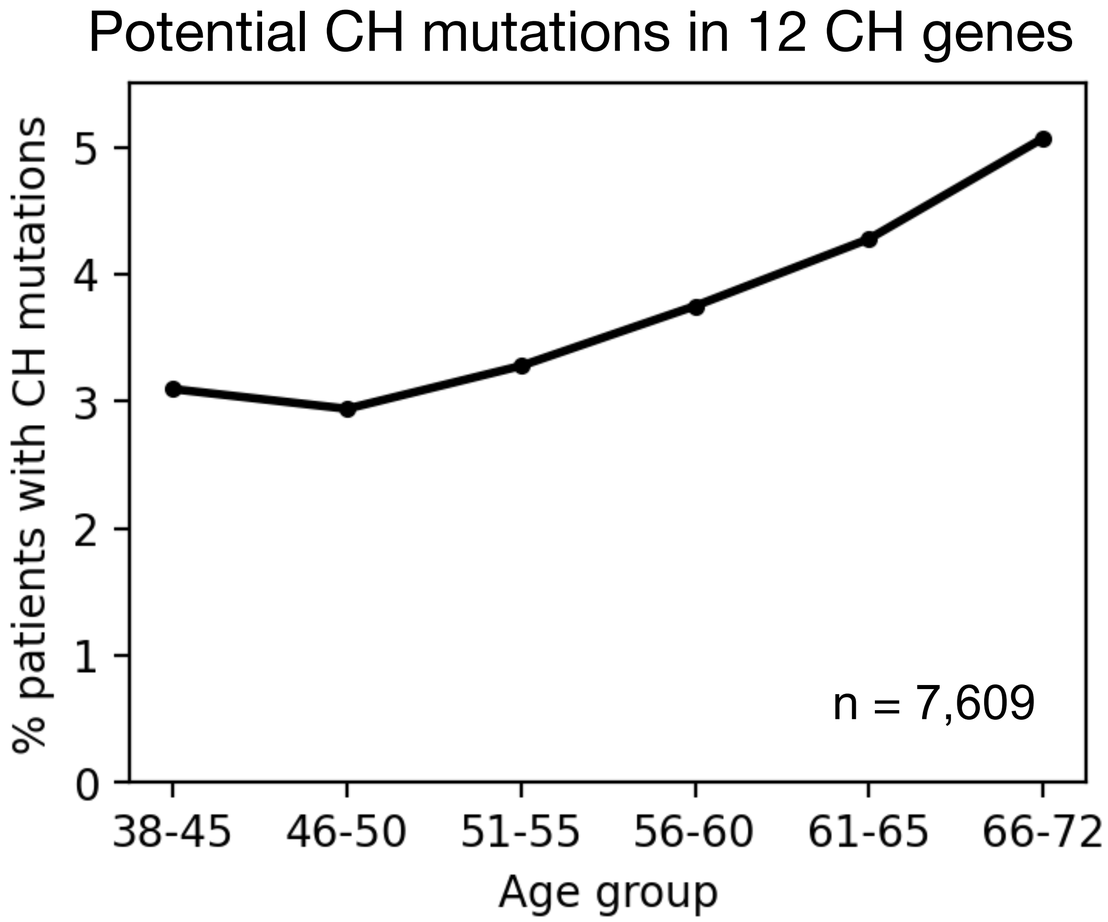
All predicted DNMT3A drivers:
missense & nonsense mutations
in two functional domains and two clusters

Explanation
Observed DNMT3A drivers



Finding CH mutations in 200,000 individuals (UK Biobank)

Potential CH mutations are associated with age but show a high rate of false positives

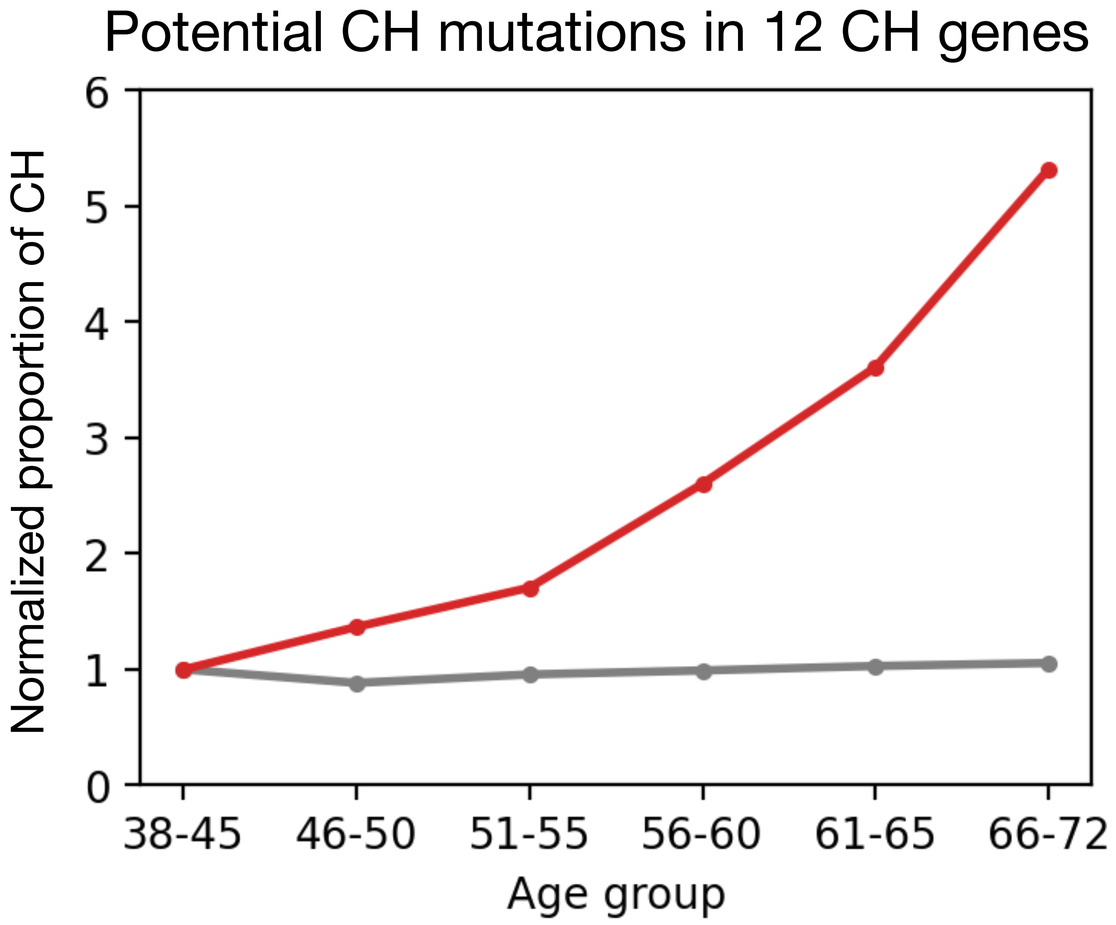


Some method to select specific mutations is needed to eliminate false positive mutations

Whole exome sequencing: DeepVariant filtered by AD > 3, VAF < 0.30, non-synonymous, SNVs, low gnomAD,...

Only CH mutations predicted as drivers by BoostDM-CH highly correlate with age

Identification of driver mutations from the potential CH mutations by BoostDM-CH



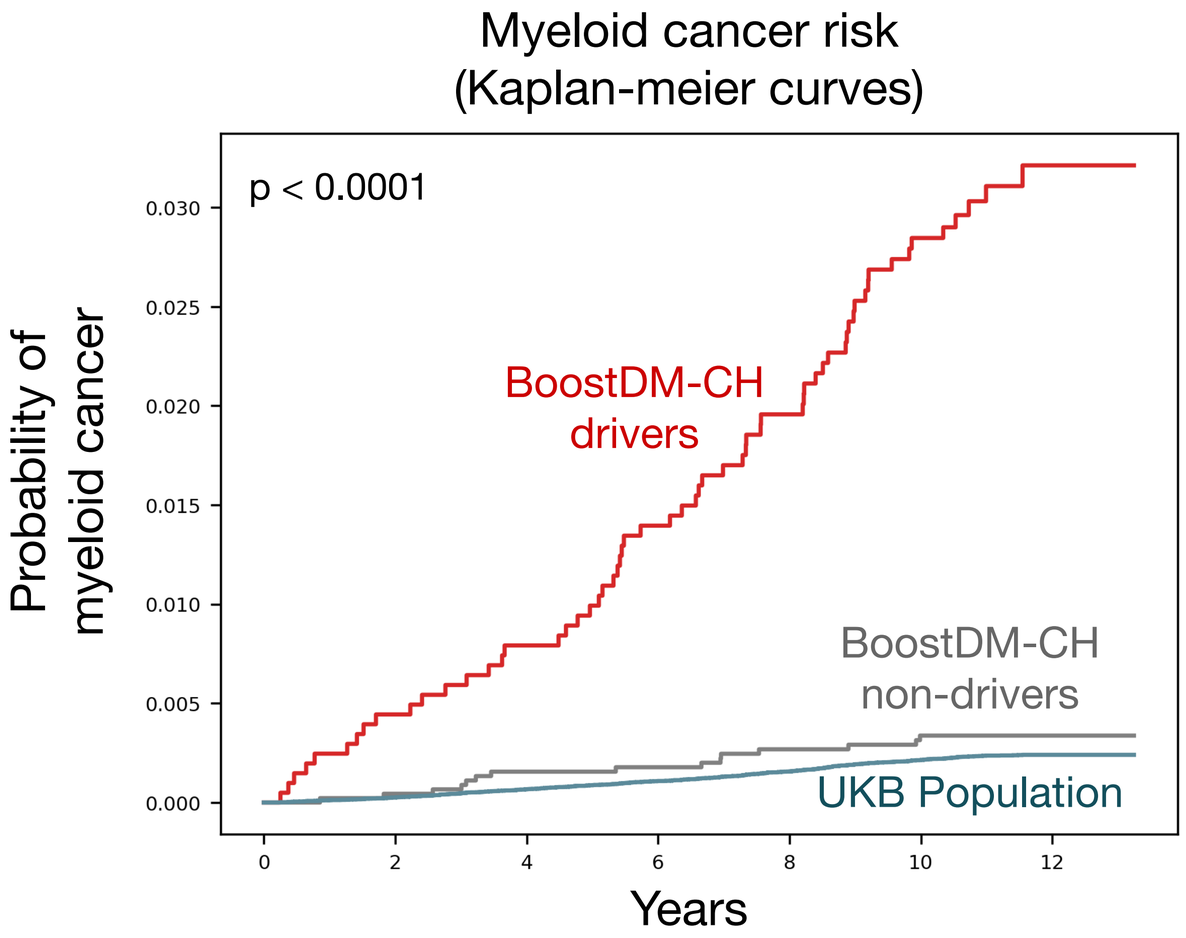
BoostDM-CH drivers
n = 2,298 (~30%)

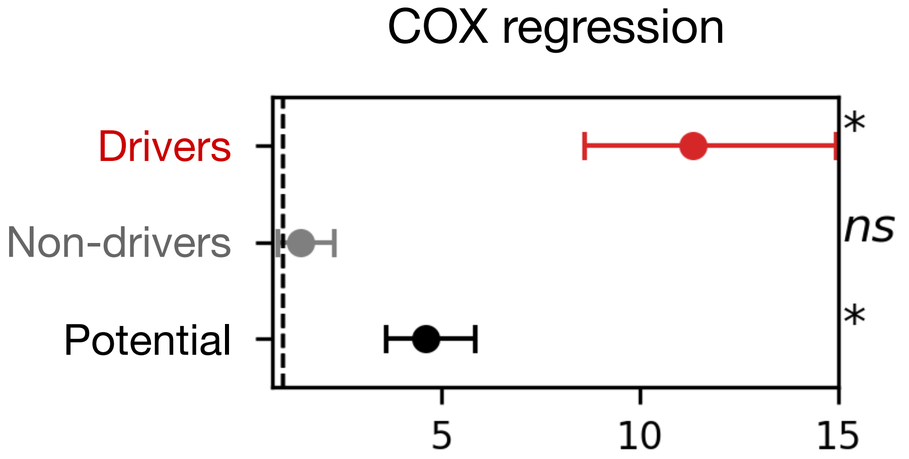
BoostDM-CH non-drivers
n = 5,311 (~70%)

Logistic regressions:
Drivers p-val = 6e-72
Non-drivers p-val = *ns*

biobank uk

Only CH mutations predicted as drivers by BoostDM-CH are associated with an increased risk of hematological cancer

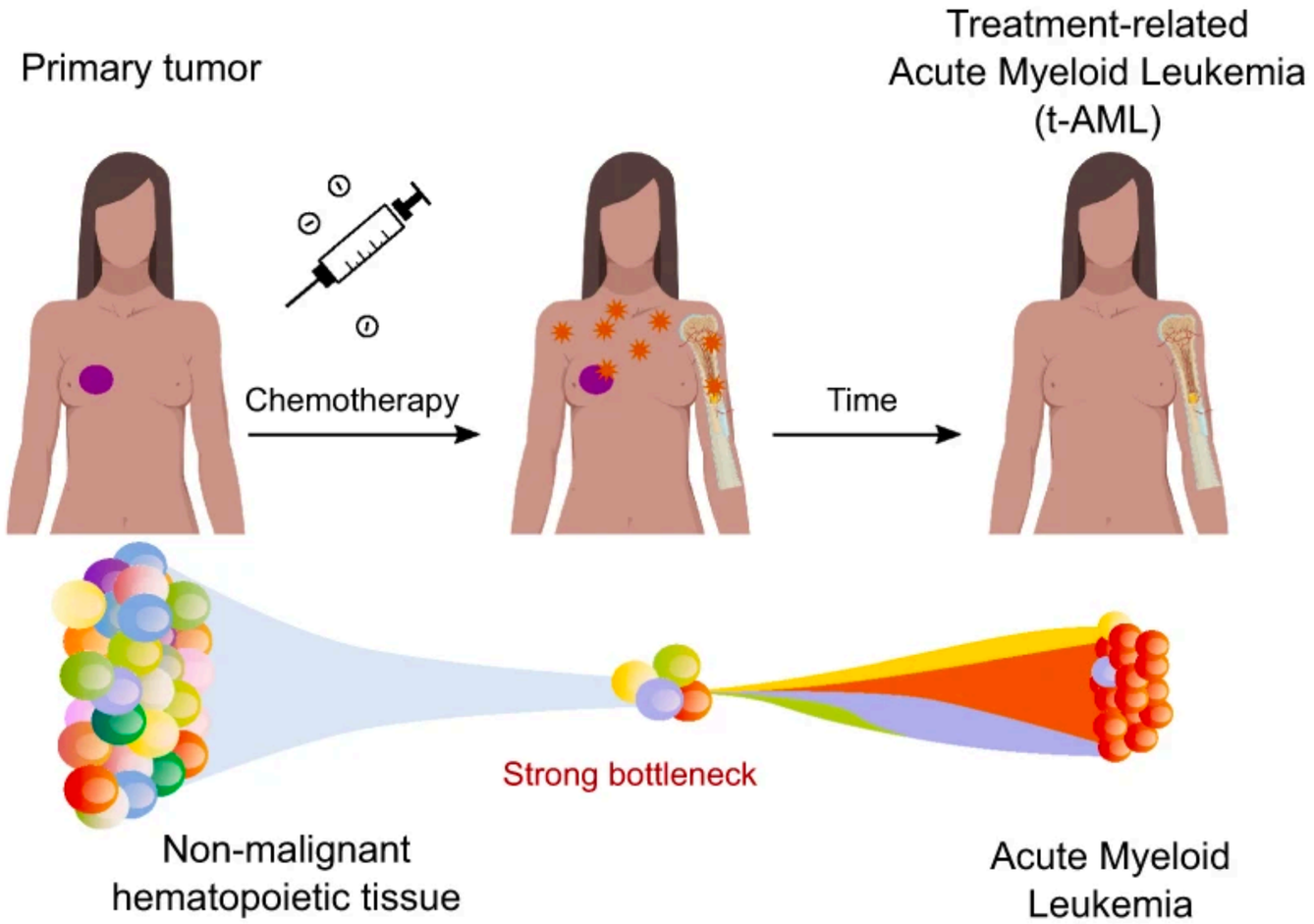




(covariates: age, sex, ancestor)

- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- Identifying Clonal Hematopoiesis Drivers
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

Treatment-related Acute Myeloid Leukemia (tAML)



Pich et al., Nature Communications 2021

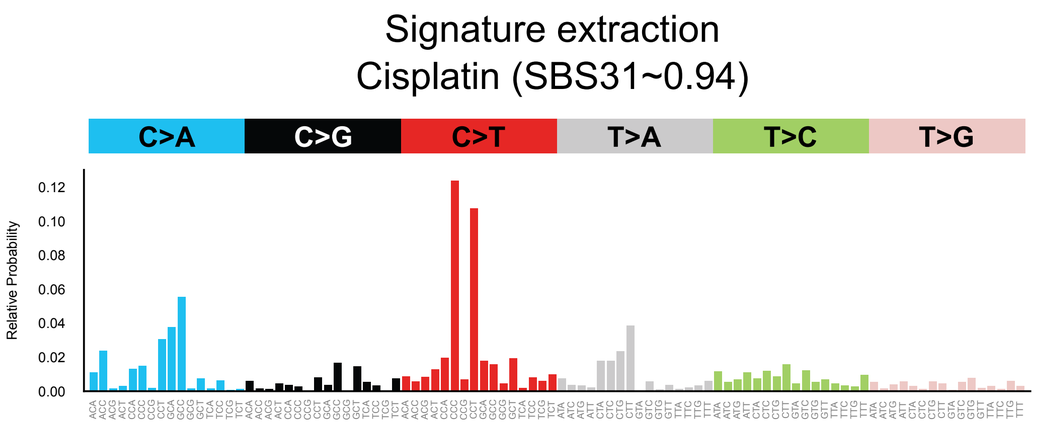
HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA

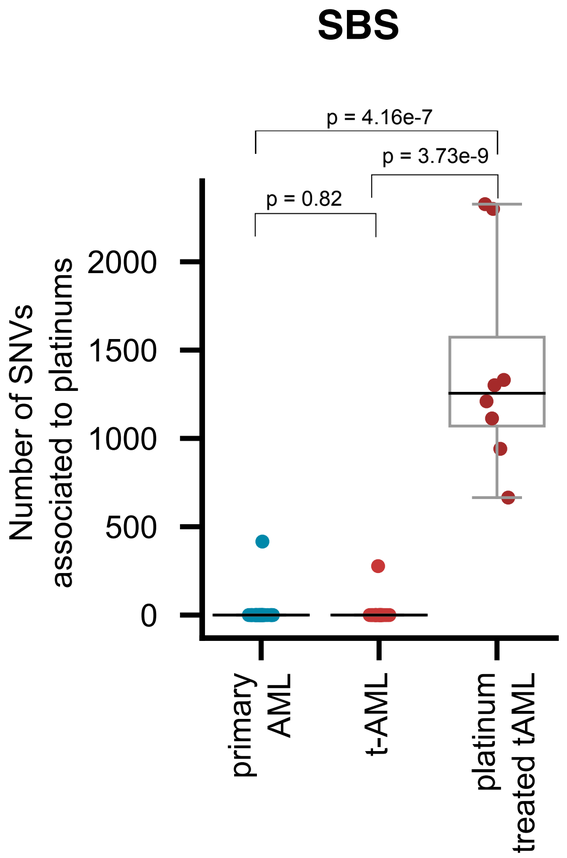
Albert Cortés
Marta Pratcorona

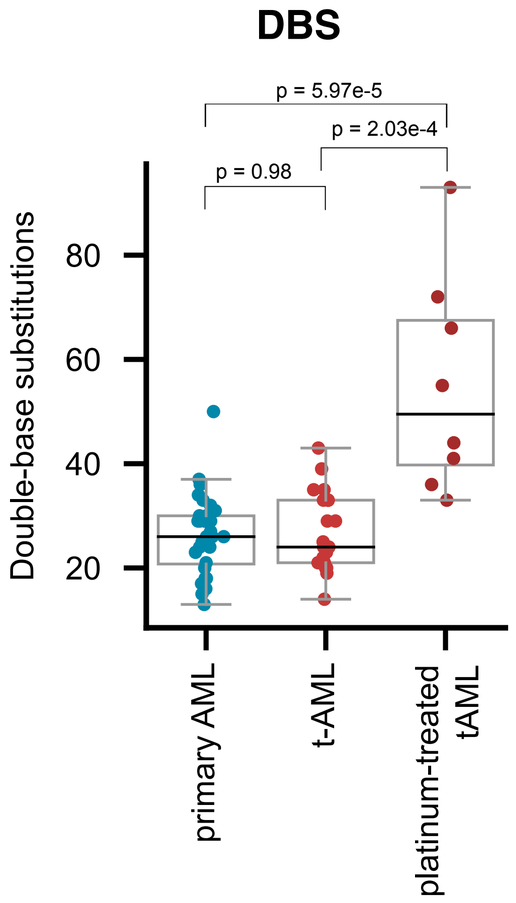
Oriol Pich

Abel Gonzalez-Perez

Platinum mutations detected as clonal in tAML

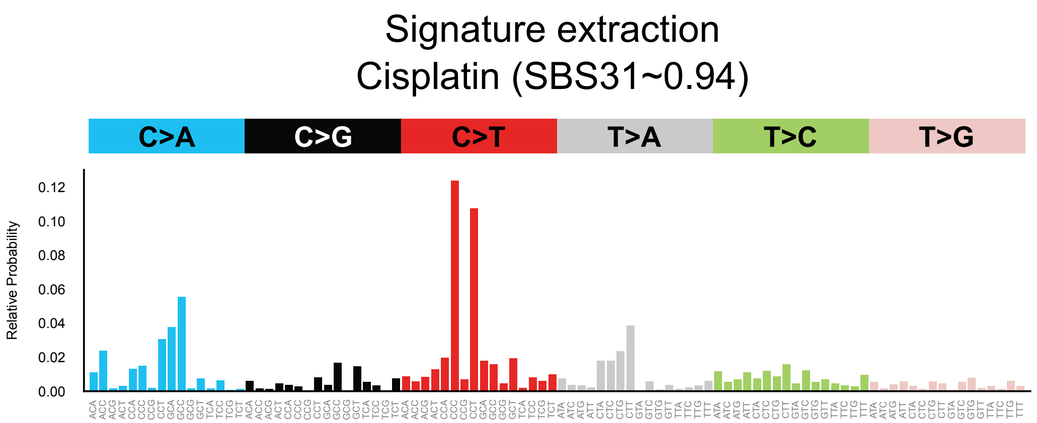


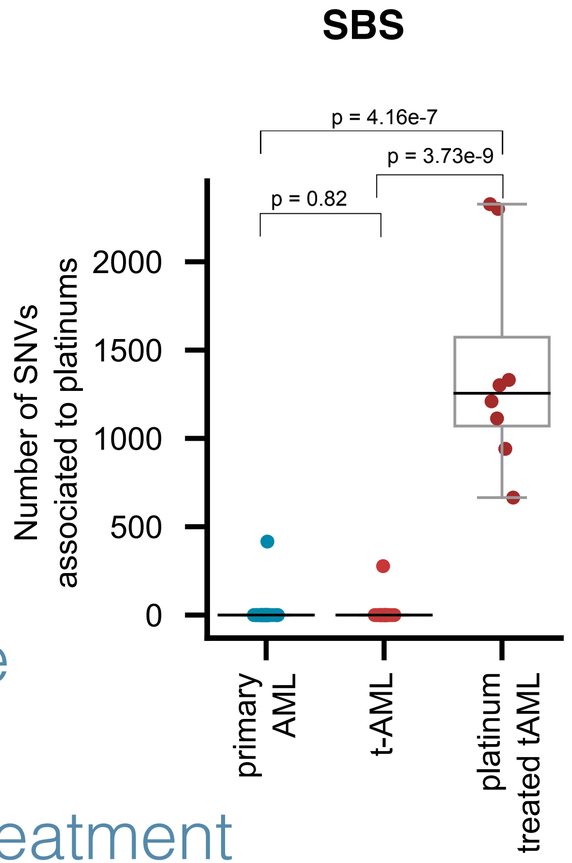


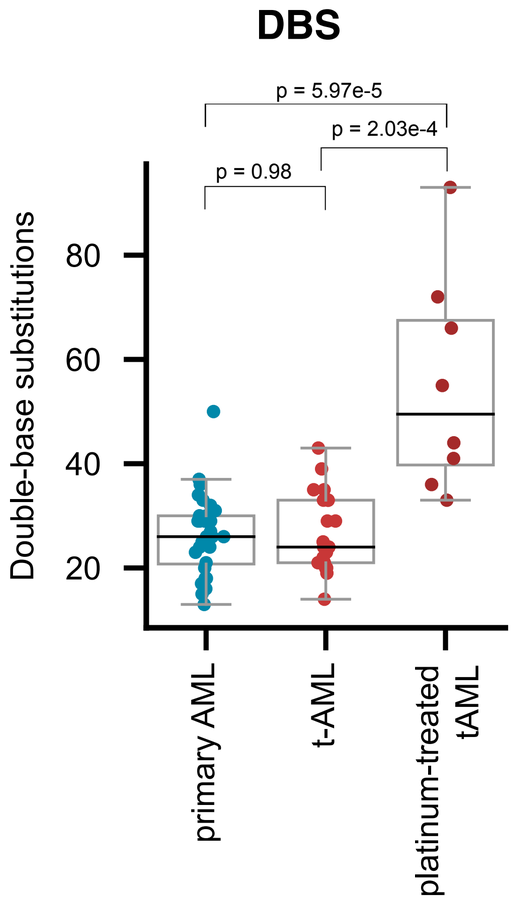


Pich et al., Nature Communications 2021

Platinum mutations detected as clonal in tAML



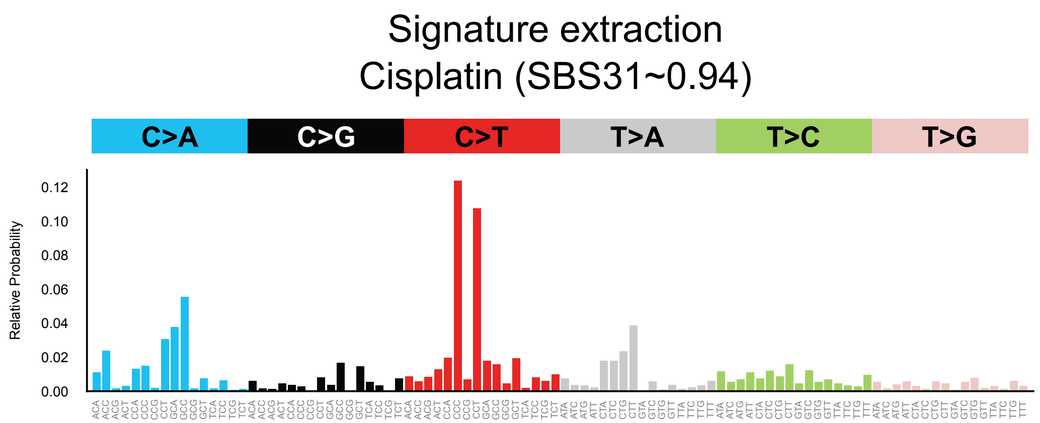


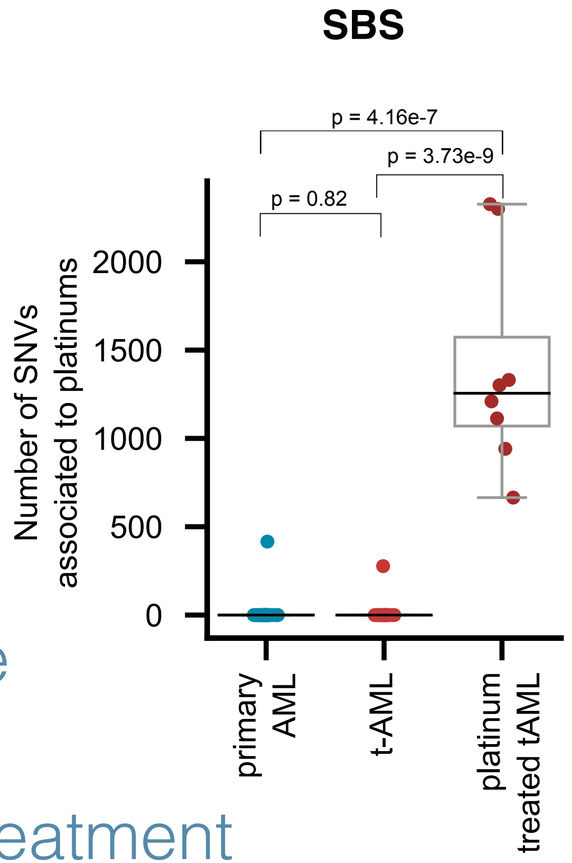


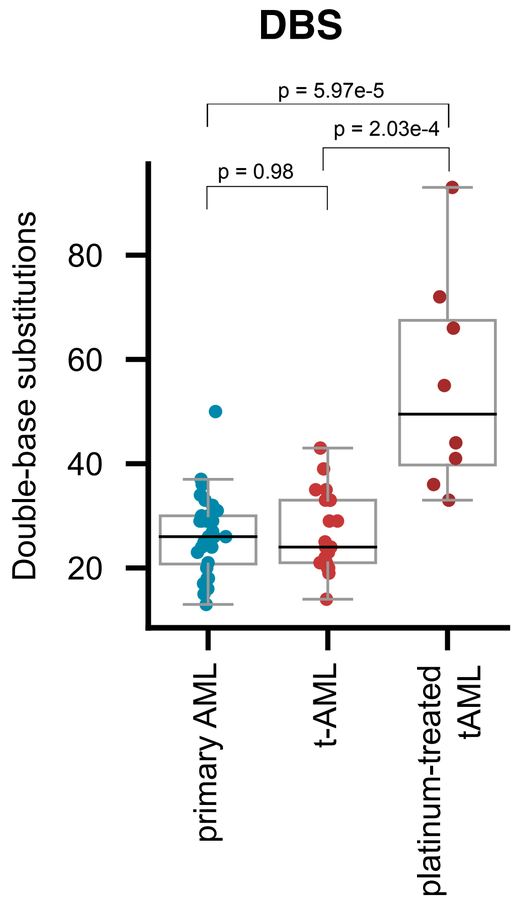
1. Healthy hematopoietic cells receive platinum mutations
2. Full clonal expansion posterior to treatment

Pich et al., Nature Communications 2021

Platinum mutations detected as clonal in tAML







1. Healthy hematopoietic cells receive platinum mutations
2. Full clonal expansion posterior to treatment

Mutational signature of treatment as a barcode of clonal expansion

Pich et al., Nature Communications 2021

Chemotherapy mutational signatures as barcode to time clonal expansion before or after treatment

Pich et al., Nature Communications 2021

Identifying blood somatic mutations by Reverse Mutation Calling

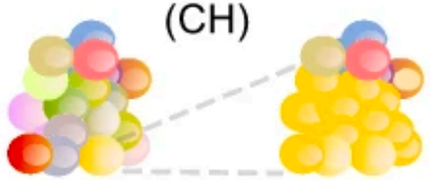
3,785 patients (metastasis cohort)
(1,766 treated with cytotoxic therapies)

Blood sample ↔ Tumor sample

1,429,110 blood somatic mutations

↓

Clonal Hematopoisesis (CH)



Hematopoietic stem cells (HSC) — Clonal Hematopoiesis (CH)

Pich et al., Nature Communications 2021

Identifying blood somatic mutations by Reverse Mutation Calling

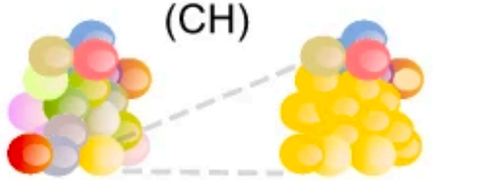
3,785 patients (metastasis cohort)
(1,766 treated with cytotoxic therapies)

Blood sample ⟷ Tumor sample

1,429,110 blood somatic mutations

↓

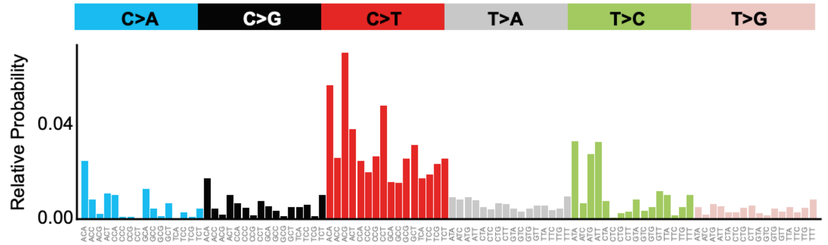
Clonal Hematopoisesis (CH)



Hematopoietic stem cells (HSC) | Clonal Hematopoiesis (CH)

We find HSC signature

Hematopoietic stem cell (HSC) signature in healthy blood (cos similarity = 0.96)



Pich et al., Nature Communications 2021

Identifying blood somatic mutations by Reverse Mutation Calling

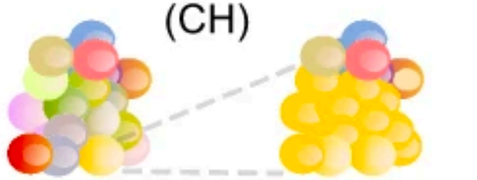
3,785 patients (metastasis cohort)
(1,766 treated with cytotoxic therapies)

Blood sample ⟷ Tumor sample

1,429,110 blood somatic mutations

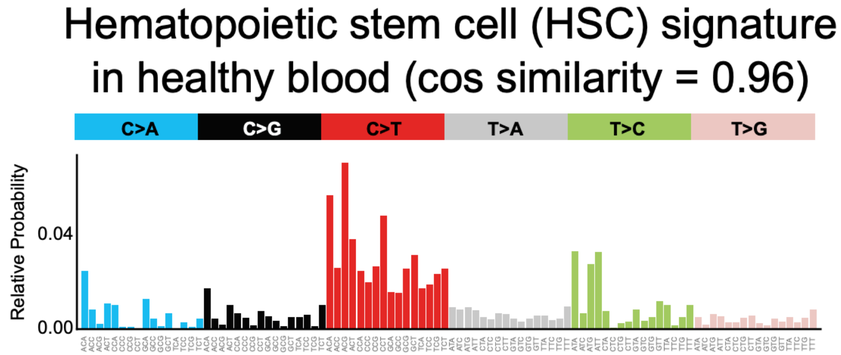
↓

Clonal Hematopoisesis (CH)



Hematopoietic stem cells (HSC) — Clonal Hematopoiesis (CH)

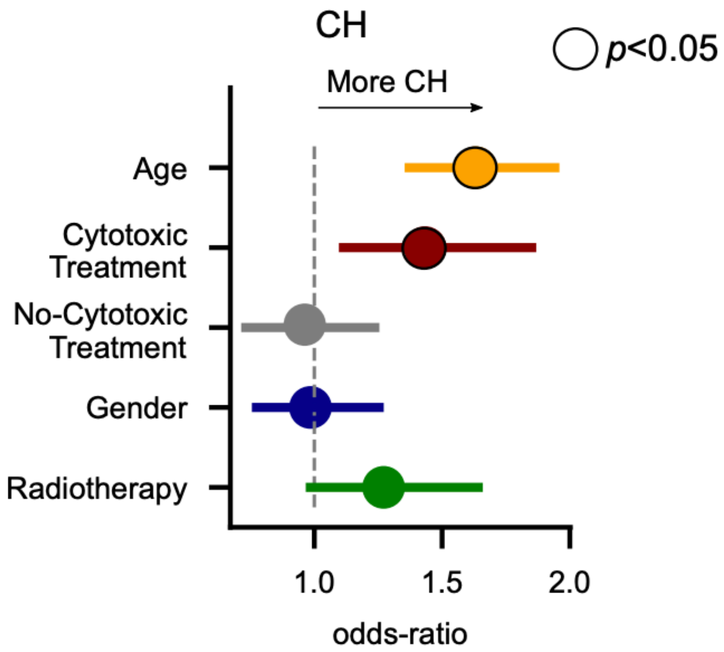
We find HSC signature

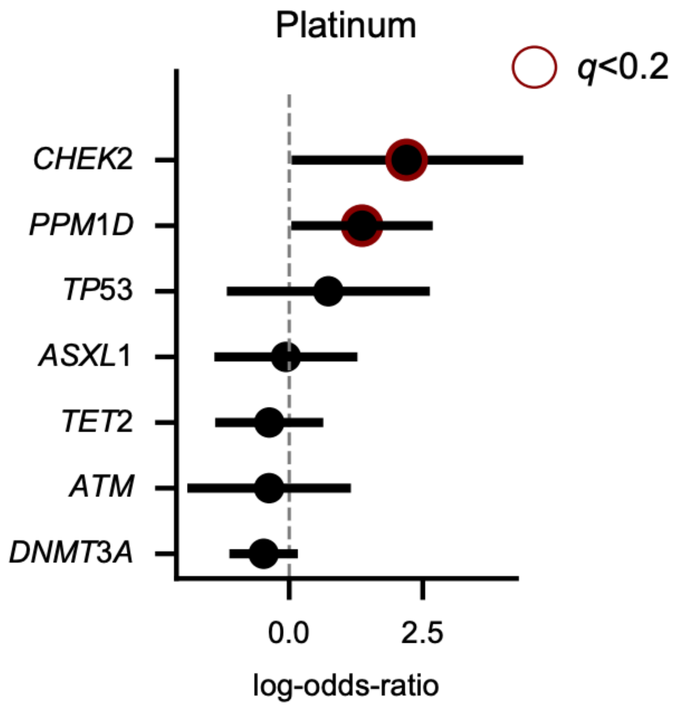


In contrast we do not find the chemotherapy mutational signatures

Pich et al., Nature Communications 2021

Chemotherapy is associated with clonal hematopoiesis with preference for mutations in certain genes

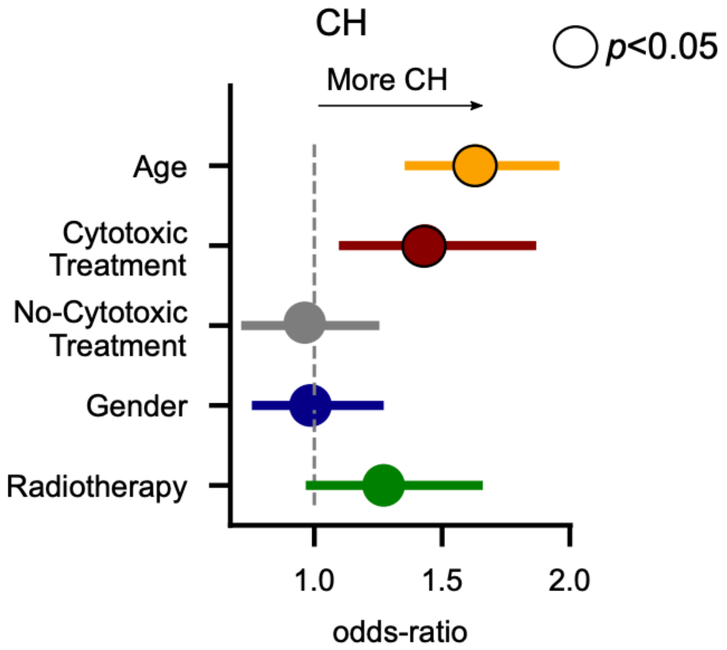


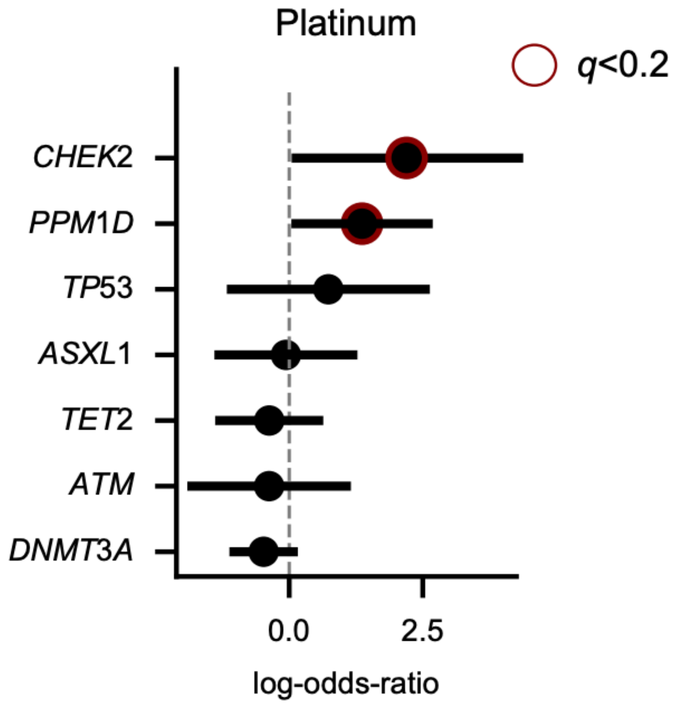


Pich et al., Nature Communications 2021

Bolton et al., Nature Genetics 2020 (Papaemmanuil lab)

Chemotherapy is associated with clonal hematopoiesis with preference for mutations in certain genes



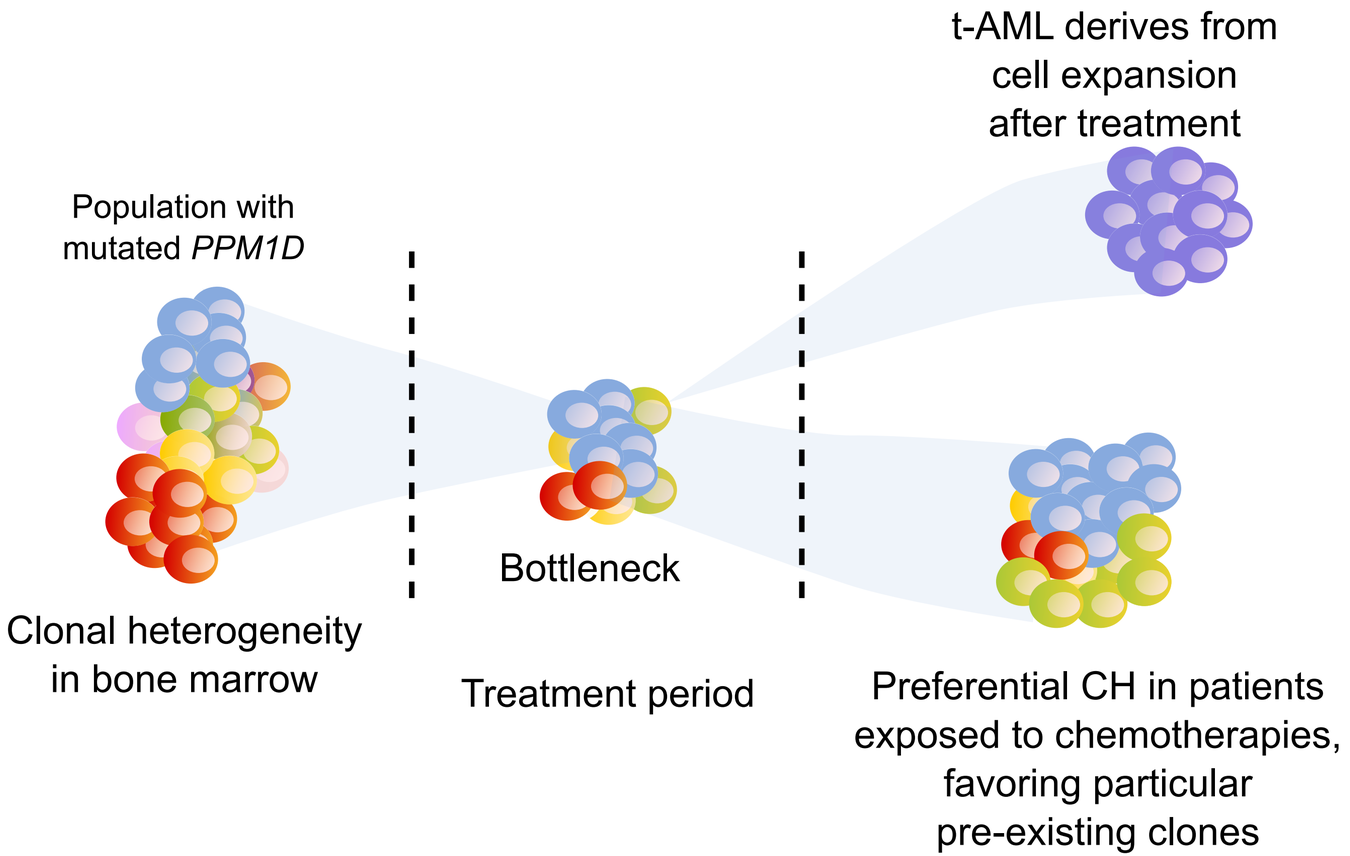


Chemotherapy selects preexisting clones with specific mutations

Pich et al., Nature Communications 2021

Bolton et al., Nature Genetics 2020 (Papaemmanuil lab)

Evolution of hematopoietic cells under cancer therapy

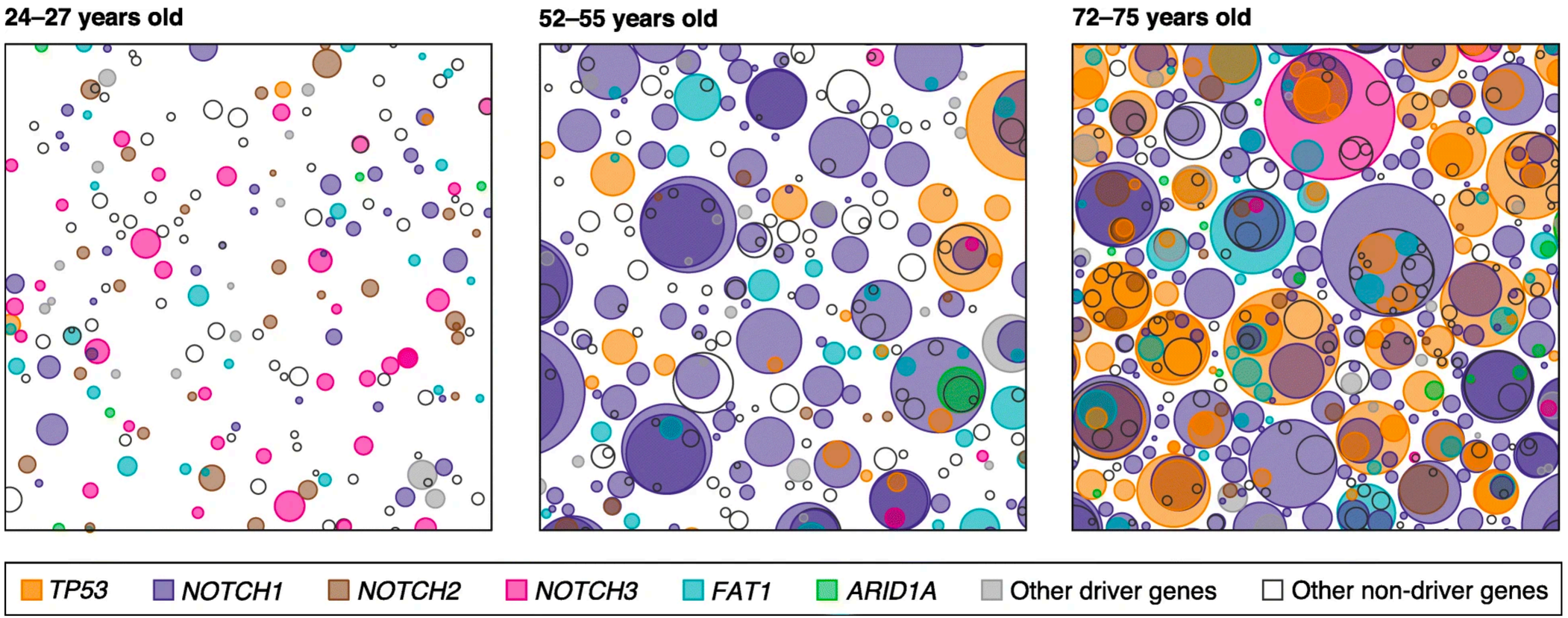


Pich et al., Nature Communications 2021

- Identifying Cancer Drivers
- Understanding Neutral Mutagenesis
- Identifying Clonal Hematopoiesis Drivers
- Chemotherapy effect in hematopoiesis
- Cancer Promotion

Driver mutations are necessary

Driver mutations are necessary but not sufficient



Mutant cell colonization of healthy esophageal epithelium with age

Martincorena Genome Biology 2019
Martincorena et al., Science 2015
Martincorena et al., Science 2018

Driver mutations and clonal expansions in normal tissue

Many carcinogens are not mutagens

nature genetics

ARTICLES

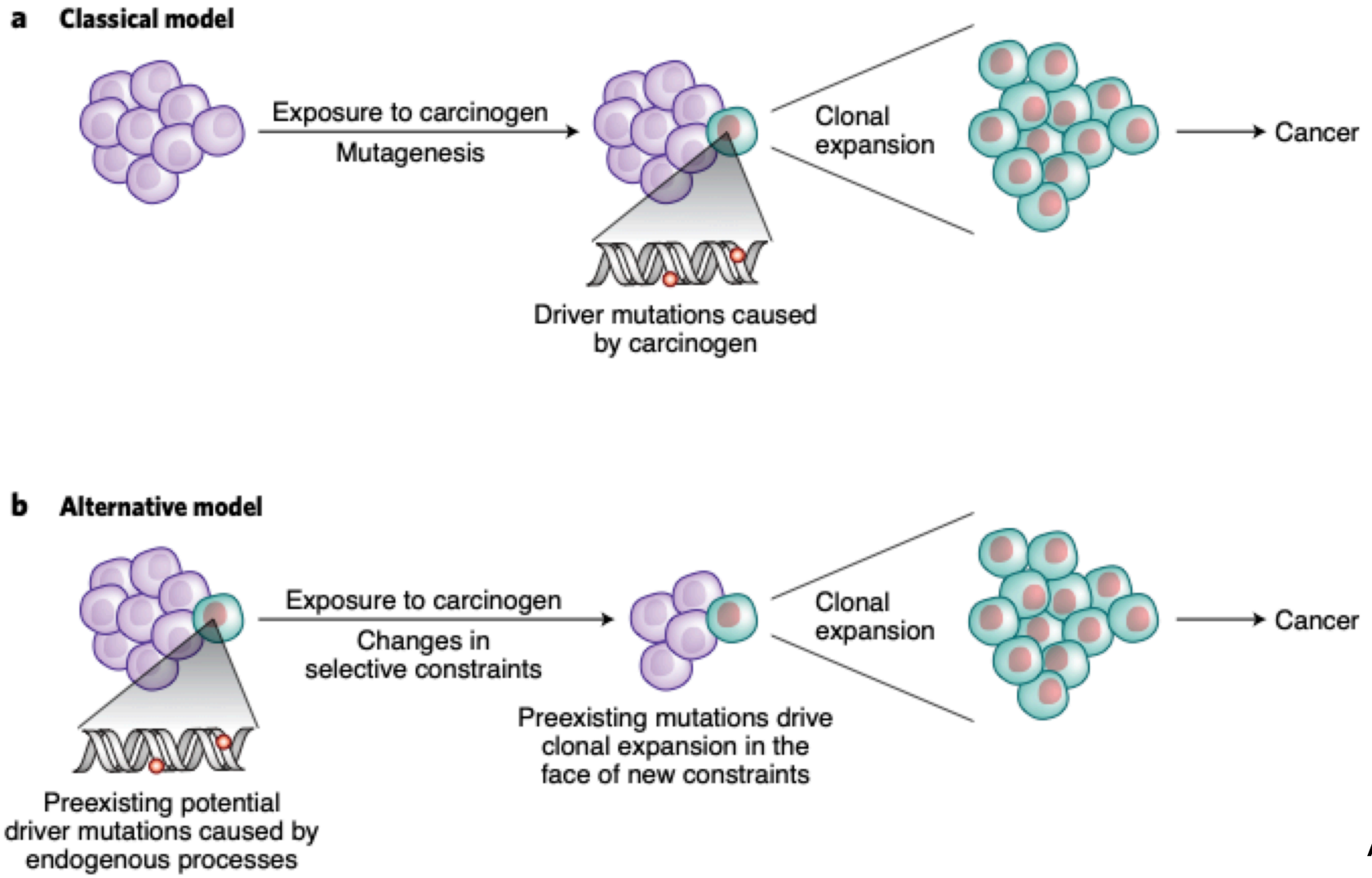
https://doi.org/10.1038/s41588-020-0692-4

Check for updates

The mutational signature profile of known and suspected human carcinogens in mice

Laura Riva[1,5], Arun R. Pandiri[2,5], Yun Rose Li[3,5], Alastair Droop[1], James Hewinson[1], Michael A. Quail[1], Vivek Iyer[1], Rebecca Shepherd[1], Ronald A. Herbert[2], Peter J. Campbell[1], Robert C. Sills[2], Ludmil B. Alexandrov[4], Allan Balmain[3,6] ✉ and David J. Adams[1,6] ✉

Many carcinogens are not mutagens



Abel Gonzalez-Perez

N&V about Riva et al., Nature Genetics 2020

Lopez-Bigas and Gonzalez-Perez. N&V Nature Genetics 2020

CANCER GRAND CHALLENGES

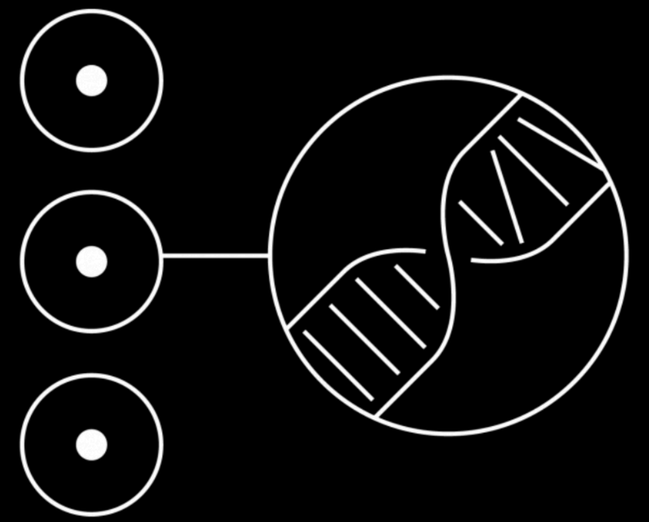
Driving progress through unprecedented collaboration

Cancer Grand Challenges is a global funding initiative founded by Cancer Research UK and the National Cancer Institute. We set ambitious challenges, providing diverse, global teams with £20m to come together, think differently, with the aim to make the progress against cancer the world urgently needs.

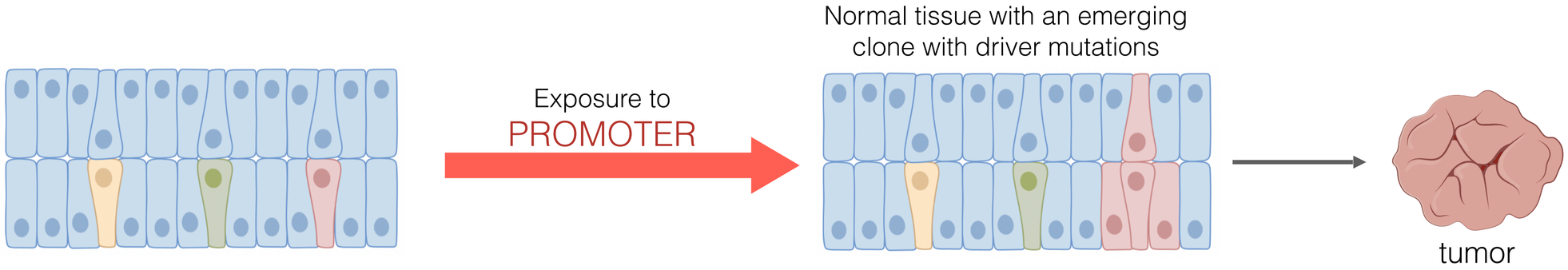
Normal phenotypes

CHALLENGE:

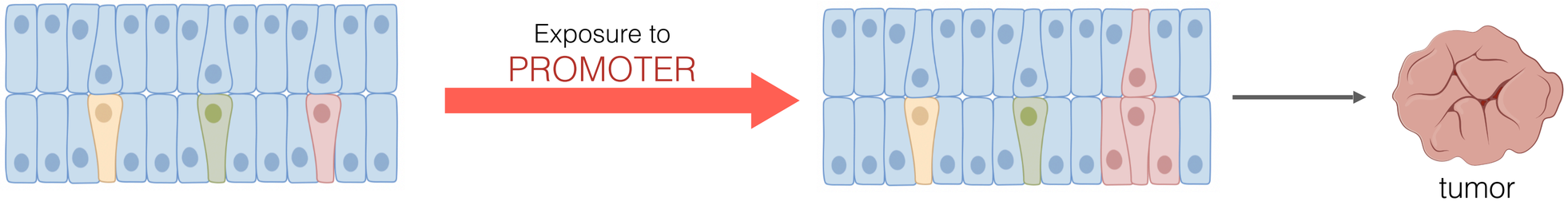
Understand how cells and tissues maintain “normal” phenotypes whilst harbouring oncogenic mutations and how they transition to become a tumour



How does exposure to promoters change the normal tissue to eventually lead to cancer?



How does exposure to promoters change the normal tissue to eventually lead to cancer?

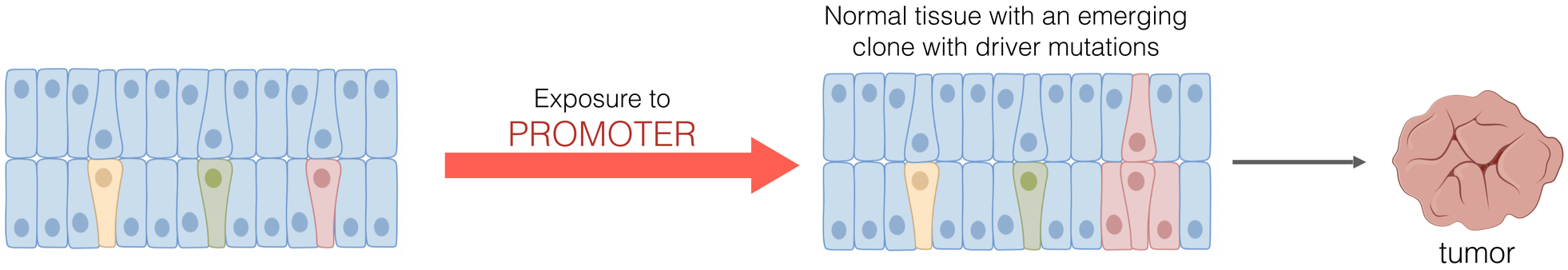


Exposed to promoter

Non-exposed to promoter

Detect emerging clones with driver mutations in normal tissue of individuals exposed and non-exposed to a promoter

How does exposure to promoters change the normal tissue to eventually lead to cancer?



Exposed to promoter

Non-exposed to promoter

Detect emerging clones with driver mutations in normal tissue of individuals exposed and non-exposed to a promoter

- Deep mutagenesis to identify emerging clones
- Single cell profiling with clone genotyping
- Spatial proteomics/transcriptomics with in situ mutation detection

Two stage model of carcinogenesis
Initiation + Promotion

Berenblum and Shubik, 1947

“….the initiating process represents a sudden and irreversible change in a small minority of the cells of the treated area, giving rise to isolated “latent tumour cells” …..
“The presence of these latent tumour cells is only demonstrable by subsequent promoting action, which converts them into morphological tumours.”

PROMINENT TEAM

Co-Leaders:

Allan BALMAIN

UCSF
University of California
San Francisco

Paul BRENNAN

International Agency
for Research on Cancer
World Health
Organization

Nuria LOPEZ-BIGAS

INSTITUTE
FOR RESEARCH
IN BIOMEDICINE
IRB
BARCELONA

Co-investigators:

Kim RHOADS

UCSF
University of California
San Francisco

Luke GILBERT

UCSF
University of California
San Francisco

Calvin J KUO

Stanford
University

Marc GUNTER

International Agency
for Research on Cancer
World Health
Organization

Emma LUNDBERG

KTH
VETENSKAP
OCH KONST

Stanford
University

Chris COUNTER

Duke
UNIVERSITY

Thanks to:

Those who did the work

BBGLab
BARCELONA BIOMEDICAL GENOMICS LAB

IRB BARCELONA
INSTITUTE FOR RESEARCH IN BIOMEDICINE

ICREA

Those who generate and share data

ICGC

TCGA

Hartwig MEDICAL FOUNDATION

And many others

Funding agencies

erc

asociación española contra el cáncer

ciberonc

The Mark Foundation for Cancer Research

elixir SPAIN

Generalitat de Catalunya
Departament d'Empresa i Coneixement
Secretaria d'Universitats i Recerca

CANCER GRAND CHALLENGES

GOBIERNO DE ESPAÑA
MINISTERIO DE CIENCIA E INNOVACIÓN

AGENCIA ESTATAL DE INVESTIGACIÓN

wellcome

European Commission
Horizon 2020
European Union funding for Research & Innovation

isc Instituto de Salud Carlos III