Session 8: Identifying Cancer Drivers

Emerging Approaches For Tumor Analyses
in Epidemiological Studies

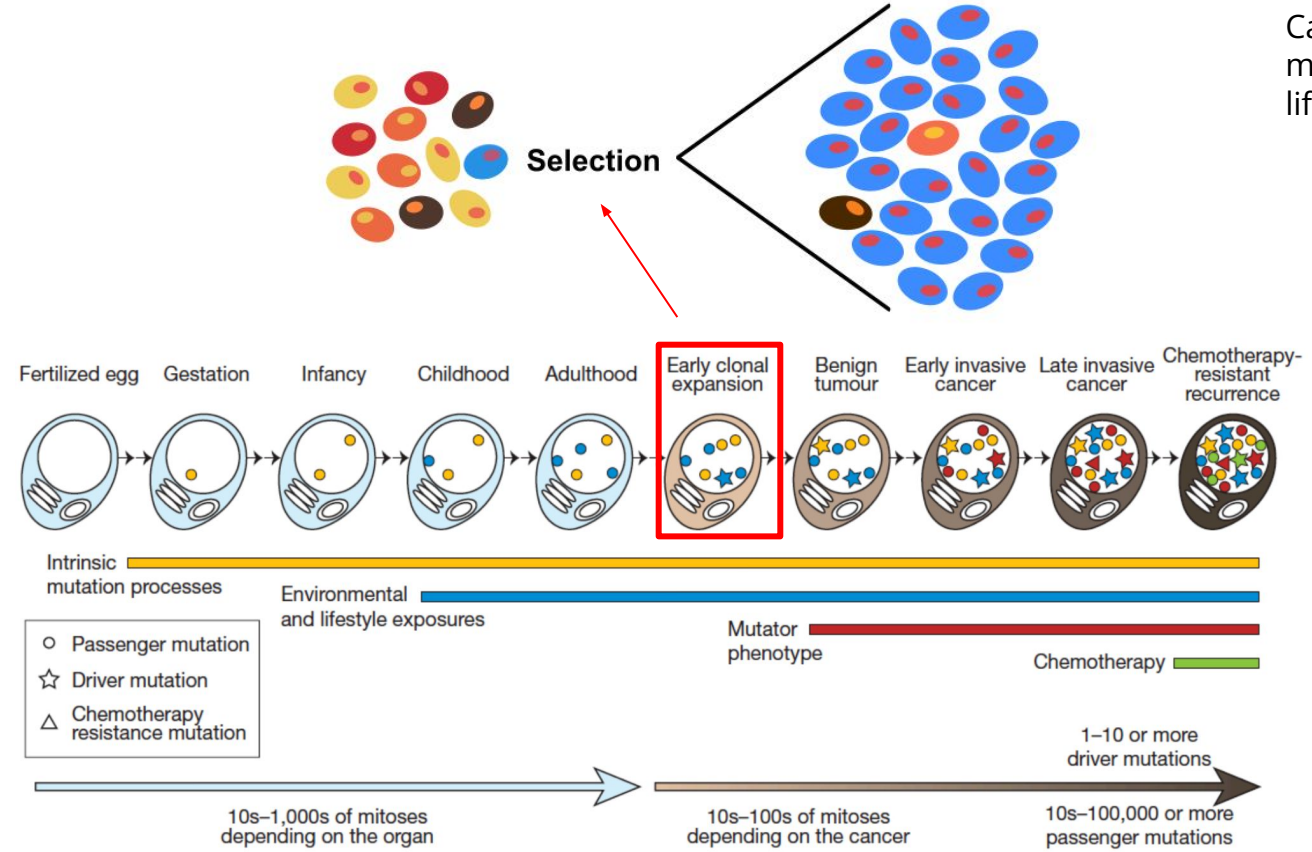
March 13, 2023
9:30 AM- 12:00 PM

Outline

- Introduction: What are cancer drivers? Passenger versus driver mutations, Oncogenes versus tumor suppressor genes
- Bioinformatics methods for driver gene identification
- Identification of driver mutations in cancer genes
- Other genomic/epigenomic cancer drivers: Epigenomic (e.g. methylation), SVs, SCNA, etc.
- Non-coding drivers
- Experimental validation/Clinical applications

Introduction to cancer drivers

Driver Mutations and Cancer Driver Genes

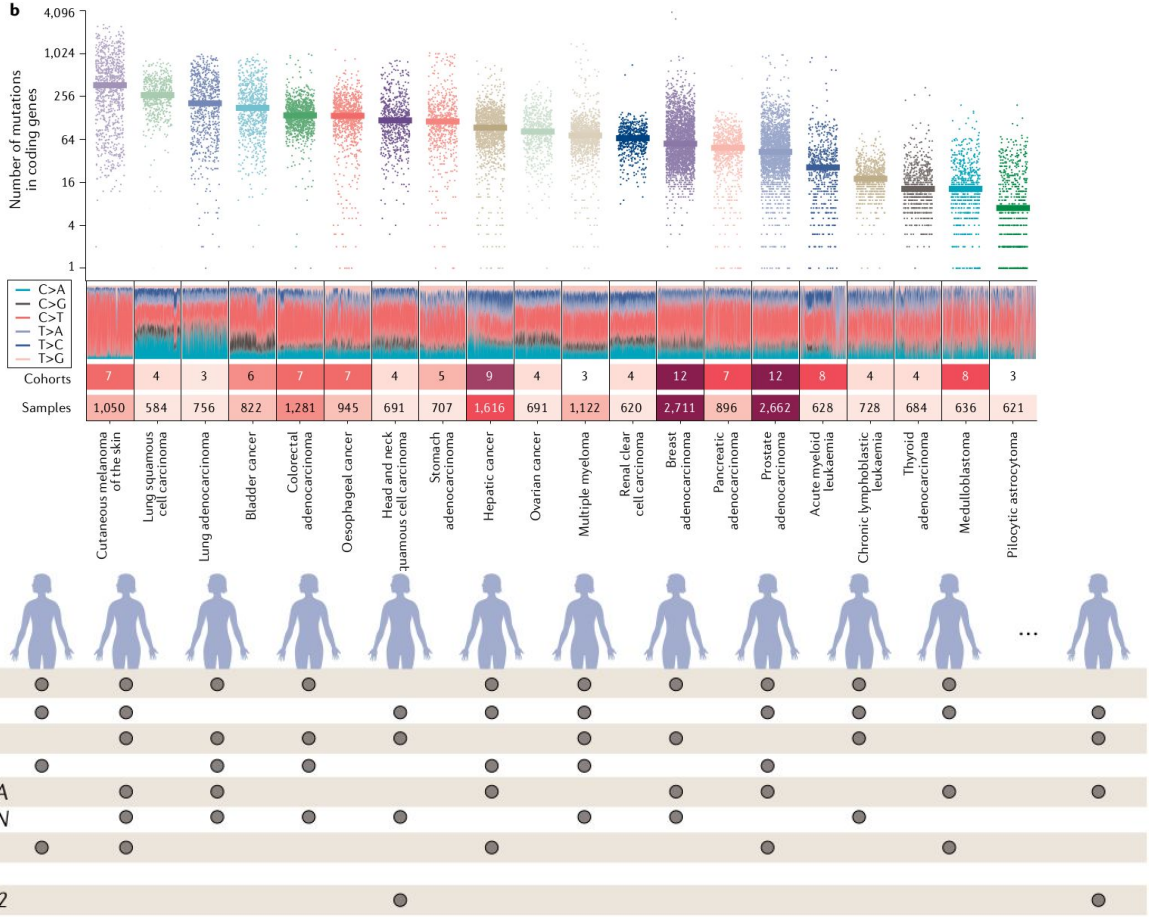


Stratton, Campbell & Futreal. Nature, 2009

Cancer progression results from mutations accumulated during lifetime

- Mutations can be acquired by intrinsic processes (e.g. cell division) or exogenous mutagens (e.g. UV light, tobacco smoke).
- Few driver mutations, many passenger mutations.
- Passenger mutations do not have effect on the cells. Driver mutations confer growth advantage, are positively selected on the microenvironment and cause clonal expansion.
- **Driver mutations** occur in a set of genes called **"Cancer Driver Genes"**.

Which somatic mutations are cancer drivers?



Martinez-Jimenez *et al. Nat Reviews Cancer*, 2020

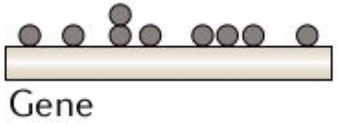
Oncogenes and tumor suppressor genes

- Two types of driver genes: oncogenes (caused by mutations in proto-oncogenes in normal cells) and tumor suppressor genes (TSGs)

	Oncogenes	Tumor Suppressor Genes
Driver mutations	Activating or new functions	Inactivating
Mutated alleles in cancer	Dominant - mutation of 1 allele is sufficient	Recessive - require mutations of both alleles
Effects on cell growth	Promote cell growth	Inhibit cell growth
Germline transmission of mutant allele	Rare	Frequent
Common somatic mutations mechanisms	Point mutations, amplification, chromosomal translocation	Point mutations, chromosomal deletion, SV disruption
Well-known examples	*MYC, RET, MET, KIT, FLT3, EGFR, BRAF*	*RB1, TP53, BRCA1/2, PTEN, CHEK2, CDKN2A, TGFRB2, APC*

Bioinformatics methods for driver gene identification

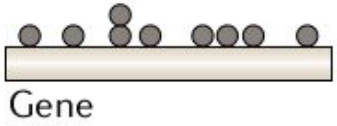
So, how to identify cancer driver genes?

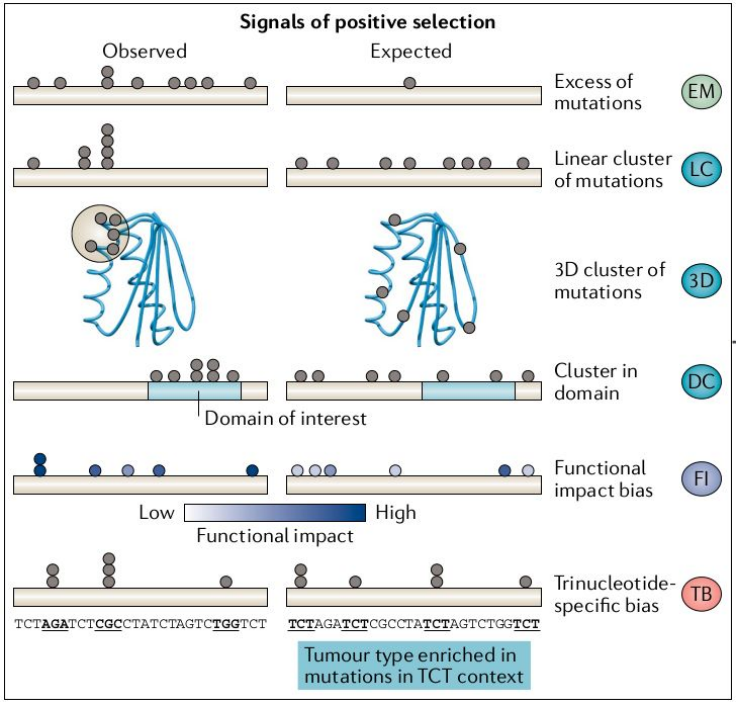


Is it under positive selection in tumorigenesis?

Do observed mutational patterns deviate from the expectation under neutrality?

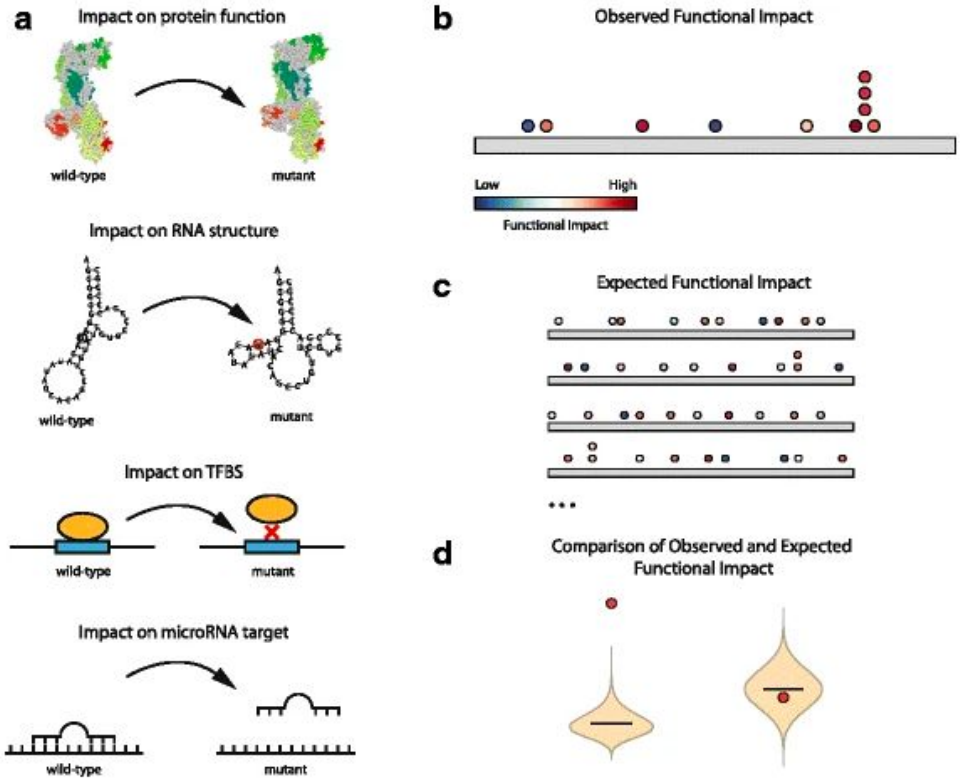
Bioinformatics approach to identify cancer drivers





- dNdScv: Martincorena *et al.*, *Cell*, 2017
- OncodriveCLUSTL: Arnedo-Pac *et al.*, *Bioinformatics*, 2019
- MotMaps: Tokheim *et al.*, *Cancer Res.*, 2016
- SMRegions: Martinez-Jimenez *et al.*, *Nat. Cancer.*, 2019
- OncodriveFML: Mularoni *et al.*, *Genome Biol.*, 2019
- Mutpanning: Dietlin *et al.*, *Nat. Gen.*, 2020

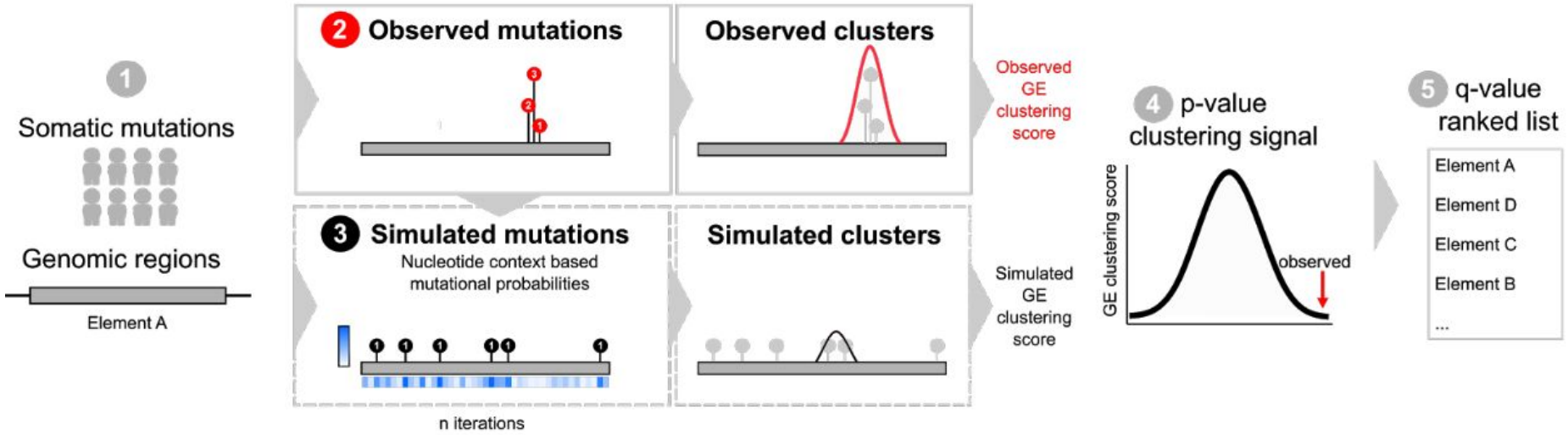
The key: estimating the expectation under neutrality



Taken from Mularoni *et al*., *Genome Biology*, 2016

OncodriveFML

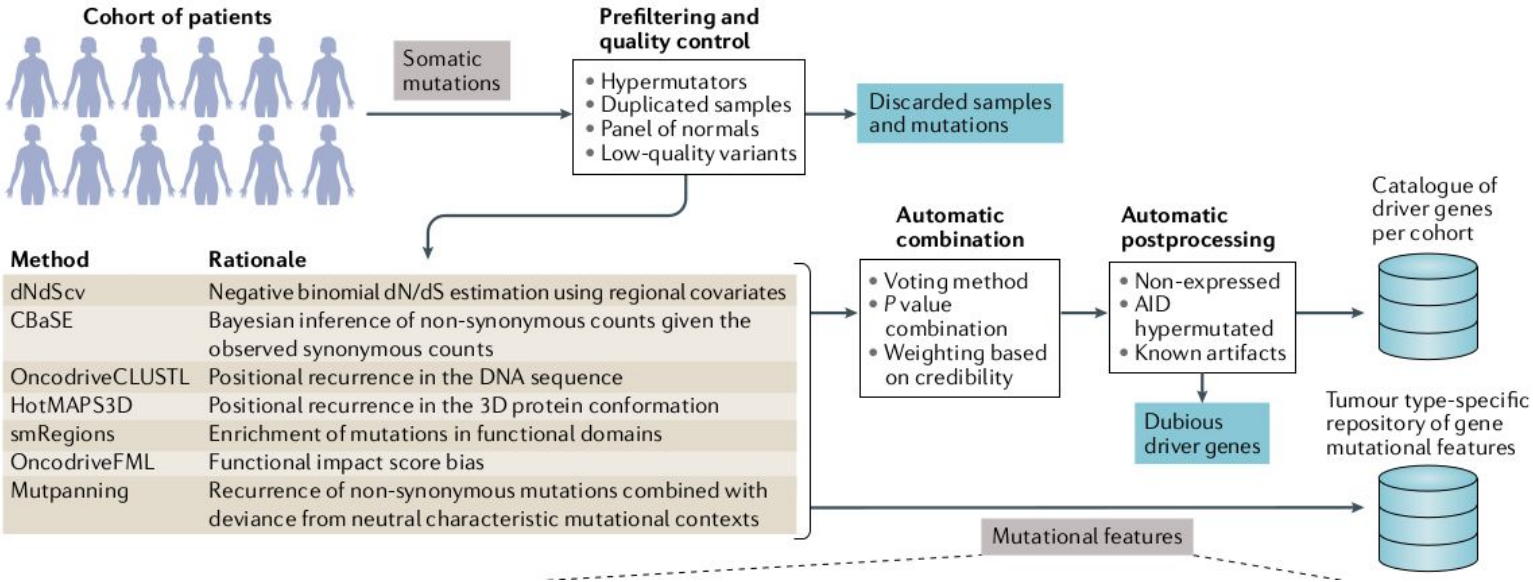
The key: estimating the expectation under neutrality



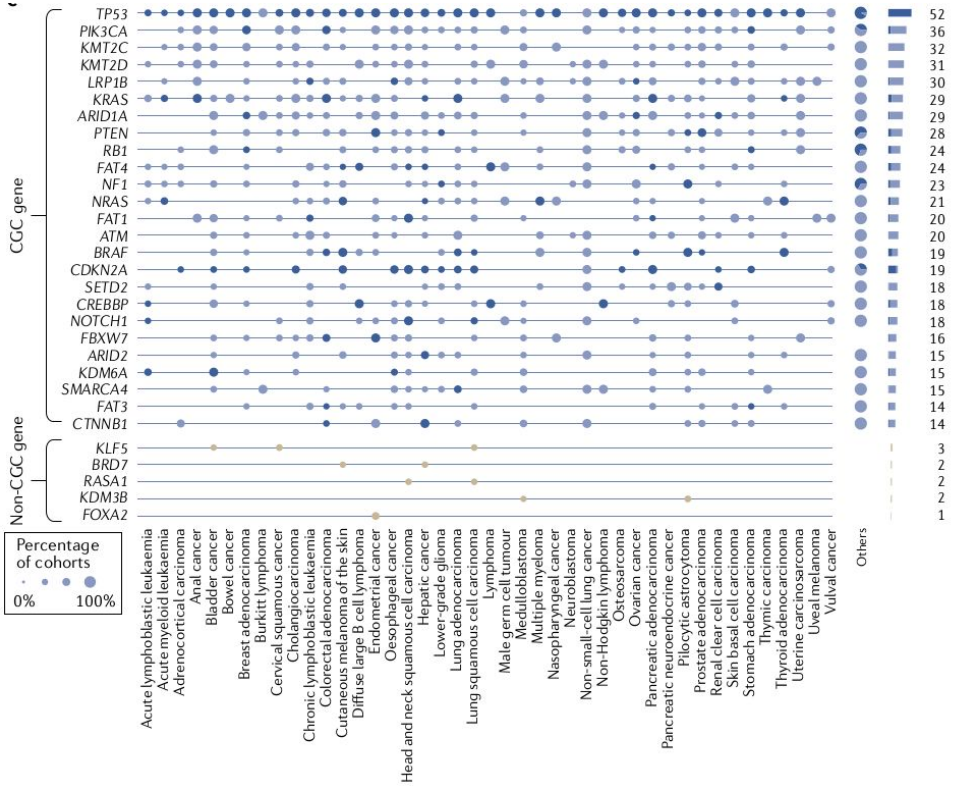
Taken from Martinez-Jimenez *et al.*, *Nat Rev Cancer*, 2020

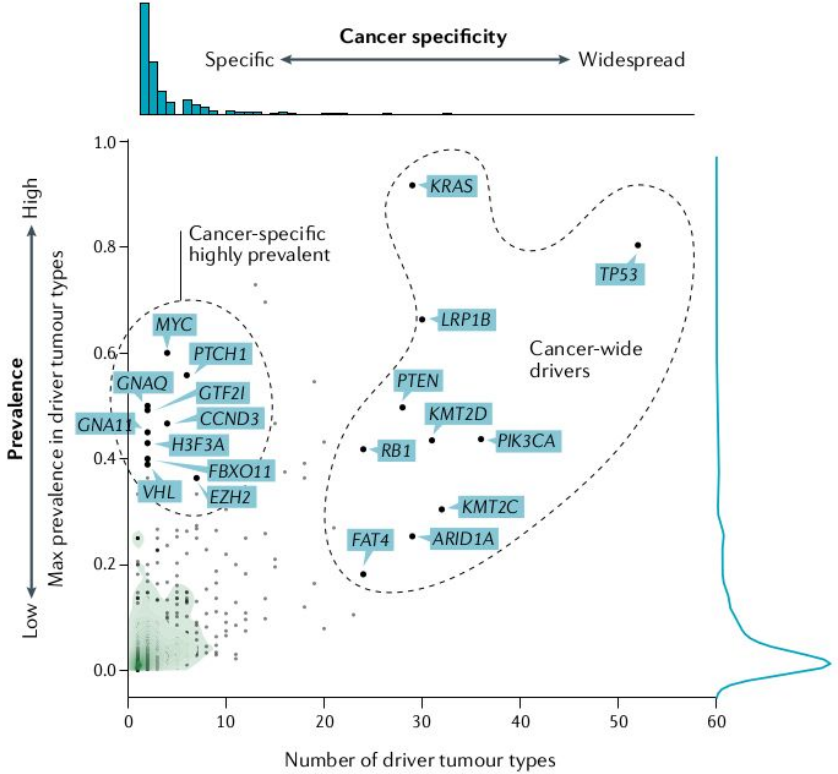
OncodriveCLUSTL

IntOGen (one platform to rule them all)



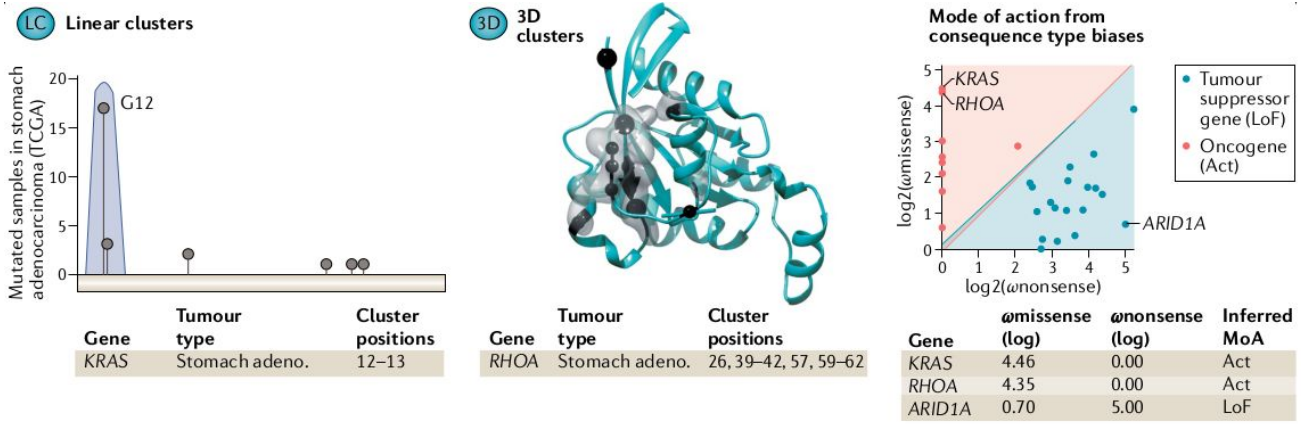
IntOGen


CGC gene
Non-CGC gene
TP53
PIK3CA
KMT2C
KMT2D
LRP1B
KRAS
ARID1A
PTEN
RB1
FAT4
NF1
NRAS
FAT1
ATM
BRAF
CDKN2A
SETD2
CREBBP
NOTCH1
FBXW7
ARID2
KDM6A
SMARCA4
FAT3
CTNNB1
KLF5
BRD7
RASA1
KDM3B
FOXA2
52
36
32
31
30
29
29
28
24
24
23
21
20
20
19
19
18
18
18
16
15
15
15
14
14
3
2
2
2
1
Others
Percentage of cohorts
0%
100%
Acute lymphoblastic leukaemia
Acute myeloid leukaemia
Adrenocortical carcinoma
Anal cancer
Bladder cancer
Bowel cancer
Breast adenocarcinoma
Burkitt lymphoma
Cervical squamous cancer
Cholangiocarcinoma
Chronic lymphoblastic leukaemia
Colorectal adenocarcinoma
Cutaneous melanoma of the skin
Diffuse large B cell lymphoma
Endometrial cancer
Oesophageal cancer
Head and neck squamous cell carcinoma
Hepatic cancer
Lower-grade glioma
Lung adenocarcinoma
Lung squamous cell carcinoma
Lymphoma
Male germ cell tumour
Medulloblastoma
Multiple myeloma
Nasopharyngeal cancer
Neuroblastoma
Non-small-cell lung cancer
Non-Hodgkin lymphoma
Osteosarcoma
Ovarian cancer
Pancreatic adenocarcinoma
Pancreatic neuroendocrine cancer
Pilocytic astrocytoma
Prostate adenocarcinoma
Renal clear cell carcinoma
Skin basal cell carcinoma
Stomach adenocarcinoma
Thymic carcinoma
Thyroid adenocarcinoma
Uterine carcinosarcoma
Uveal melanoma
Vulval cancer


Cancer specificity
Specific
Widespread
Prevalence
High
Low
Max prevalence in driver tumour types
Cancer-specific highly prevalent
Cancer-wide drivers
KRAS
TP53
LRP1B
MYC
PTCH1
GNAQ
GTF2I
GNA11
CCND3
H3F3A
FBXO11
VHL
EZH2
PTEN
KMT2D
PIK3CA
RB1
KMT2C
FAT4
ARID1A
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
60
Number of driver tumour types

IntOGen

Mutational features of cancer driver genes



Gene	Tumour type	Cluster positions
KRAS	Stomach adeno.	12–13

Gene	Tumour type	Cluster positions
RHOA	Stomach adeno.	26, 39–42, 57, 59–62

Gene	ωmissense (log)	ωnonsense (log)	Inferred MoA
KRAS	4.46	0.00	Act
RHOA	4.35	0.00	Act
ARID1A	0.70	5.00	LoF

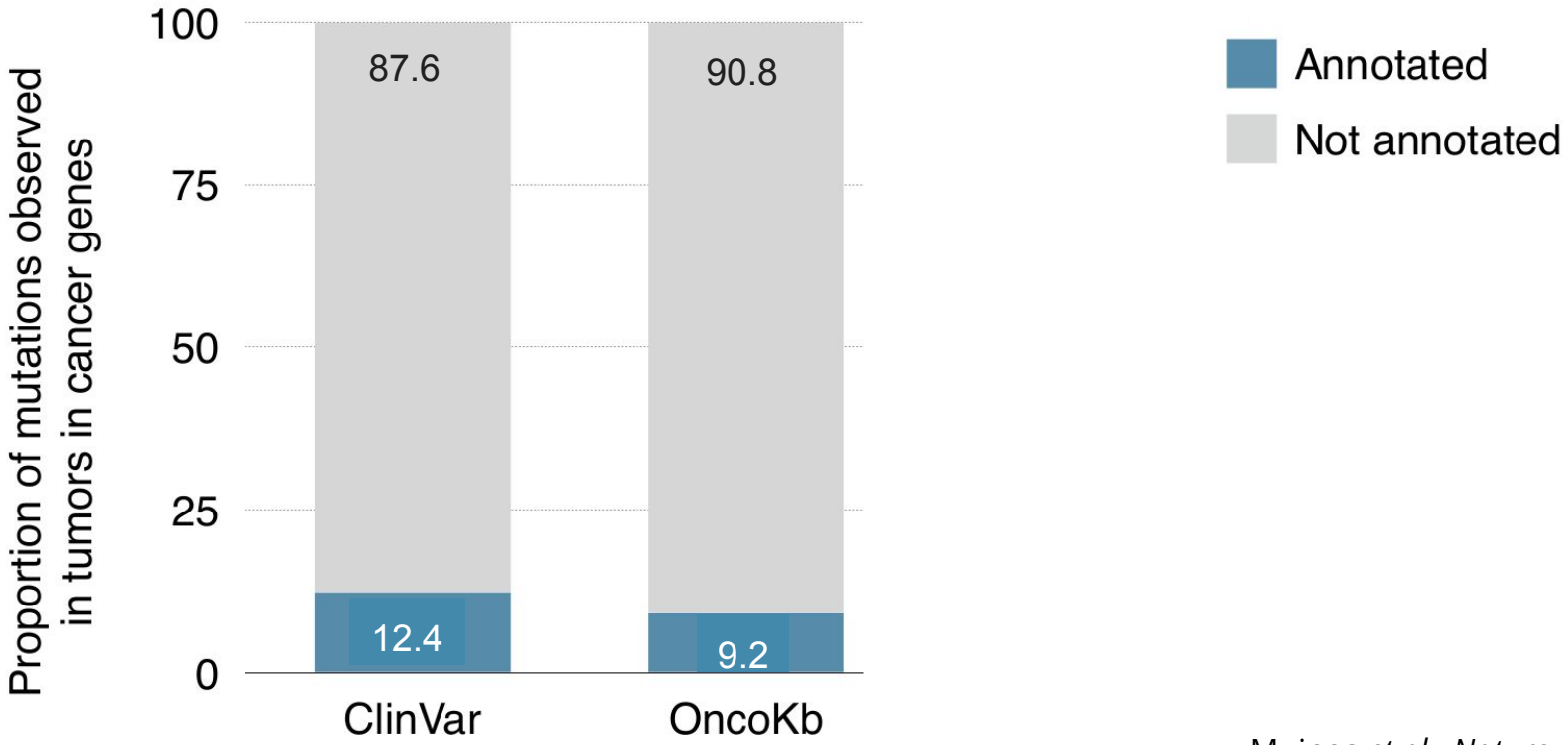
Gene	Tumour type	PFAM domain
SMAD4	Stomach adeno.	MH2 domain

Gene	Tumour type	Consequence type	Excess rate
ARID1A	Stomach adeno.	Missense	0.50
ARID1A	Stomach adeno.	Nonsense	0.99
ARID1A	Stomach adeno.	Splice	0.99

Identification of driver mutations in cancer genes

From cancer driver genes to driver mutations

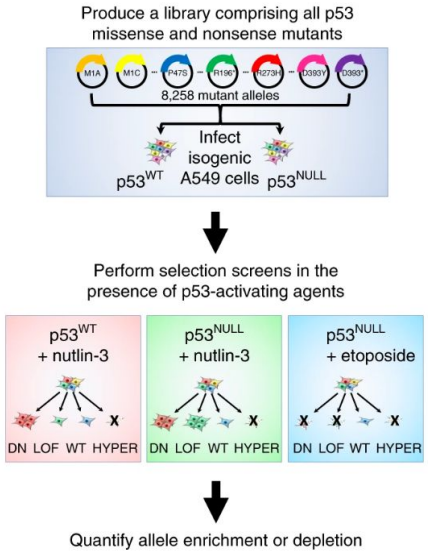
How many mutations in driver genes are annotated as tumorigenic?

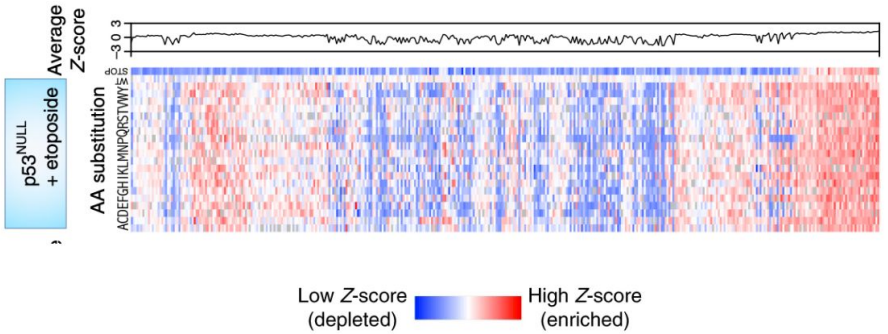


Muinos *et al*., *Nature*, 2021

From cancer driver genes to driver mutations

How to distinguish driver from passenger mutations in cancer genes?



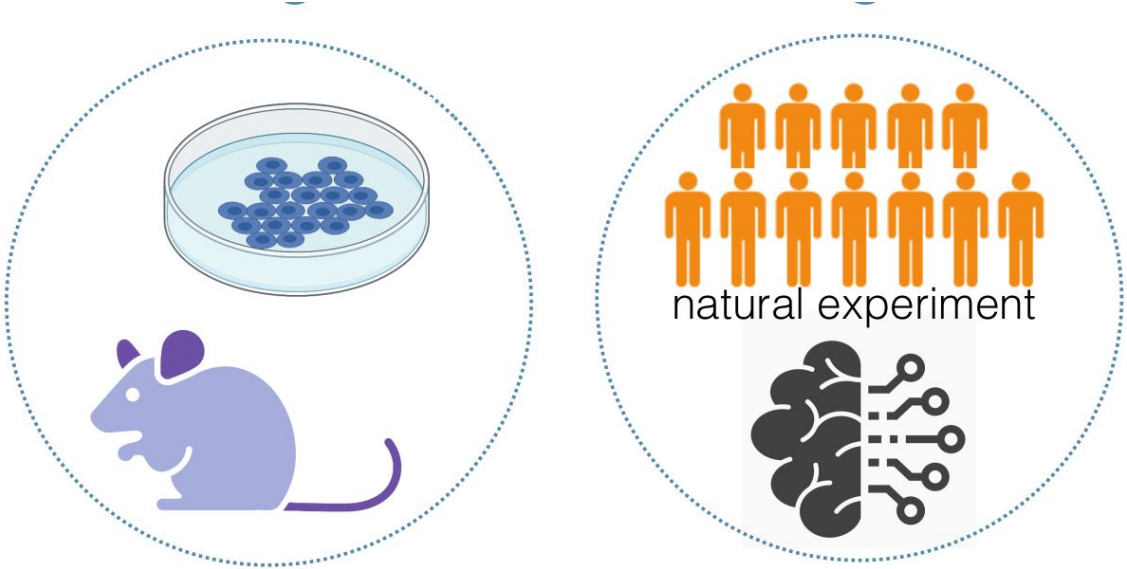


Giacomelli et al Nature Genetics 2018

Experimental saturation mutagenesis

From cancer driver genes to driver mutations

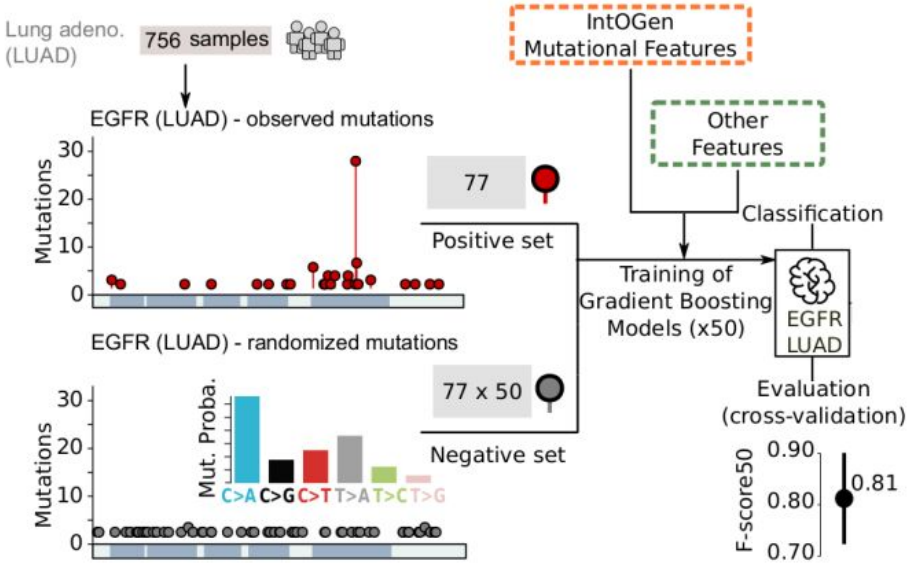
How to distinguish driver from passenger mutations in cancer genes?



In silico saturation mutagenesis

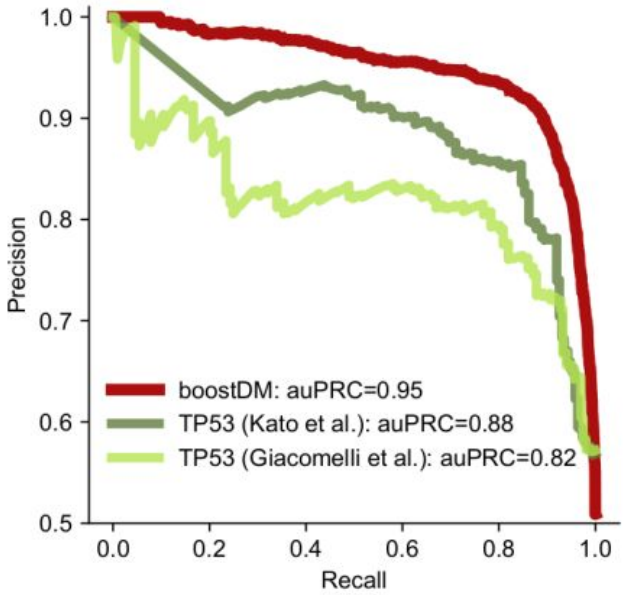
From cancer driver genes to driver mutations

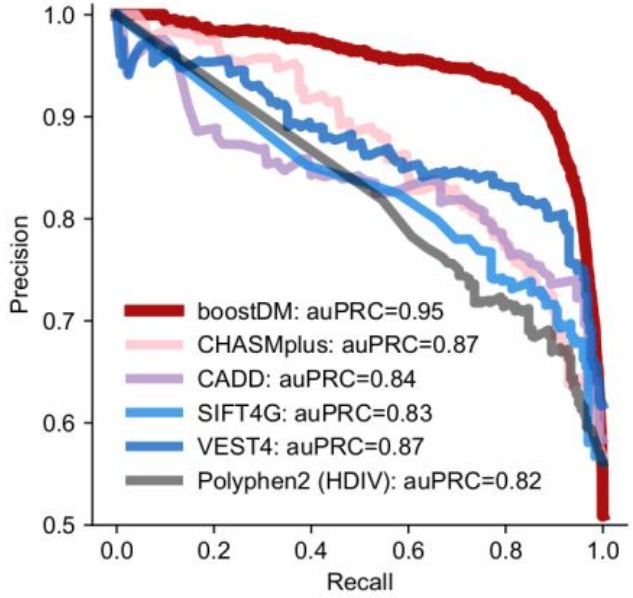
How to distinguish driver from passenger mutations in cancer genes?



BoostDM gene-tumor type-specific models

From cancer driver genes to driver mutations

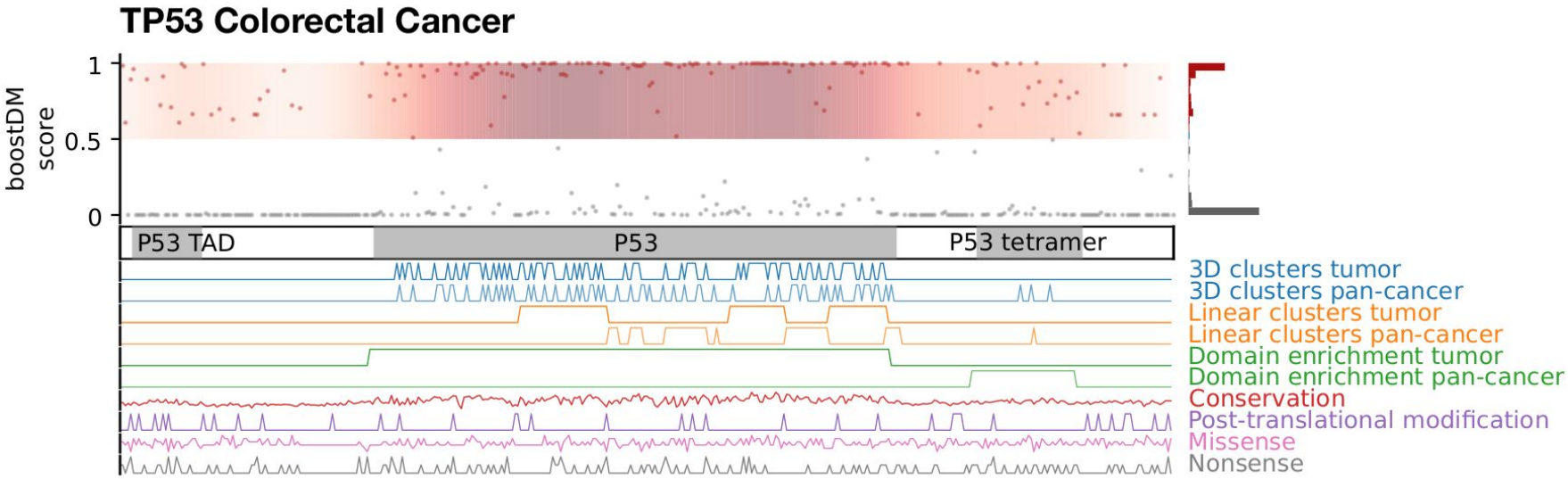




Validation and benchmarking of boostDM TP53-colorectal model

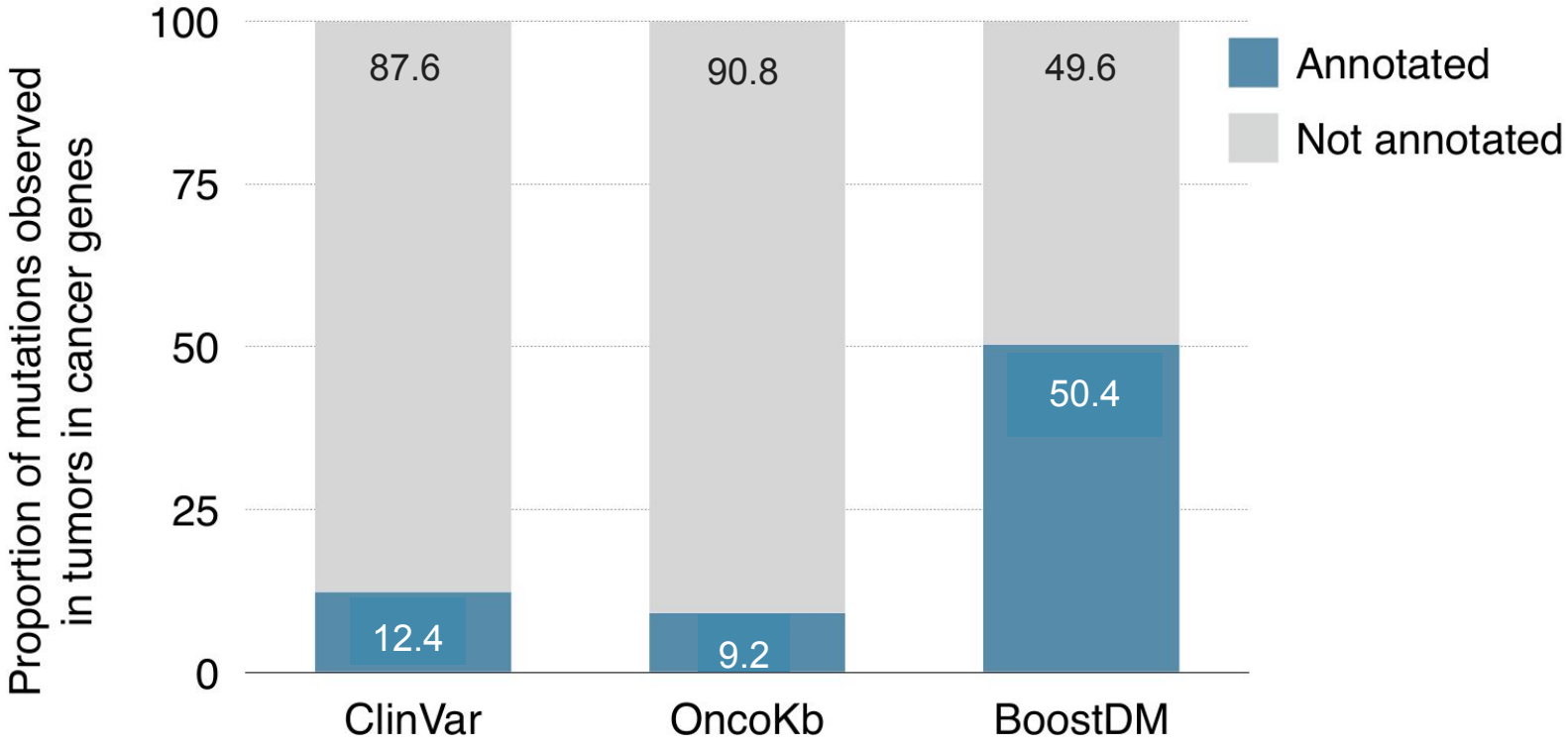
From cancer driver genes to driver mutations

Blueprint of TP53 driver mutations in colorectal tumors



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

From cancer driver genes to driver mutations

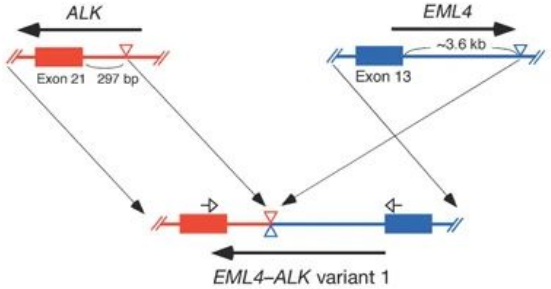


Other genomic/epigenomic drivers

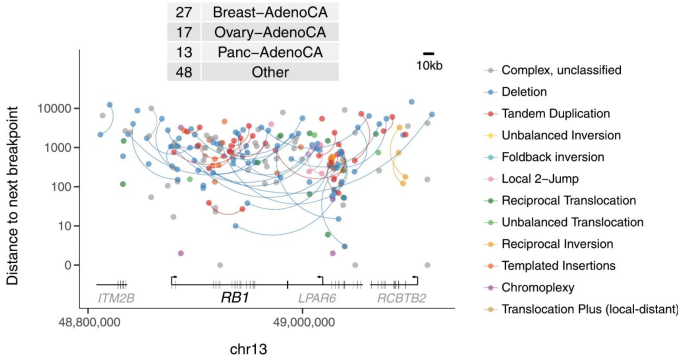
Somatic genomic rearrangement drivers

These could include

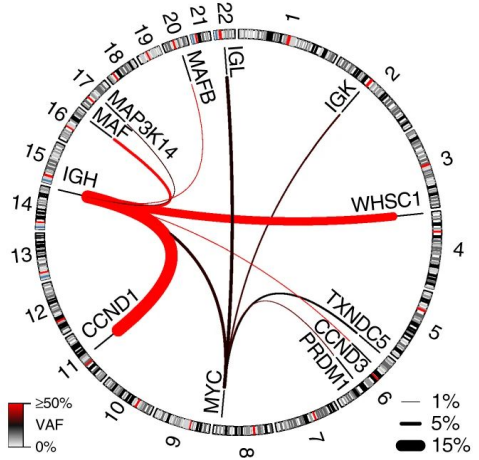
- Gene fusion involving oncogenes - good to validate with expression data for expression of fusion transcripts
- Truncation of tumor suppressors (e.g. SV breakpoints affecting exons)
- Cis-activating rearrangements (e.g. promoter rearrangement and enhancer hijacking), accompanied with changes in expression



EML4-ALK fusion in lung cancer
(Session 6 practical)
Soda *et al. Nature,* 2007



SV breakpoints inactivating *RB1*
in PCAWG cohort
Li *et al. Nature,* 2020

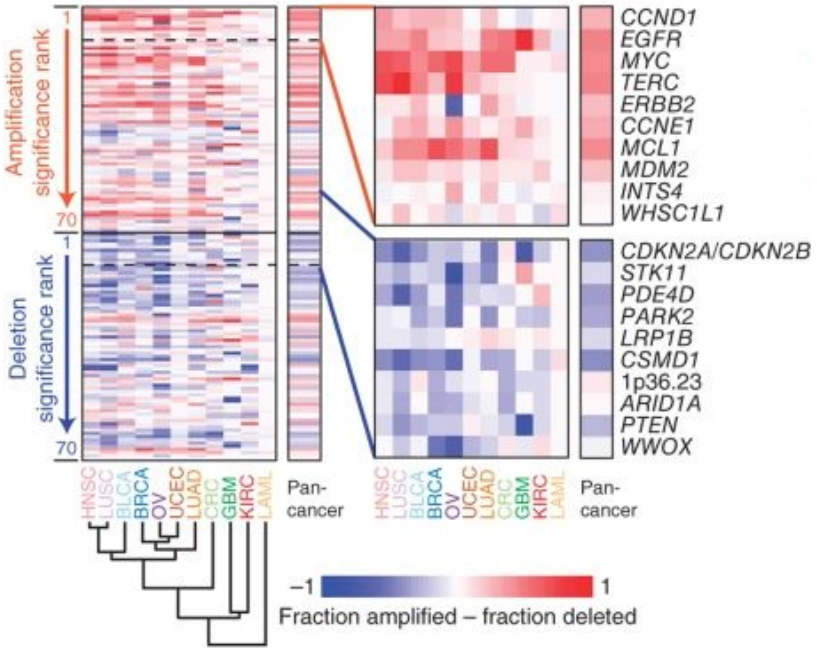


IGH enhancers translocation is a common driver in ~50% multiple myeloma
Barwick *et al. Nature Communications,* 2019

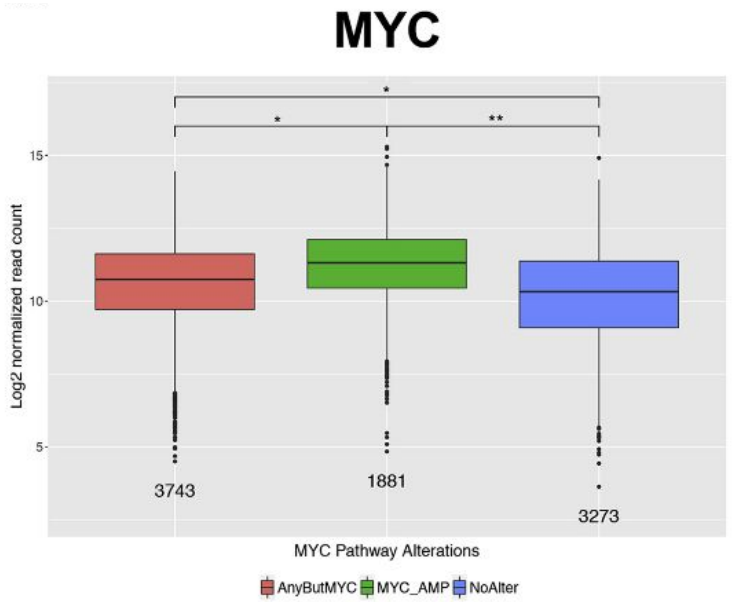
Somatic Copy Number Alterations Driver

Common approach to identify SCNA drivers

- Identify significantly recurrent SCNA across tumors (e.g. Using GISTIC - session 7)
- With peaks overlapping established driver genes, compare expression of driver gene within the peak between tumors with and without SCNAs (if available).

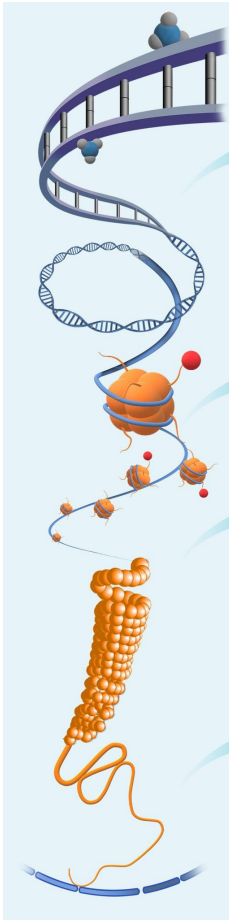


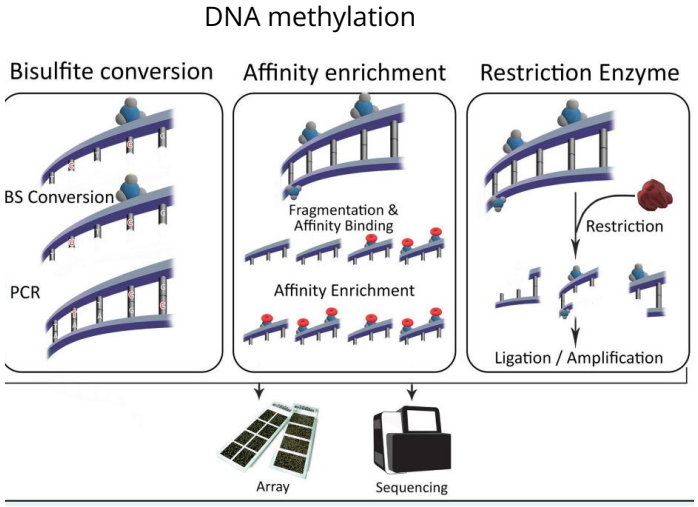
Significantly recurrent focal SCNAs from TCGA cohort
Zack *et al. Nature Genetics*, 2013

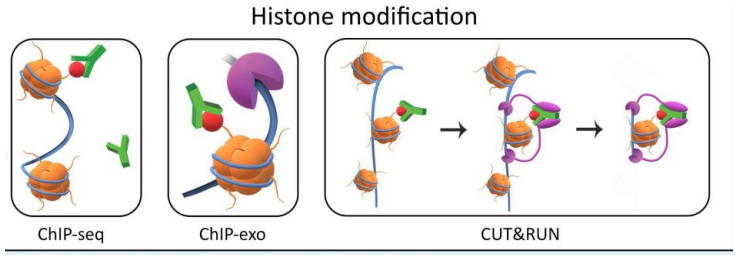


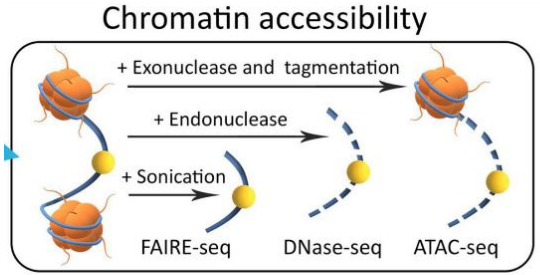
MYC amplification and gene expression in TCGA cohort. Schaub *et al. Cell Systems,* 2018

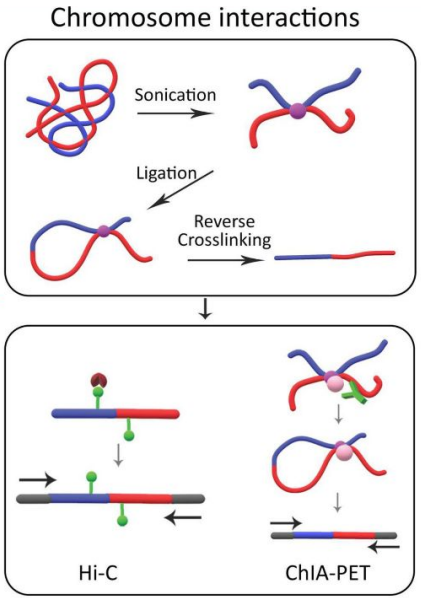
Epigenome and common assays for detection

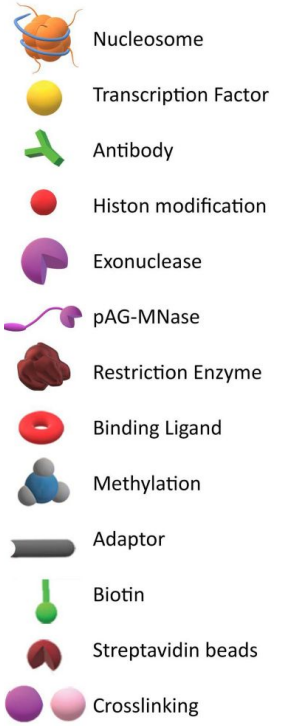






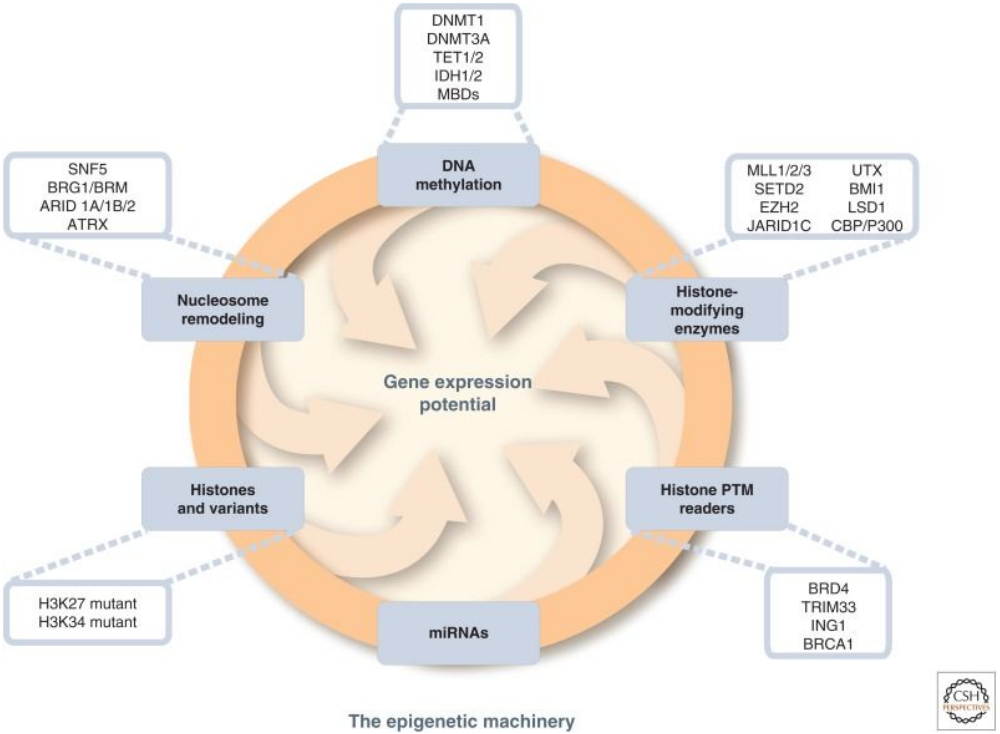






Mehrmohamadi *et al. Front. Cel. Dev. Biol.*, 2021

Epigenomic drivers

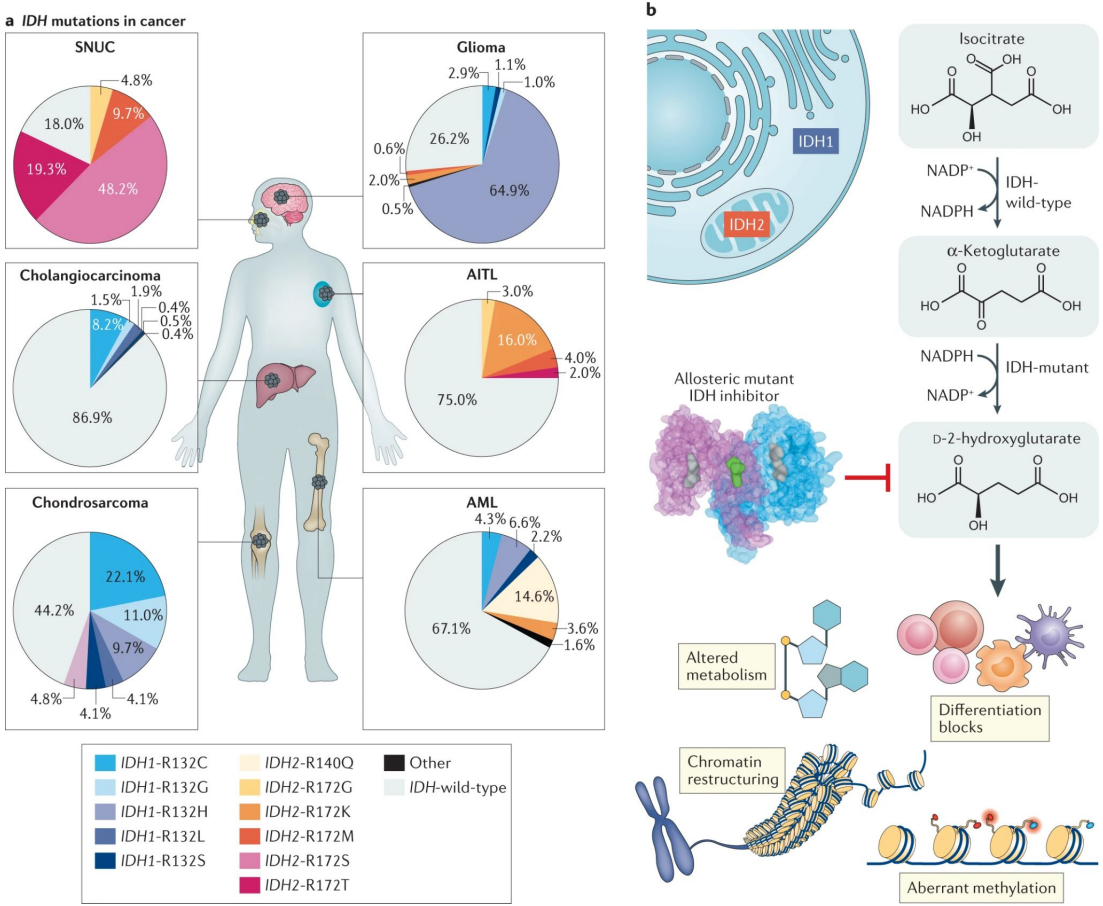


- Genetic mutations of the epigenetic modifiers could cause genome-wide epigenetic alterations in cancer.
- Potentially lead to large genome-wide changes in gene expression in cancer.

Genetic mutations of epigenetic modifiers

Baylin and Jones, *Cold Spring Harb Perspect Biol.,* 2016

IDH mutations as epigenetic drivers in cancer

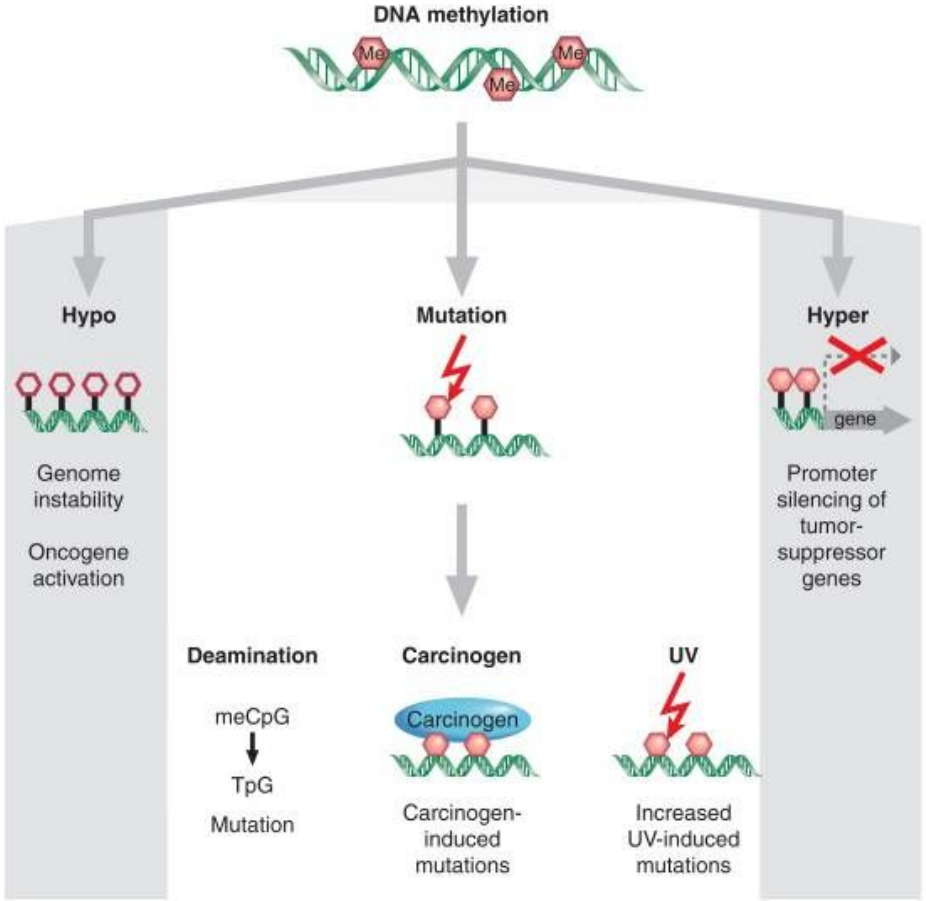


IDH1 and IDH2 are mutated at varying frequencies in several cancers:

- IDH1/2 mutants lead to overproduction of D-2-hydroxyglutarate
- This leads to altered metabolism, aberrant DNA and histone methylation, chromatin restructuring and blocks to normal differentiation patterns.

Pirozzi & Yan, *Nat. Rev. Clin. Oncol.*, 2021

DNA methylation in cancer



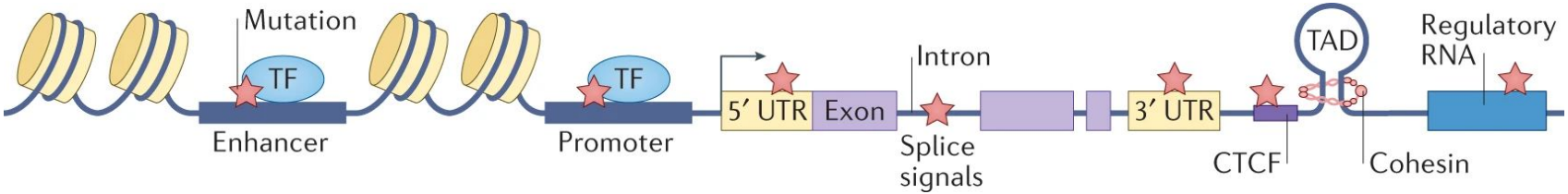
Alteration in DNA methylation can contribute to tumorigenesis by various mechanisms:

- Local hypomethylation can lead to genomic instability and oncogene activation
- Local hypermethylation often at promoter regions can lead to silencing of TSGs
- Altered methylation can lead to increased possibility of carcinogen-induced and/or UV-induced mutations

Baylin and Jones, *Cold Spring Harb Perspect Biol.,* 2016

Noncoding drivers

Noncoding drivers

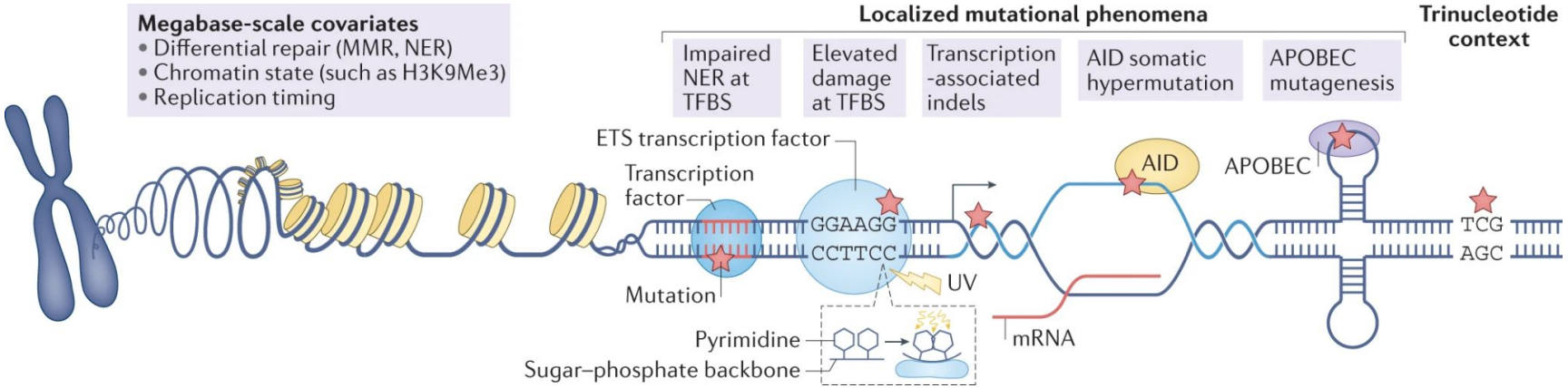


Elliott & Larsson, Nat Rev Cancer 2021

Non-coding mutations can contribute to tumorigenesis via multiple mechanisms:

- Alter transcriptional regulation (e.g. mutations in enhancer, promoter)
- mRNA translation and stability (e.g. mutations in 5′ UTR, 3′ UTR)
- Alter regulatory elements that control splicing (e.g. mutations in intron)
- Disrupt chromatin domain structure, resulting in altered gene expression (mutations affecting CTCF or its binding sites)
- Alter function of regulatory non-coding RNAs

Challenges in identifying non-coding drivers



- Multiple key covariates across genomic regions need to be taken into account to reliably identify positive selection signals (mutations occur at higher frequency than expected by chance) e.g. differential repair, chromatin state, and replication timing compared to coding regions
- Various localized mutational phenomena poorly understood can confound non-coding driver detection
- More difficult to evaluate the functional impact of mutations

Elliott & Larsson, *Nat Rev Cancer,* 2021

Useful public databases for regulatory features

	Name	Element class	Technique
Large scale studies	ENCODE	TFBS, histone modifications, genome-wide DNA:DNA interactions, and others	ChIP-seq, 5C, Hi-C, DNaseI-seq, and many more
	Roadmap Epigenomics	TFBS, histone modifications, DNA methylation, transcribed regions, and others	ChIP-seq, DNaseI-seq, WGBS, RNA-seq, and many more
	FANTOM	FANTOM5 & 6: promoters, enhancers, lncRNAs, and miRNAs	CAGE, deepCAGE, other CAGE methods, full-length cDNA technology
		Element class	**Databases included**
Metadatabases	Ensembl Regulation	TFBS, CTCF binding sites, TSS, miRNA target sites; annotation of open chromatin, promoters, enhancers, and others	ENCODE, FANTOM5, DianaTarBase, VISTA, and more
	UCSC	TFBS, histone modifications, DHS, CpG islands, DNA:DNA interactions, sno/miRNA target sites, promoters, enhancers, and others	ENCODE, ORegAnno, GeneHancer, VISTA, and more
		Element class	Abbreviation: **CTCF**: CCCTC-binding transcription factor **ChIP**: chromatin immunoprecipitation **DHS**: DNaseI-hypersensitive site **lncRNA**: long non-coding RNA **miRNA**: micro RNA **snoRNA**: small nucleolar RNA **TFBS**: transcription factor binding site **TSS**: transcription start site **WGBS**: whole genome bisulfite sequencing
Literature-derived databases	EnDB	Enhancer	
	EnDisease	Enhancer	
	DiseaseEnhancer	Enhancer	
	JASPAR	TFBS	
	GTDR	TFBS	
	ORegAnno	TFBS	
	RegulomeDB	TFBS, promoters	

Garda *et al., Med Gen.,* 2021

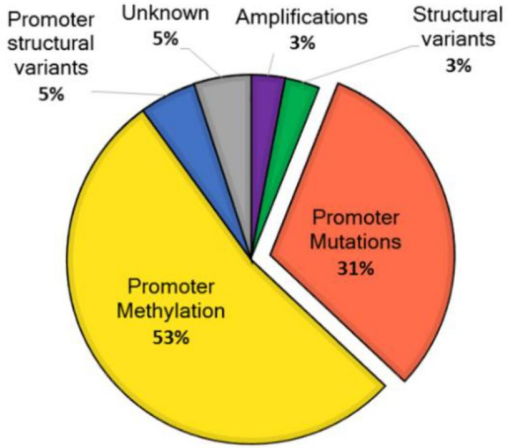
Can help reduce computation burden and increase the chance of finding non-coding drivers with functional impacts

Common tools to detect noncoding drivers

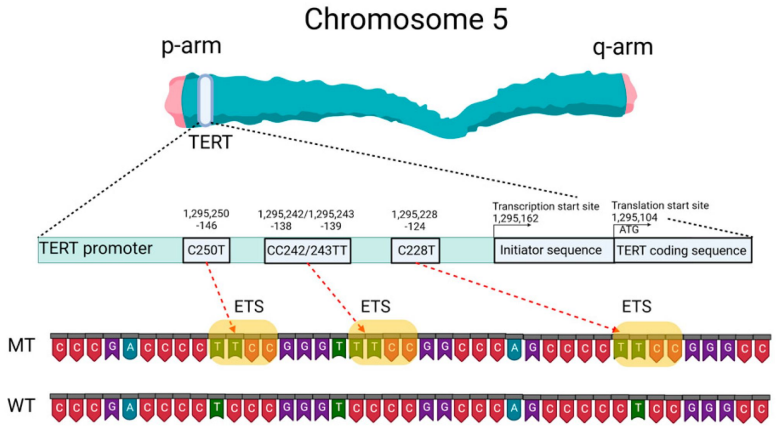
Tool name	Basic function	Characteristics accounted for				
		Key covariates[a]	Local mutation rate[b]	Trinucleotide model[c]	Localized phenomena[d]	Functional impact[e]
ActiveDriverWGS[81]	Quantifies enrichment of mutations in predefined genomic regions relative to a local expectation model	No	Yes	Yes	No	No
CNCDriver[76]	Combines functional impact and recurrence with background mutation rate computed by sampling of similar regions	Yes	No	Yes	AID	Yes
Driver Power[94]	Uses mutational burden and functional impact evidence to identify driver mutations in coding and non-coding regions	Yes	Yes	Yes	No	Yes
ExinAtor[95]	Identifies genes with an excess load of SNVs, focusing on lncRNAs	No	No	Yes	No	No
fishHook[52]	Uses generalized linear modelling of mutation densities to detect enrichment or depletion of indels and SNVs	Yes	Yes	Yes	No	No
LARVA[96]	Identifies elements with a significant mutation burden above a covariate corrected background in annotated regions	Yes	No	No	No	No
MOAT[97]	Divides the genome into user-defined bins to determine local background mutation rate	No	Yes	Yes	No	No
MutEnricher[98]	Calculates both the overall mutation burden and hotspot enrichments for coding and non-coding regions	Yes	Yes	No	No	No
MutSigCV[26]	Detects mutation excess relative to a background model that considers patient-specific and gene-specific mutation rates	Yes	Yes	Yes	No	Yes
MutSpot[85]	Performs feature selection across epigenetic and sequence features followed by estimation of position-specific and patient-specific background somatic mutation probabilities	Yes	Yes	Yes	Yes	No
ncdDetect2[99]	Uses sample-specific mutational signatures, long-range mutation rate variation and position-specific impact	Yes	Yes	Yes	No	Yes
ncDriver[57]	First identifies recurrently mutated elements and then evaluates based on combined significance of cancer-type specificity and conservation	Yes	No	Yes	No	Yes
OncodriveFML[100]	Assesses the functional impact of somatic mutations in coding and non-coding regions relative to simulated mutations	No	Yes	Yes	No	Yes
regDriver[101]	Identifies excess mutations at TFBSs using a global mutation rate model	No	No	No	No	Yes
SMuRF[102]	Uses a user-defined set of regions as input and identifies, filters and annotates significantly mutated regions	Yes	No	No	No	No

Elliott & Larsson,
Nat Rev Cancer, 2021

TERT promoter mutations in cancer



Different mechanisms of TERT reactivation in cancer. Hafezi and Percoff, *cells,* 2020

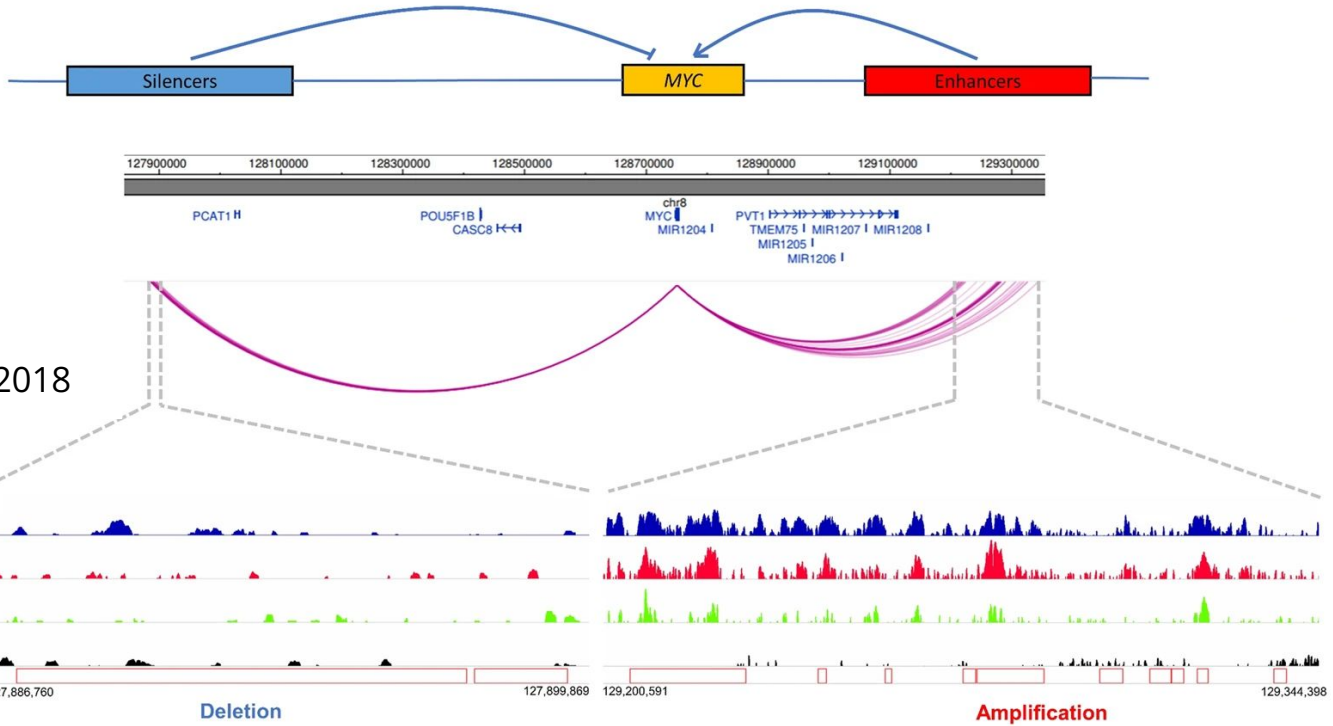


Hasanau *et al. biomedicine,* 2022

- *TERT* is silent in most somatic cells, and is reactivated in cancer cells, allowing them with unrestricted proliferation capacity
- Two canonical mutations in TERTp (C228T and C250T) observed in multiple cancer types create de novo ETS binding motifs -> transcriptional activation.
- Less frequent tandem mutations CC242/243TT have also been observed

An example of drivers in non-coding regions

- Mutations/SCNAs in the regulatory noncoding regions are also being actively investigated as drivers
- MYC is known to be overexpressed through MYC translocation and amplification in multiple myeloma
- SCNAs affecting the non-coding regulatory regions as an alternative mechanisms altering MYC expression



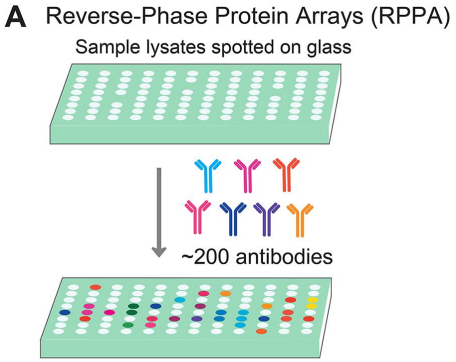
Hoang *et al. Leukemia,* 2018

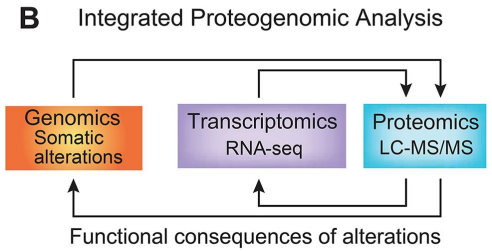
Experimental validation and clinical application

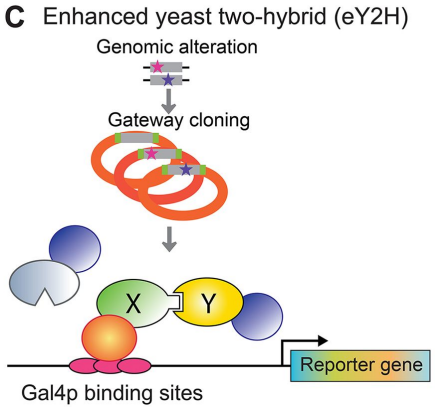
Functional validation of candidate driver genes

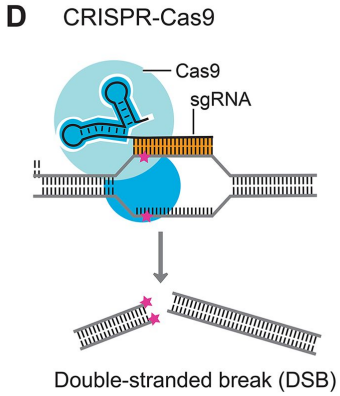
- Bioinformatics methods help identify potential driver genes candidates and prioritize for functional testing
- Gold standard: introduction of the mutation produces cellular phenotype that contributes a selective advantage to growth and survival
- Consideration:
  - Model organisms with different biology between species: e.g. most mouse cells have active telomerase but not most human cells -> mask the effects of drivers activating telomerase in mice vs human.
  - Cell types: Ideally testing on cell types of cancer origins, but some cancers do not have known cell of origins. Cancer cell lines might also have mutations in the same pathways that tested drivers are affecting.
  - Interdependence of mutations: some drivers acting co-occurring or mutually exclusive with others

Examples of experimental strategies









A. RPPA technology is a common protein microarray that uses antibodies to measure the relative expression levels of proteins in tissues or cells.
Ng et al. measured the impact of somatic alterations on gene expression.
https://doi.org/10.1016/j.ccell.2018.01.021

B. Integrated proteogenomic analysis can detect the protein abundance differences and modification caused by somatic alterations.

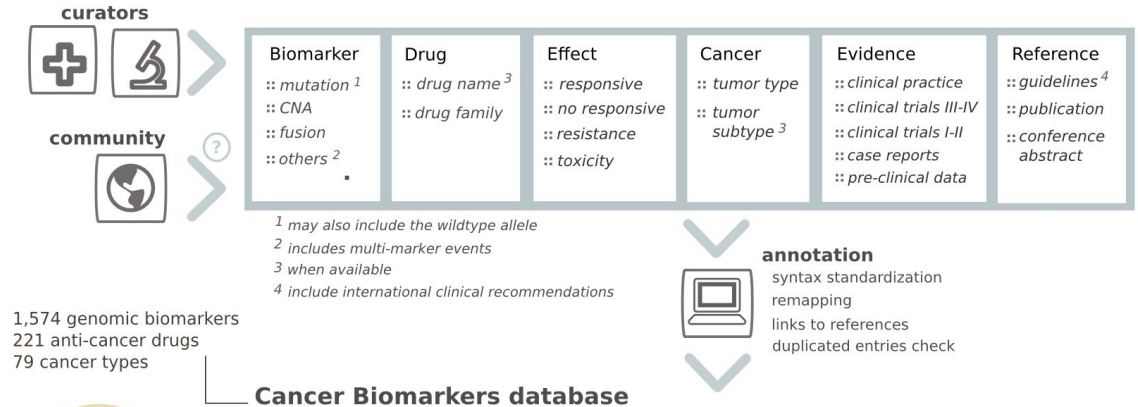
C. eY2H can help elucidate how somatic mutations can alter protein—protein interactions (PPIs), protein—DNA interactions, and protein—metabolite interactions.

D. CRISPR-Cas9 offers high efficacy to introduce mutations into the cellular/animal model to observe any tumorigenic differences between variant and wild type models.

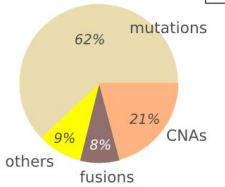
Nussinov *et al. PLOS Computational Biology*, 2019

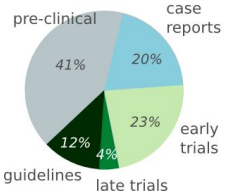
Example of clinical applications

CANCER GENOME INTERPRETER



1,574 genomic biomarkers
221 anti-cancer drugs
79 cancer types





Cancer Biomarkers database

Biomarker	Drug	Effect	Evidence	Cancer	Reference
ABL1 (T315A,F317L,F317V,F317I,F317C,V2..	Nilotinib (BCR-ABL inhibitor 2nd gen)	Responsive	NCNN guidelines	CML	PMID: 21562040
ABL1 (I242T,M244V,K274R,L248V,G250E,G..	Imatinib (BCR-ABL inhibitor 1st gen)	Resistant	European Leukem..	CML	PMID: 21372080
ALK (L1196M,S1206Y,G1269A,I1171T)	Ceritinib (ALK inhibitor)	Responsive	FDA guidelines	LUAD	PMID: 24670109
ALK (I1171T)	Alectinib (ALK inhibitor)	Resistant	Case report	LUAD	PMID: 25226534
AKT2 amplification	MK2206 (Allosteric AKT inhibitor)	Responsive	Pre-clinical	CANCER	ENA 2015 (abstr 373)
B2M oncogenic mutation	PD1 Ab inhibitors (immune checkpoint..	Resistant	Case report	CM	PMID: 27433843
BRAF (V600E)	Vemurafenib (BRAF inhibitor)	No responsive	Early trials	COREAD	PMID: 26287849
BRCA1 oncogenic mutation	Platinum agent (Chemotherapy)	Responsive	Late trials	OV	PMID: 22406760; 225..
DPYD splice donor variant	Tegafur (Fluoropyrimidine)	Toxicity	CPIC guidelines	CANCER	PMID: 239688873
EGFR exon 19 deletions	Erlotinib (EGFR inhibitor 1st gen)	Responsive	FDA guidelines	NSCLC	PMID: 289203045
ESR1-YAP1 fusion	ESR1 inhibitors	Resistant	Pre-clinical	BRCA	PMID: 24055055
G6PD (V98M) + G6PD (N156D)	Dabrafenib (BRAF inhibitor)	Toxicity	FDA guidelines	CANCER	PMID: 26578950
IL7R (S185C) + SH2B3 deletion	MTOR inhibitors	Responsive	Pre-clinical	ALL	PMID: 22955920
JAK2 (V617F)	Ruxolitinib (JAK inhibitor)	Responsive	FDA guidelines	MY	PMID: 28675839
KIT mutations in exon 9,11,13,14 or 17	Regorafenib (Pan-kinase inhibitor)	Responsive	FDA guidelines	GIST	PMID: 25438920
KRAS oncogenic mutation	PI3K inhibitor + MEK inhibitor	No responsive	Early trials	PA	ASCO 2015 (abstr 4119)
MET amplification + BRAF (V600E)	Crizotinib + Vemurafenib (ALK inhibitor +..	Responsive	Case report	COREAD	PMID: 27325282
PIK3CA oncogenic mutation + ERBB2 amplif..	Everolimus + Trastuzumab + Chemother..	Responsive	Late trials	BRCA	PMID: 27091708
PML-RARA fusion	Volasertib (PLK1 inhibitor)	Responsive	Early trials	AML	NCT02198482 NCT0166..

Tamborero *et al.*, *Genome Medicine*, 2019

Interpreting tumor genomes

CANCER GENOME INTERPRETER

ALTERATIONS | PRESCRIPTIONS

Mutations | **CNAs**

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

Sample ID	Gene	Protein Change	Oncogenicity	Mutation	Consequence	Oncogenic annotation	Transcript
Search here...							
TCGA-AG-3999	KRAS	G12S	driver	chr12:25398285 C>T	missense variant		ENST00000256078
TCGA-AG-3999	TP53	R213*	driver	chr17:7578212 G>A	stop gained		ENST00000269305
TCGA-AA-A00D	TP53	R196*	driver	chr17:7578263 G>A	stop gained		ENST00000269305
TCGA-AA-A00D	PIK3CA	H1047L	driver	chr3:178952085 A>T	missense variant		ENST00000263967
TCGA-AA-A00D	APC	R1450*	driver	chr5:112175639 C>T	stop gained		ENST00000257430
TCGA-AA-A00D	BRAF	V600E	driver	chr7:140453136 A>T	missense variant		ENST00000496384
TCGA-AG-3999	APC	E190*	driver	chr5:112116523 G>T	stop gained		ENST00000257430
TCGA-AA-A00D	APC	R564*	driver	chr5:112164616 C>T	stop gained		ENST00000257430
TCGA-AG-3999	BCL9L	Q1041*	driver	chr11:118771331 G>A	stop gained		ENST00000334801
TCGA-AG-3999	PTPRU	R1297Q	driver	chr1:29649914 G>A	missense variant		ENST00000345512
TCGA-AG-3999	PTPRT	R1340H	driver	chr20:40714387 C>T	missense variant		ENST00000373193
TCGA-AG-3999	UBR5	G1638R	driver	chr8:103299706 C>T	missense variant		ENST00000520539
TCGA-AG-3999	PNLIP	R54C	passenger	chr10:118306919 C>T	missense variant		ENST00000369221
TCGA-AA-A00D	C10orf90	R651*	passenger	chr10:128118366 G>A	stop gained		ENST00000284694
TCGA-AG-3999	DDX21	G295V	passenger	chr10:70725230 G>T	missense variant		ENST00000354185

Tamborero *et al*., *Genome Medicine*, 2019

Interpreting tumor genomes

CANCER GENOME INTERPRETER

ALTERATIONS | PRESCRIPTIONS

Show entries with:
- ☑ alterations described as biomarkers for the **selected tumor type**
- ☐ alterations described as biomarkers for a **different tumor type**
- ☐ mutations in genes described as biomarkers with a **different aminoacid change**
- ☐ alterations in genes described as biomarkers upon **other alteration types**

Sample ID	Alterations	Biomarker	Drugs	Diseases	Response	*Evidence*	Match	Source	BioM	Resist.
Search here...										
TCGA-AG-3999	KRAS (G12S)	KRAS (12,13)	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma	Resistant	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS (12,13,59,61,117,146)	Panitumumab (EGFR mAb inhibitor)	Colorectal adenocarcinoma	Resistant	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Panitumumab (EGFR mAb inhibitor)	Colorectal adenocarcinoma	Resistant	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Cetuximab (EGFR mAb inhibitor)	Colorectal adenocarcinoma	Resistant	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	EGFR inhibitors	Lung	Resistant	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS (D119N,G12F,F156L,G60R,F28I	Panitumumab + Cetuximab	Colorectal adenocarcinoma	Resistant	A	✓		C	
TCGA-AA-A00D	PIK3CA (H1047L)	PIK3CA oncogenic mutation	Alpelisib (PI3K inhibitor) + Fulvestrant (Estrogen re	Breast adenocarcinoma	Responsive	A	✓		C	
TCGA-AA-A00D	BRAF (V600E)	BRAF (V600E)	Trametinib (MEK inhibitor) + Dabrafenib (BRAF inh	Non-small cell lung	Responsive	A	✓		C	
TCGA-AA-A00D	BRAF (V600E)	BRAF (V600E)	Encorafenib (BRAF inhibitor) + Cetuximab (EGFR r	Colorectal adenocarcinoma	Responsive	A	✓		C	
TCGA-AA-A00D	PIK3CA (H1047L)	PIK3CA (C420R,E542K,E545A,E545D	Alpelisib (PI3K inhibitor) + Fulvestrant (Estrogen re	Breast adenocarcinoma	Responsive	A	✓		C	
TCGA-AA-A00D	BRAF (V600E)	BRAF (V600E)	Dabrafenib + Trametinib (BRAF inhibitor + MEK inh	Lung adenocarcinoma	Responsive	A	✓		C	
TCGA-AA-A00D	BRAF (V600E)	BRAF (V600E,V600K)	Dabrafenib + Trametinib (BRAF inhibitor + MEK inh	Cutaneous melanoma	Responsive	A	✓		C	
TCGA-AA-A00D	BRAF (V600E)	BRAF (V600E,V600K)	Vemurafenib + Cobimetinib (BRAF inhibitor + MEK	Cutaneous melanoma	Responsive	A	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Trastuzumab + Lapatinib (ERBB2 mAb inhibitor + E	Colorectal adenocarcinoma	Resistant	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS (A146T,G13D,G12C,.,A146P,Q6	Cetuximab	Colorectal adenocarcinoma	Resistant	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS (G12C,G12.,G12A,G12V,G12D,(	Gefitinib	Lung	Resistant	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS (G12D,G12C,G12A,G12S)	Melphalan	Multiple myeloma	Resistant	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Trametinib	Non-small cell lung	Responsive	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Temsirolimus + Ridaforolimus	Endometrial adenocarcinoma	Responsive	B	✓		C	
TCGA-AG-3999	TP53 (R213*)	TP53 oncogenic mutation	Alemtuzumab	Chronic lymphocytic leukemia	Responsive	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Lysergide	Lung adenocarcinoma	Responsive	B	✓		C	
TCGA-AG-3999	TP53 (R213*)	TP53 (R175H,.,R249.)	Doxorubicin	Breast adenocarcinoma	Responsive	B	✓		C	
TCGA-AG-3999	TP53 (R213*)	TP53 oncogenic mutation	Chemotherapy	Stomach	Responsive	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Abemaciclib	Non-small cell lung	Responsive	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Bevacizumab	Colorectal adenocarcinoma	Resistant	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Refametinib + Sorafenib	Hepatic carcinoma	Responsive	B	✓		C	
TCGA-AG-3999	KRAS (G12S)	KRAS oncogenic mutation	Docetaxel + Selumetinib	Non-small cell lung	Resistant	B	✓		C	

Invited speaker

Date: Thursday, March 23, 2023

Time: 10:30 AM – 11:30 AM

Speaker: Núria López-Bigas, Ph.D., Institute for Research in Biomedicine (IRB) Barcelona

Title: Somatic mutations in tumors and normal tissues

THANKS FOR YOUR ATTENTION!

Questions?

Next: Practical session 8 (10:45am)

- Running different algorithms to identify cancer driver genes (dndscv, OncodriveFML, OncodriveCLUSTL)
- Demo of using Cancer Genome Interpreter to identify driver mutations and link to clinical applications