Emerging Approaches for Tumor Analyses in Epidemiological Studies Workshop

Anthology of unusual patterns of somatic mutations in cancer genomes

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NCI Designated Comprehensive Cancer Center

UC San Diego Moores Cancer Center

Faculty Disclosure -- Conflict of Interest

- Chief scientific officer, compensated consultant, and equity holder in io9, LLC.
- Inventor of a US Patent 10,776,718 for source identification by nonnegative matrix factorization.
- Inventor of U.S. provisional patent applications:
  - Clustered mutations for the treatment of cancer (63/289,601).
  - Artificial intelligence architecture for predicting cancer biomarker (63/269,033).
  - Methods and systems for detecting homologous recombination deficiency in cancer therapies (63/366,392).
  - Drugs for treating head and neck cancers with chromosome 9p loss (63/367,846).
  - Genetically-defined immune-checkpoint inhibitor resistance in aggressive precursors of HPV- head and neck squamous cancer (63/412,835).
- Spouse employed by Hologic, Inc. a publicly traded medical technology company.

Anthology Outline

HRD

Stories of The Past

- Mutational signatures as a machine learning approach that allows detecting the *unusual patterns of somatic mutations*.
- Utilizing mutational signatures for developing cancer prevention strategies.
- Utilizing mutational signatures for understanding failed DNA repair and targeted cancer treatment.

Anecdotes of The Present

- Utilizing clustered mutations for understanding cancer development and evolution.
- The repertoire of copy-number signatures in human cancer.
- A novel machine learning approach for detecting homologous recombination deficiency.

Dreams of The Future

- Beyond genomics: Utilizing AI for addressing inequalities of cancer diagnosis


Stories of The Past
UC San Diego
School of Medicine

Stories of a simpler, but not so distant, past

- Mutational signatures as a machine learning approach that allows detecting the *unusual patterns of somatic mutations.*
- Utilizing mutational signatures for developing cancer prevention strategies.
- Utilizing mutational signatures for understanding failed DNA repair and targeted cancer treatment.

Mutational signatures as a machine learning approach that allows detecting the *unusual patterns of somatic mutations*

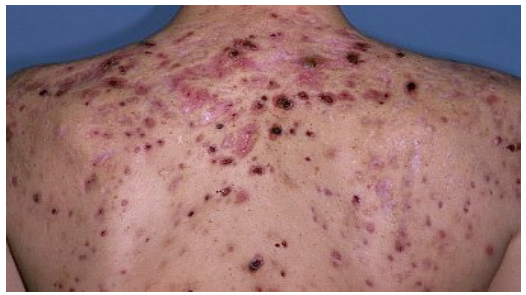
Somatic Mutations, Mutational Signatures, and Human Cancer

- **Somatic mutations** accumulate daily in every cell of the human body. These mutations originate from lifestyle choices, defective cellular machineries, and even from normal cellular processes.

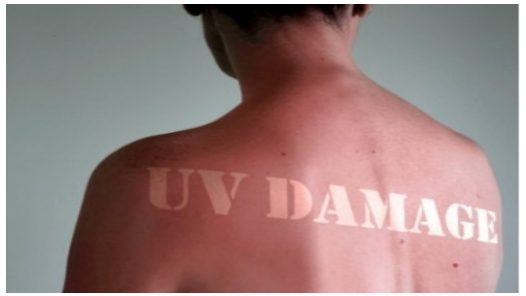
- **Cancer risk** is strongly affected by mutagenesis. Lifestyle choices can cause somatic mutations and significantly affect the risk for developing cancer. For example, from 105 patients with lung squamous cell carcinomas only 1 has never smoked.

- **Mutational signatures** analysis is a machine learning approach that allows detecting the *unusual patterns of somatic mutations* generated by different mutagenic processes from DNA sequencing data.

Human cancers and their origins

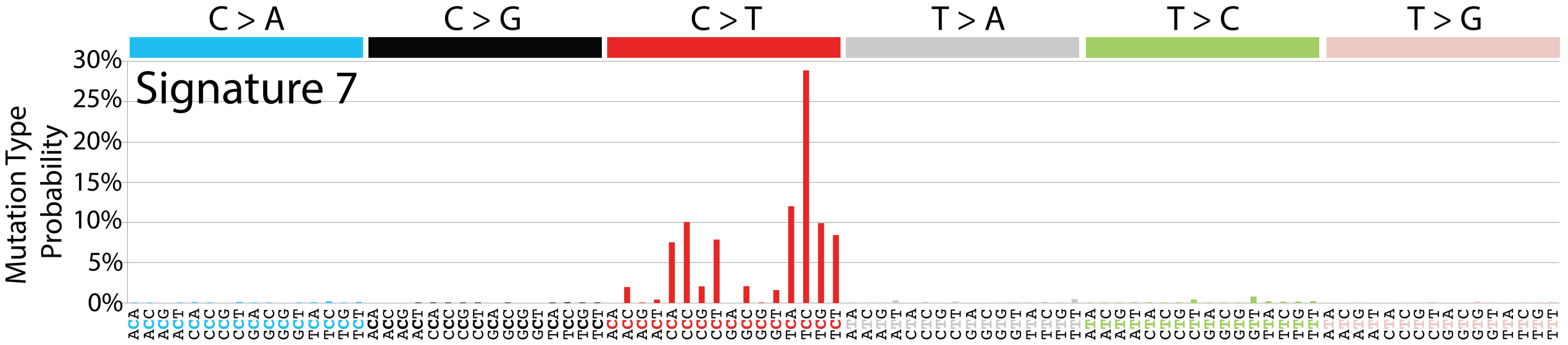


Skin Cancer



Majority caused by UV-light exposure

Predominately C>T somatic mutations



Mutational signature: a molecular fingerprint found in a cancer cell

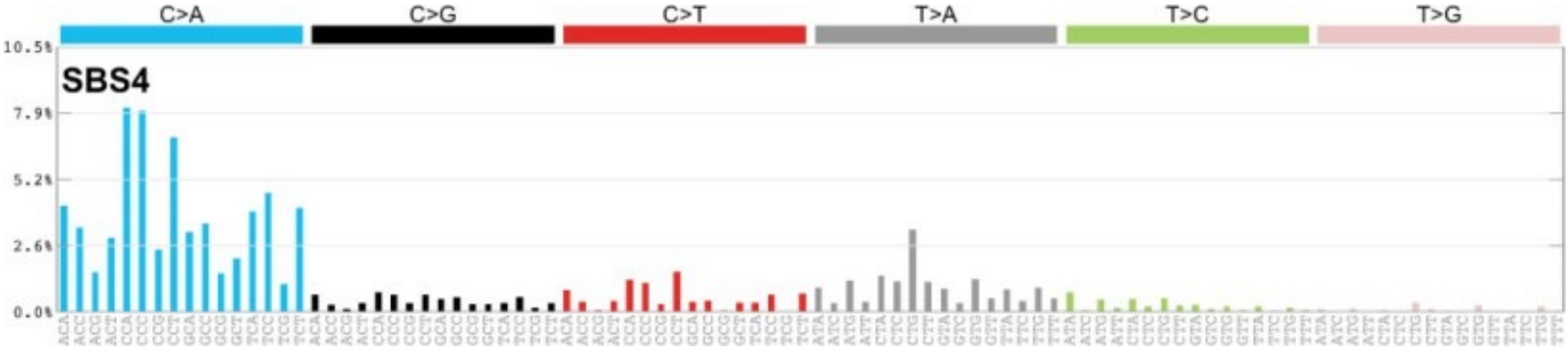
Alexandrov et al., Nature 2013

Human cancers and their origins

Lung Cancer

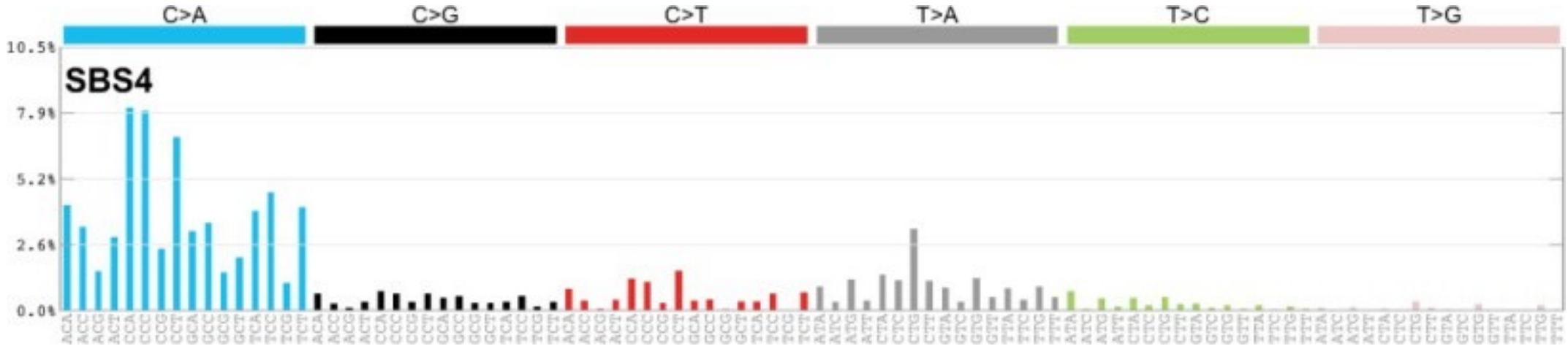
~80% caused by tobacco smoking

Predominately C>A somatic mutations



Alexandrov et al., Science 2015

Quantifying the mutations in a tobacco smoker



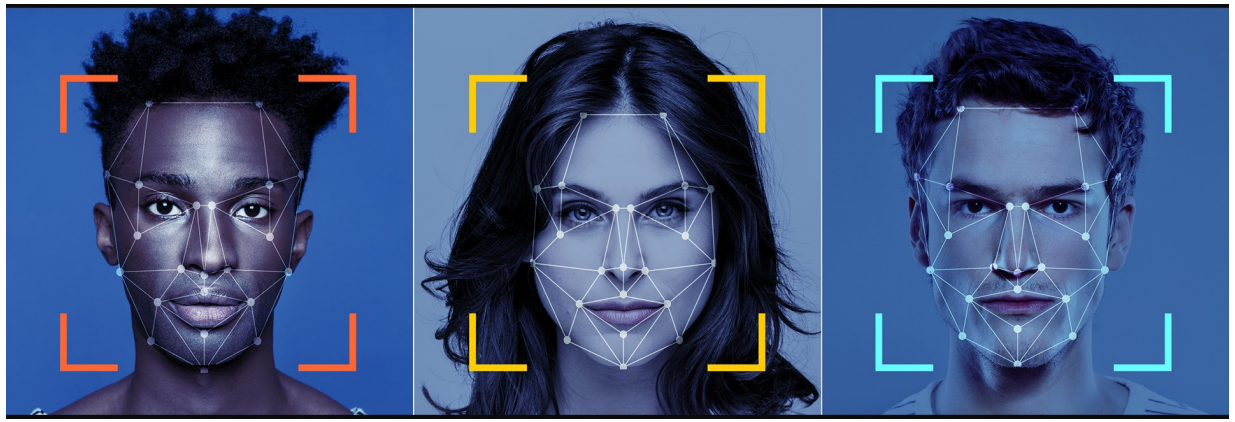
Alexandrov et al., Science 2015

How do we identify mutational signatures?

A Suite of Computational Tools

- SigProfilerMatrixGenerator
- SigProfilerMatrixGenerator2
- SigProfilerPlotting
- SigProfilerPlotting2
- SigProfilerSimulator
- SigProfilerExtractor
- SigProfilerClusters
- SigProfilerTopography
- SigProfilerAssignment
- fastNMF

SIGPROFILER



Develop and utilize state-of-the-art artificial intelligence algorithms for pattern recognition

RESEARCH ARTICLE

Nonnegative/Binary matrix factorization with a D-Wave quantum annealer

Daniel O'Malley[1,2]*, Velimir V. Vesselinov[1], Boian S. Alexandrov[3], Ludmil B. Alexandrov[4,5]

Development of next-generation of algorithms for quantum computer

Mutation Signatures in Human Cancer

Proposed Etiology:

APOBEC activity
Deamination of 5'methycytosine
Reactive oxygen species
Polymerase η activity
POLE mutation

Defective DNA MMR
Defective DNA BER
Defective DNA HRR

Temozolomide treatment
Platinum treatment
Azathioprine treatment

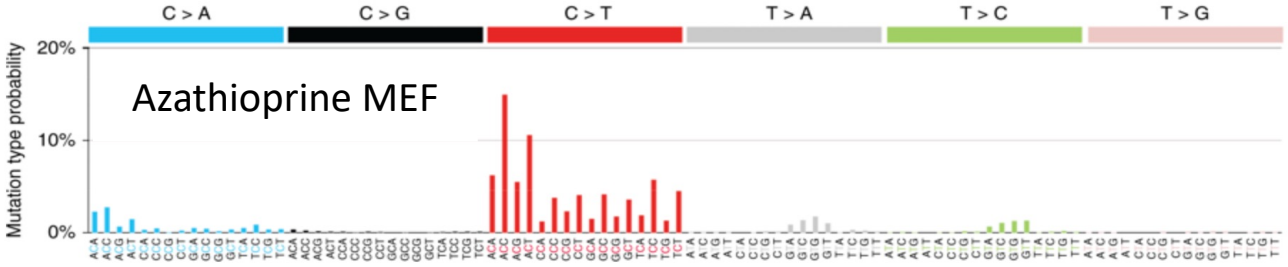
Haloalkane exposure
Aristolochic acid exposure
Aflatoxin exposure
Ultraviolet light exposure
Tobacco smoking

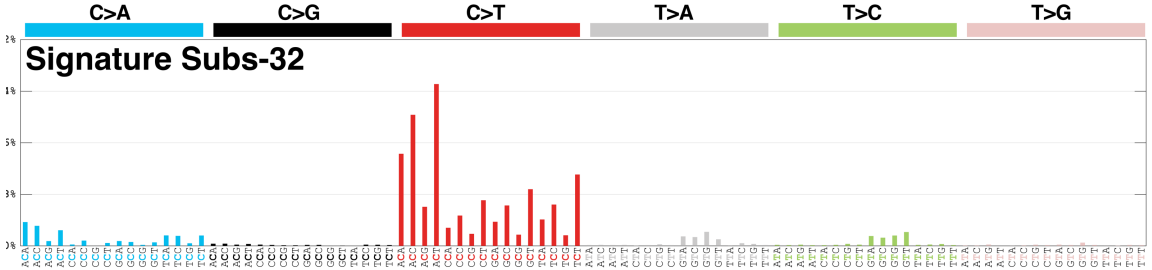
Alexandrov *et al.,* Nature 2020

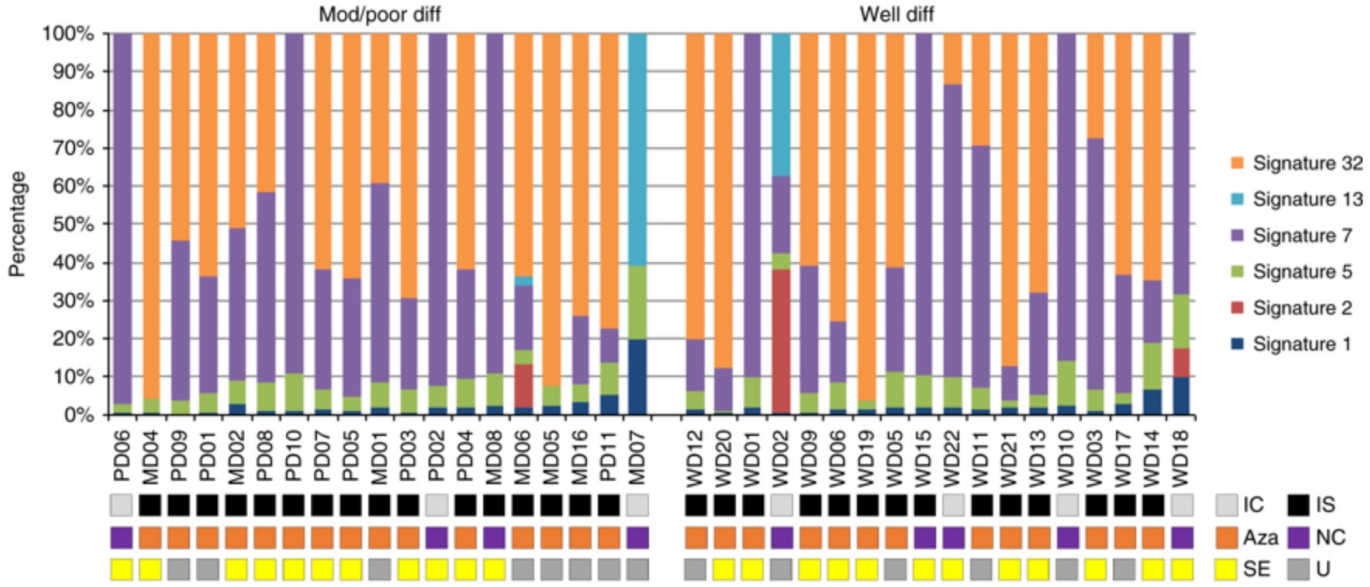
Utilizing mutational signatures for developing cancer prevention strategies

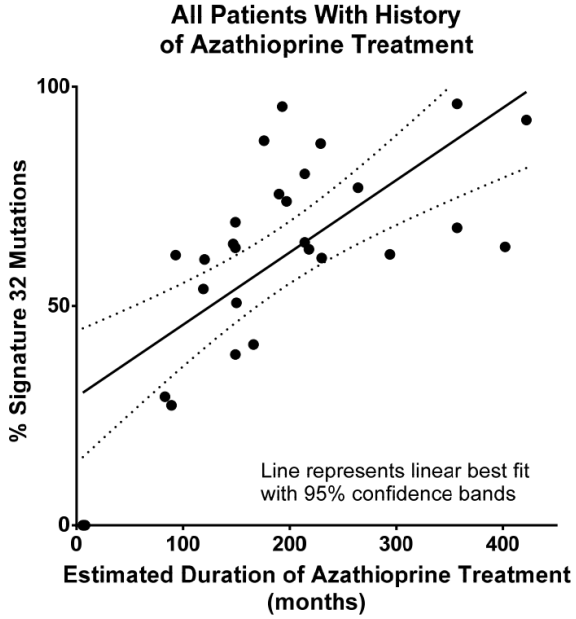
(Somewhat) unexpected carcinogens: Azathioprine

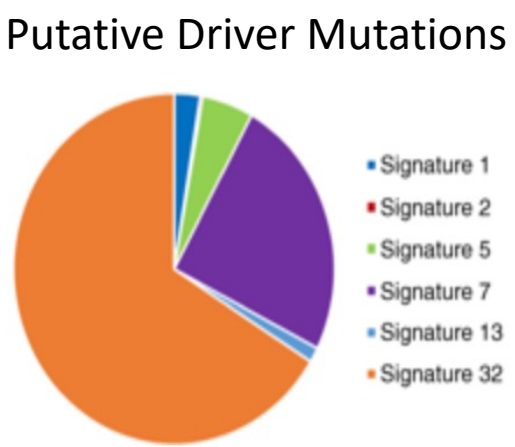
Azathioprine, sold under the brand name Imuran among others, is an immunosuppressive medication. Azathioprine is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Epidemiological studies by International Agency for Research on Cancer have provided "sufficient" evidence of azathioprine carcinogenicity in humans (Group 1), although the methodology of past studies and the possible underlying mechanisms are questioned.





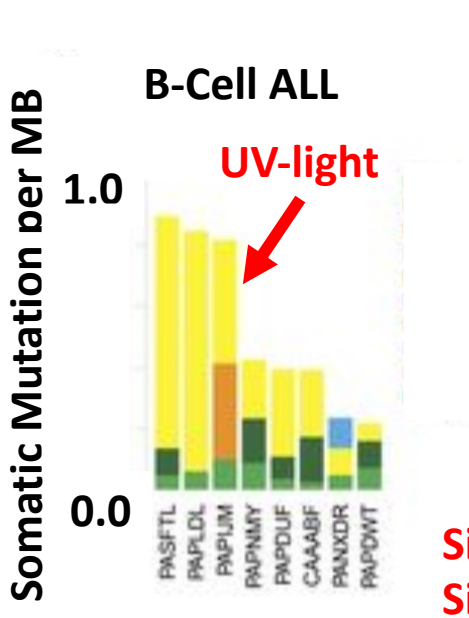


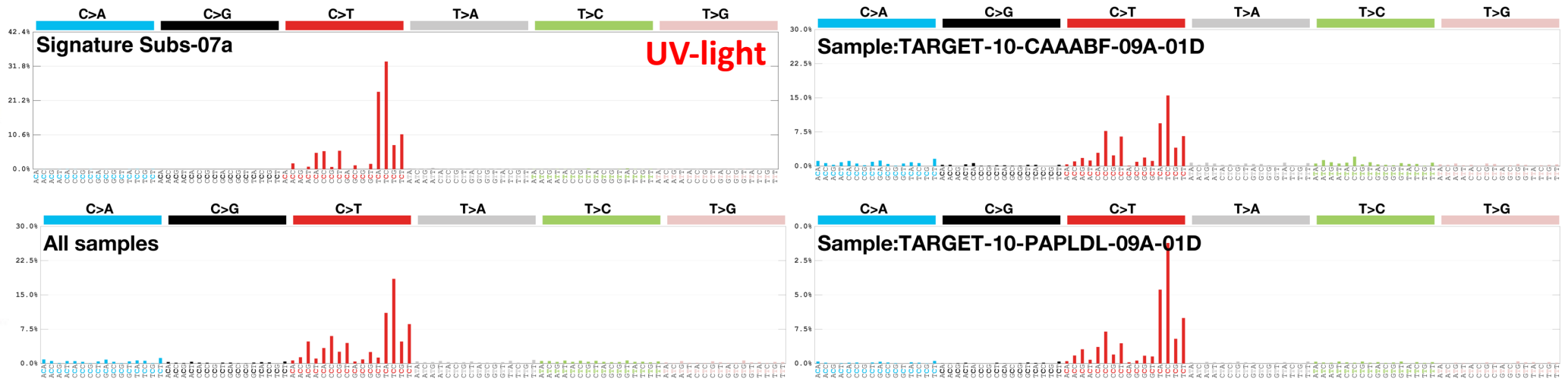




Inman et al., Nature Communications 2018

Known carcinogen in unexpected cancer types: UV-light





Similarity extends to strand bias, dinucleotide, and indel patterns. Confirmed in three other cohorts.
Signature found only in white Caucasian children. Much lower mutation burden compared to skin cancer.

Cancer Causes & Control

October 2017, Volume 28, Issue 10, pp 1075–1083 | Cite as

Residential exposure to ultraviolet light and risk of precursor B-cell acute lymphoblastic leukemia: assessing the role of individual risk factors, the ESCALE and ESTELLE studies

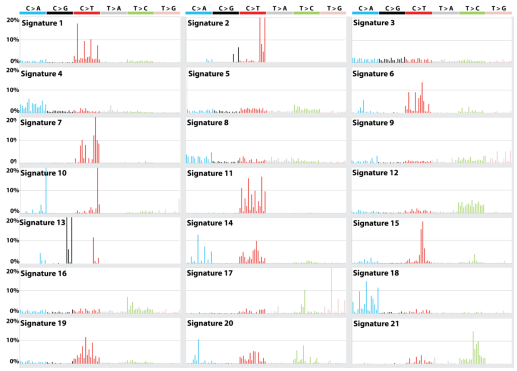
Authors | Authors and affiliations

Astrid Coste, Denis Hémon, Laurent Orsi, Mathieu Boniol, Jean-François Doré, Laure Faure, Jacqueline Clavel, Stéphanie Goujon

Ma et al., Nature 2018

Mutational Signatures for Discovery of Germline Predisposition Syndromes

2013



First map of 21 mutational signatures identified in human cancer
Alexandrov *et al.,* Nature 2013

2015

nature genetics

Analysis | Published: 09 November 2015

Clock-like mutational processes in human somatic cells

9 novel mutational signatures identified

Signature 30 discovered; etiology/cause unknown

Alexandrov *et al.,* Nature Genetics 2015

2017

RESEARCH

CANCER

Use of CRISPR-modified human stem cell organoids to study the origin of mutational signatures in cancer

Signature 30 functionally associated with failure BER due to defective *NTHL1.*

Drost *et al.,* Science 2017

2019

Cancer Cell

Mutational Signature Analysis Reveals NTHL1 Deficiency to Cause a Multi-tumor Phenotype

Signature 30 found in 29 tumors from 7 organs in 17 families. *NTHL1* germline deficiency (SNPs & indels) found in all but one patient.

Grolleman *et al.,* Cancer Cell 2019

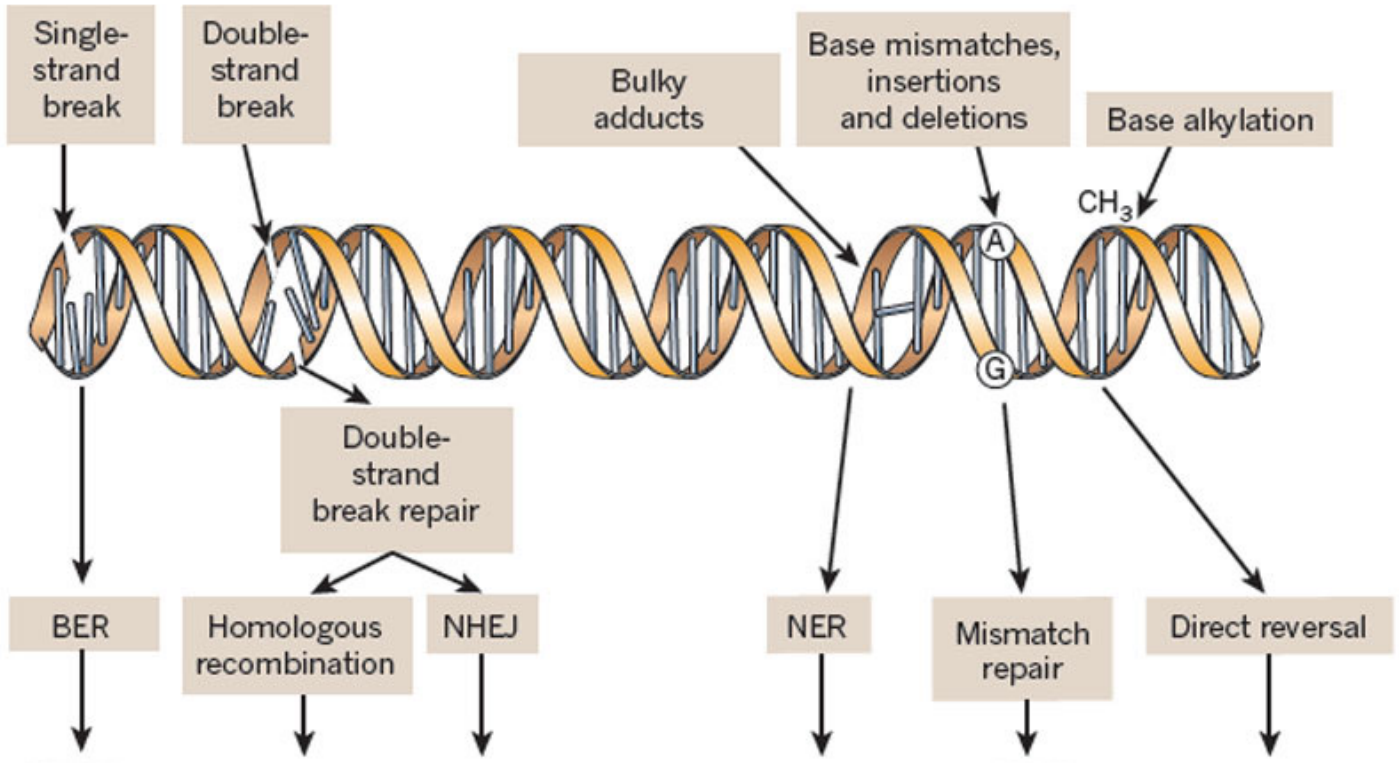
Cancer Cell main conclusions:

"Mutational signature analyses can assist to identify germline DNA repair defects."

"This study illustrates the power of mutational signature analysis in defining tumor phenotypes in rare cancer predisposition syndromes and provides proof-of-principle for recognizing new patients with cancer syndromes based on tumor sequence data."

Utilizing mutational signatures for understanding failed DNA repair and targeted cancer treatment

Mutational signatures associated with failed DNA repair

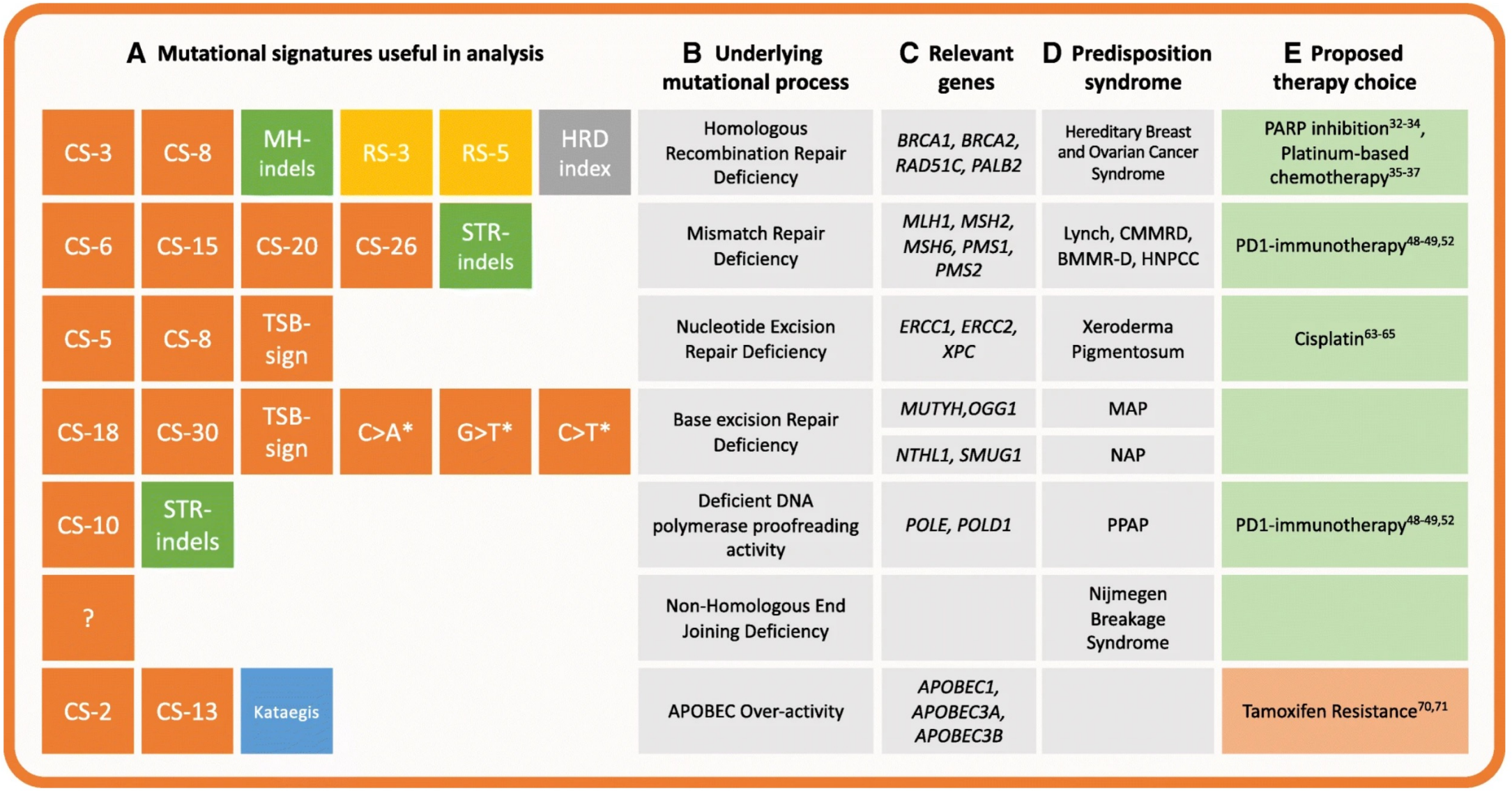


Mutational Signatures Of Failed Repair	**SBS30** **SBS36**	**SBS3** **ID6** **ID8** **DBS7***	**N/A**	**SBS5**	**SBS6/14/15** **SBS20/21** **SBS26/44** **ID1/2/7** **DBS10**	**SBS11***

*Proposed based on limited evidence

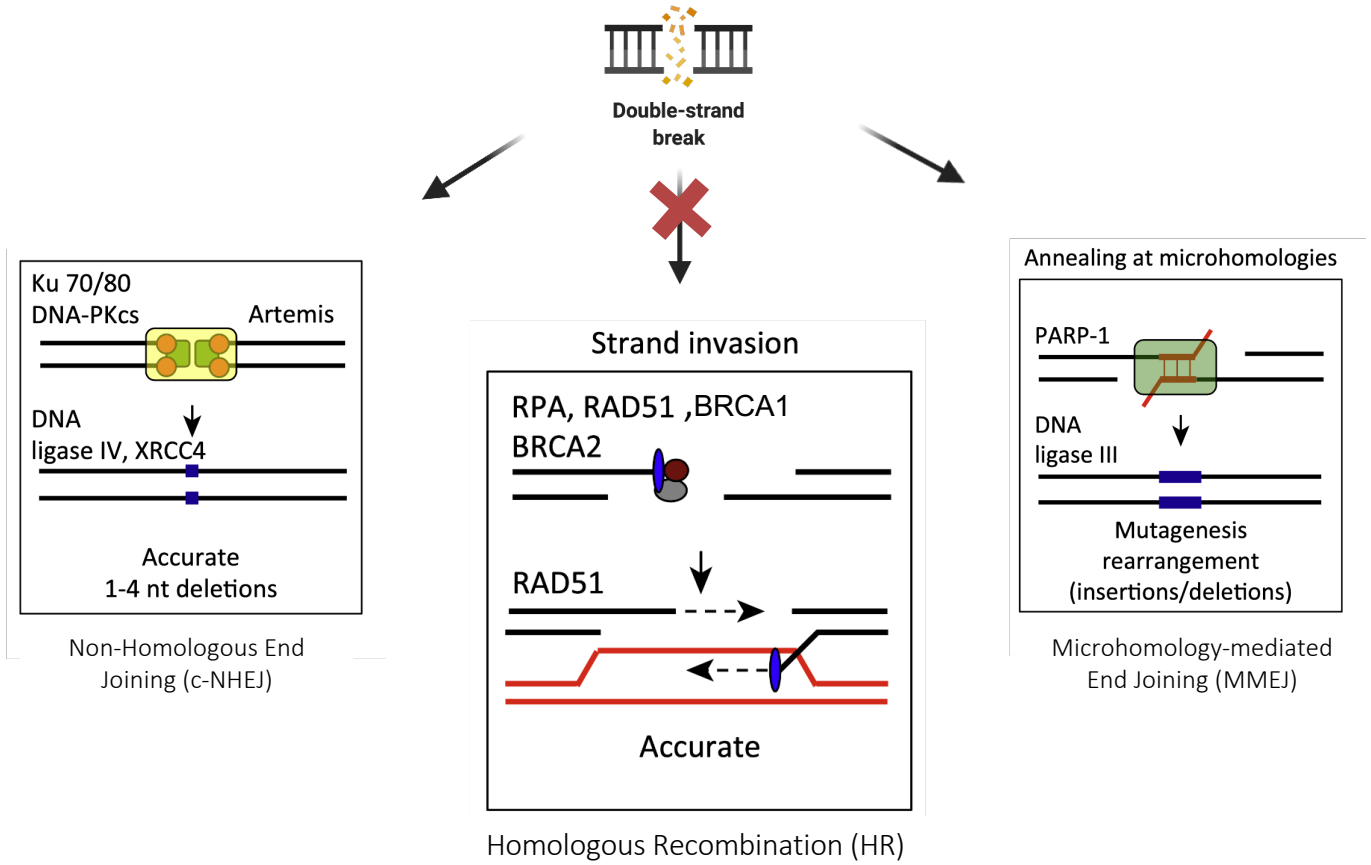
Figure adapted from Lord & Ashworth, Nature 2012
Alexandrov et al., 2020, Nature

Mutational Signatures with Known Predictive Power



A Mutational signatures useful in analysis						B Underlying mutational process	C Relevant genes	D Predisposition syndrome	E Proposed therapy choice
CS-3	CS-8	MH-indels	RS-3	RS-5	HRD index	Homologous Recombination Repair Deficiency	*BRCA1, BRCA2, RAD51C, PALB2*	Hereditary Breast and Ovarian Cancer Syndrome	PARP inhibition[32-34], Platinum-based chemotherapy[35-37]
CS-6	CS-15	CS-20	CS-26	STR-indels		Mismatch Repair Deficiency	*MLH1, MSH2, MSH6, PMS1, PMS2*	Lynch, CMMRD, BMMR-D, HNPCC	PD1-immunotherapy[48-49,52]
CS-5	CS-8	TSB-sign				Nucleotide Excision Repair Deficiency	*ERCC1, ERCC2, XPC*	Xeroderma Pigmentosum	Cisplatin[63-65]
CS-18	CS-30	TSB-sign	C>A*	G>T*	C>T*	Base excision Repair Deficiency	*MUTYH,OGG1*	MAP	
							NTHL1, SMUG1	NAP	
CS-10	STR-indels					Deficient DNA polymerase proofreading activity	*POLE, POLD1*	PPAP	PD1-immunotherapy[48-49,52]
?						Non-Homologous End Joining Deficiency		Nijmegen Breakage Syndrome	
CS-2	CS-13	Kataegis				APOBEC Over-activity	*APOBEC1, APOBEC3A, APOBEC3B*		Tamoxifen Resistance[70,71]

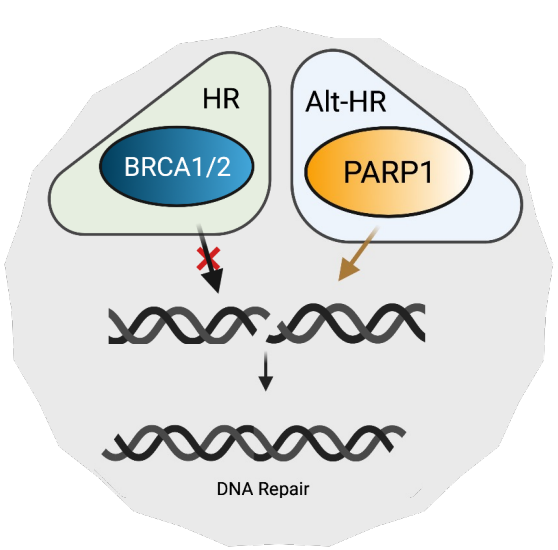
Utilizing signatures for detecting homologous recombination deficiency (HRD)



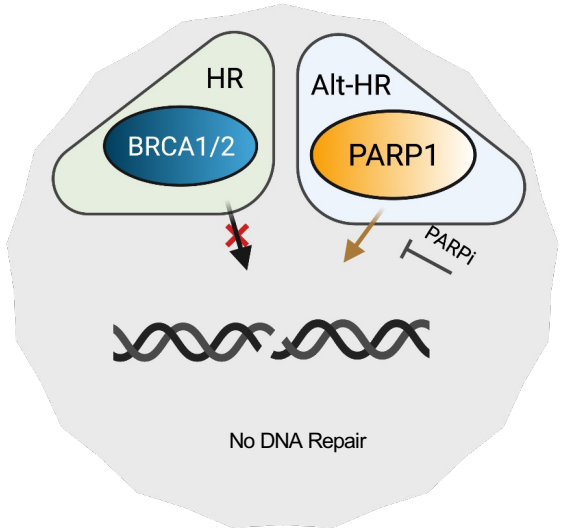
Utilizing signatures for detecting homologous recombination deficiency (HRD)

FDA Approved drugs for treating advanced-stage ovarian as well as metastatic breast and prostate cancers

PARPi leverages synthetic lethality to target HRD cancer cells



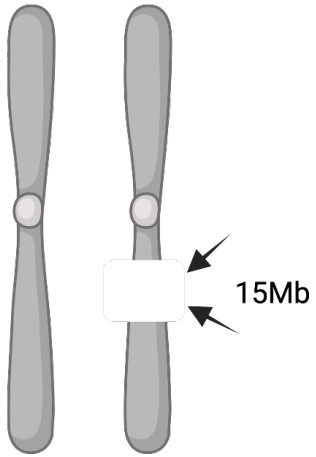
Cell Alive



Cell Death

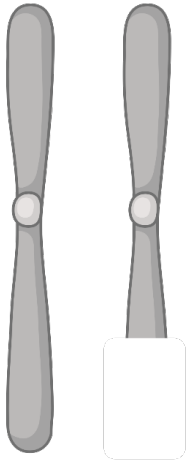
Examples of HRD Diagnostic Tests

Laboratory Name	Test Name	HRD Status determined by	Genes Assessed	List Price
Foundation Medicine	FOUNDATIONONE® CDx	BRCA1/BRCA2-positive or LOH ≥ 16 %	324 genes, including *BRCA1* and *BRCA2*	$5,800
Myriad	MYRIAD myChoice® CDx	BRCA1/BRCA2-positive or GIS ≥ 42	2 genes: *BRCA1*, *BRCA2*	$4,040



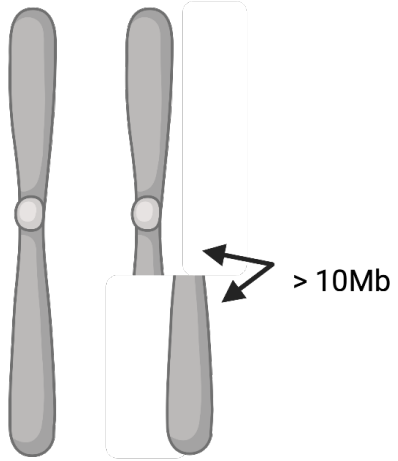
Loss of Heterozygosity (LOH)

loss of one normal copy of a gene or a group of genes



Telomeric Allelic Imbalance

unequal number of parental and maternal alleles at the telomeres

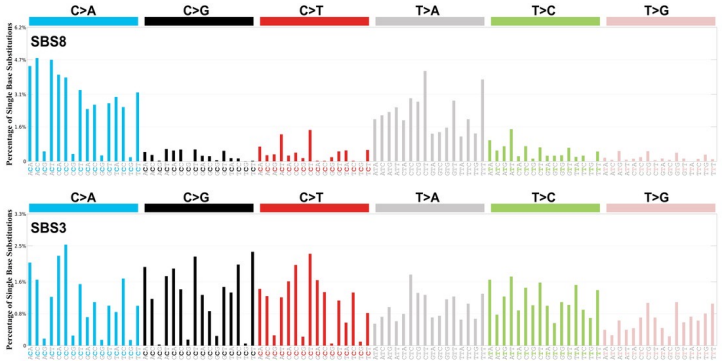


Large State Transitions (LST)

chromosomal break between adjacent regions of at least 10 Mb

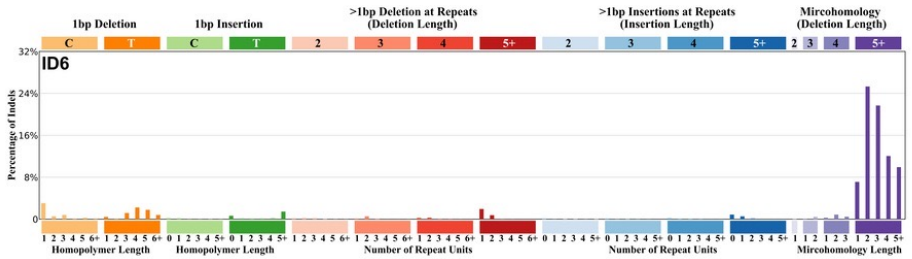
Mutational signatures/Genomic footprint of HRD

Single base substitutions



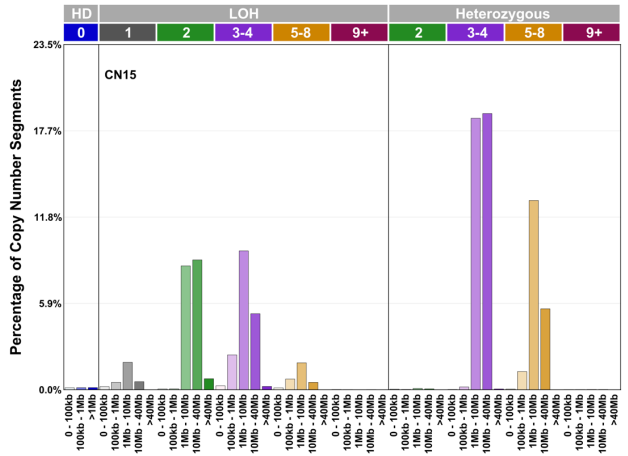
Alexandrov et al. *Nature* 2013

Microhomology-mediated deletions



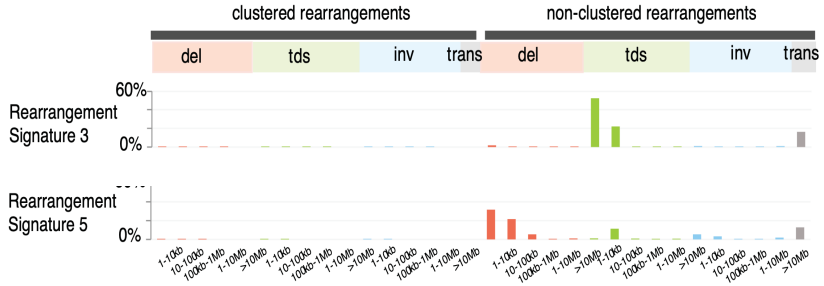
Alexandrov et al. *Nature* 2020

Copy Number Alterations



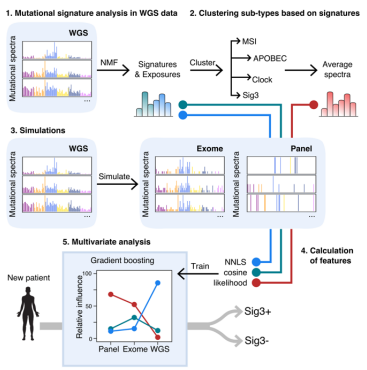
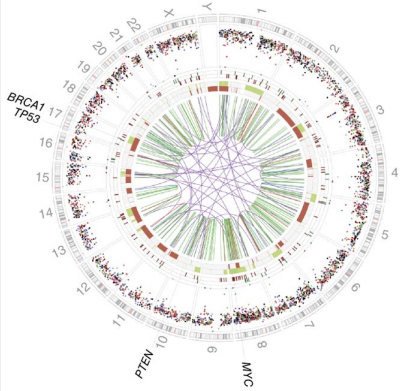
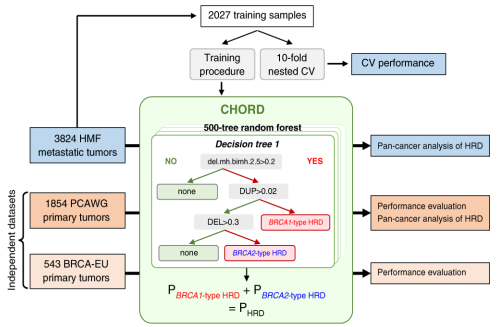
Steele et al. *Nature*, 2022

Structural Variations

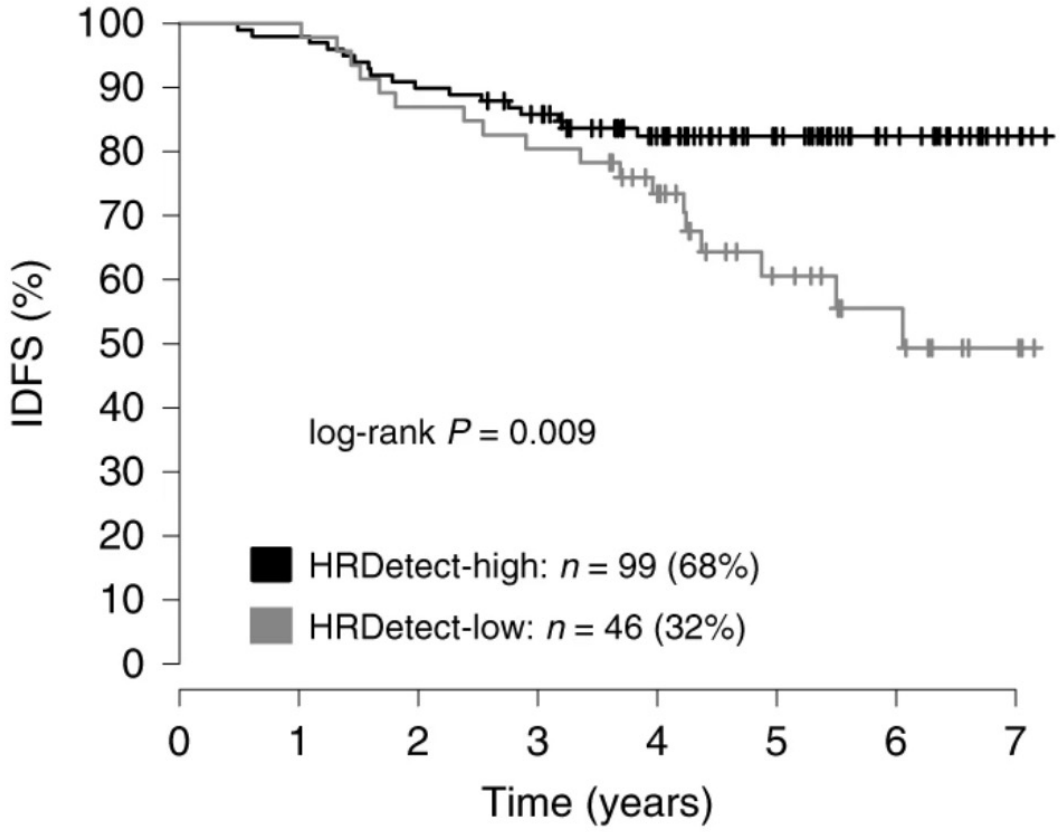


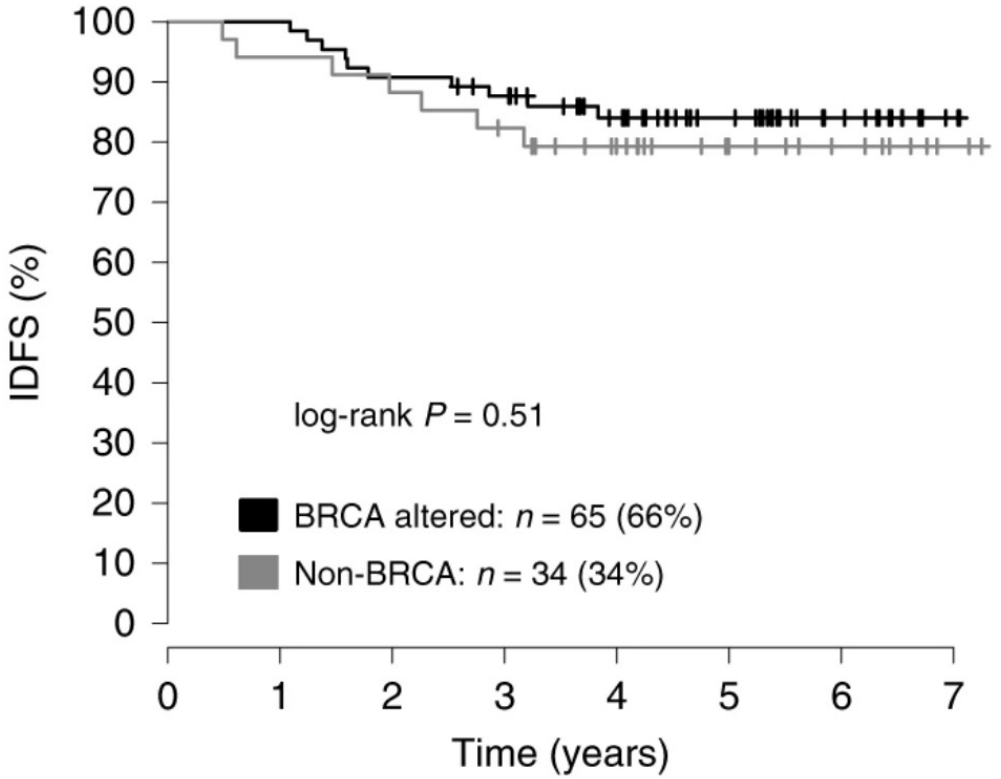
Nik-Zainal et al. *Nature* 2016

HRD Prediction tools that use mutational signatures or mutational patterns

Tools	 SigMA Gulhan, D. *et al. Nat Genet* (2019)	 HRDetect Davies, H. *et al. Nat Med* (2017)	 CHORD Nguyen, L. *et al. Nat Commun* (2020)
Features	SBS3	SBS3, SBS8, Microhomology-mediated deletions, RS3, RS5	SBS, ID, and SV mutational patterns
Sequencing Platform	WGS, WES, Panels	WGS	WGS
Advantages & Limitations	Method can be applied to WGS, WES, and panel data. SBS3 is flat and method can be used only for highly mutated panels (~25% breast cancers).	Whole-genome sequencing is expensive approach especially at high-coverage. In many cases it requires fresh cancer tissues, and it is not commonly used in clinical practice. HRDetect & CHORD can detect ~50% more samples that will respond to PARPi when compared myChoice CDx.	

Example of applying an academic HRD tool to a breast cancer cohort





IDFS: invasive disease-free survival

Staaf et al., *Nature Medicine*, 2019

Anecdotes of The Present

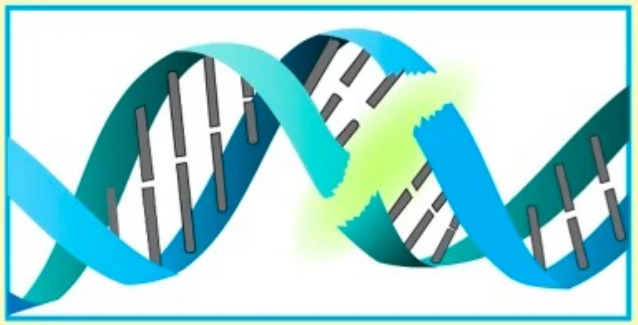
A brief look at the present with glimpses of the future

- Utilizing clustered mutations for understanding cancer development and evolution.
- The repertoire of copy-number signatures in human cancer.
- A novel machine learning approach for detecting homologous recombination deficiency.

Utilizing clustered mutations for understanding cancer development and evolution

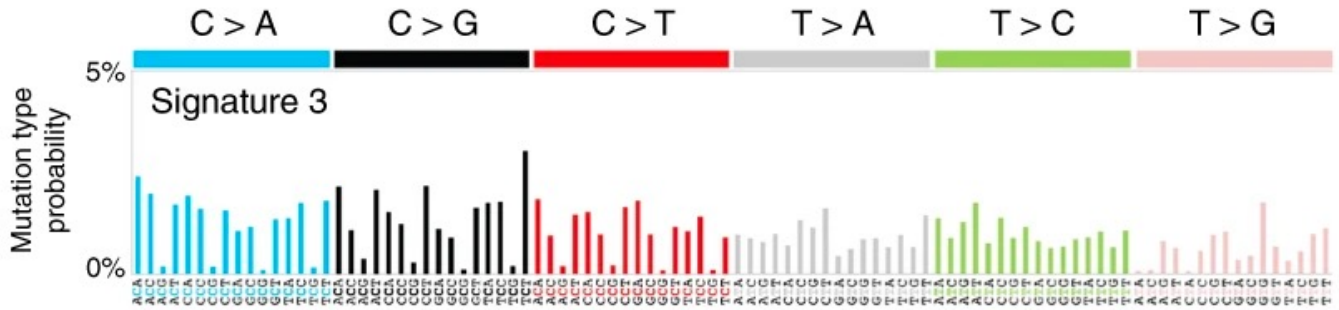
Erik Bergstrom

A subset of mutations cluster in non-random fashion

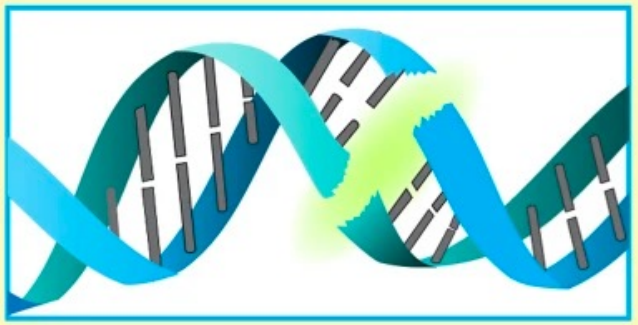


Double-strand break

Base pair mismatch



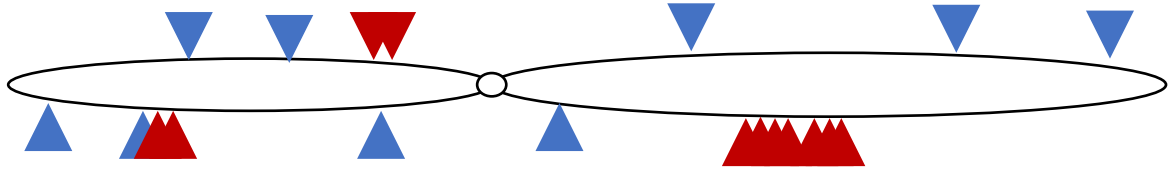
DNA repair pathway alterations

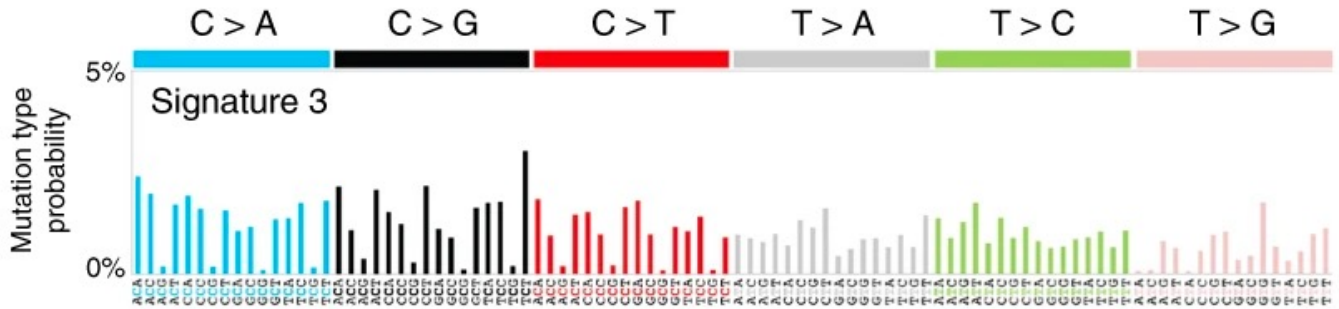


Double-strand break

Base pair mismatch

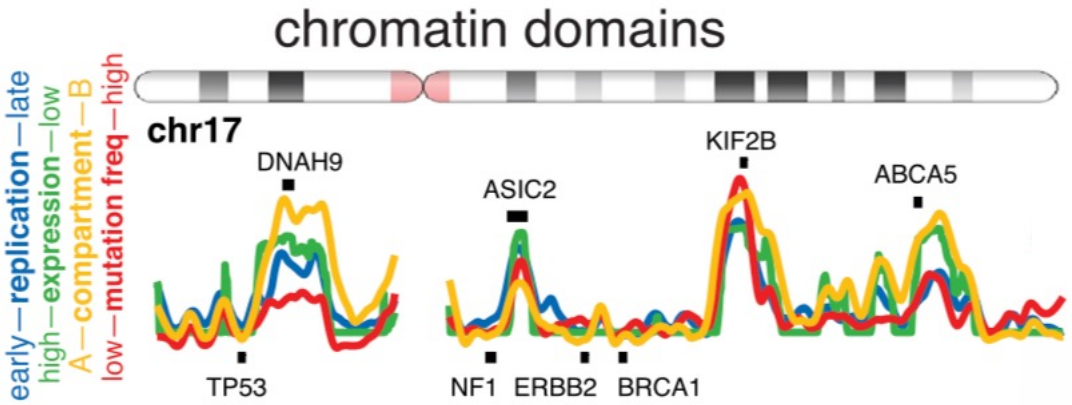
Mutations occur as single, independent events randomly across the genome





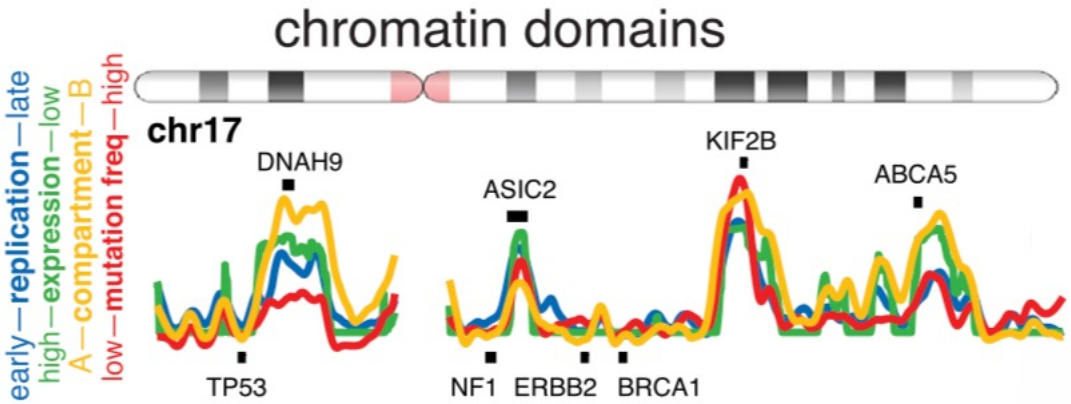
DNA repair pathway alterations

Mutation rate is dependent on a range of genomic features

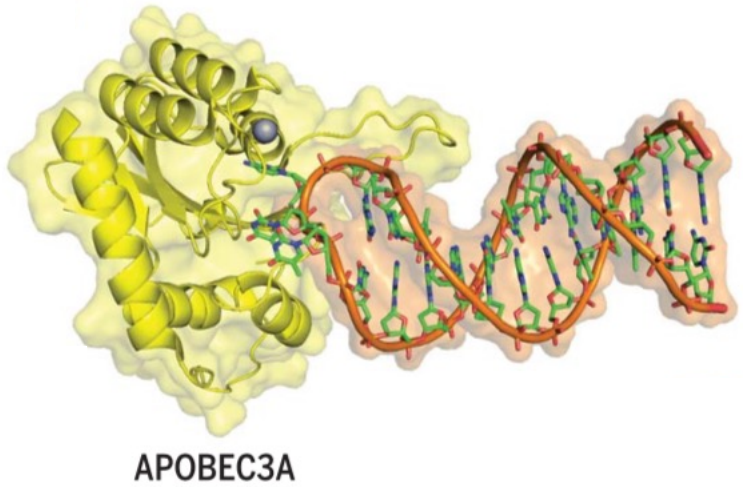


Buisson *et al.* 2019

Mutation rate is dependent on a range of genomic features



Buisson *et al.* 2019



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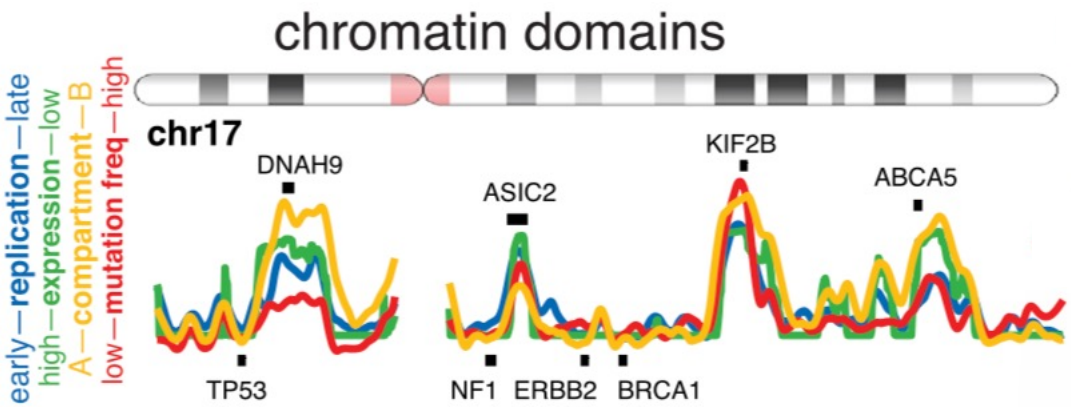
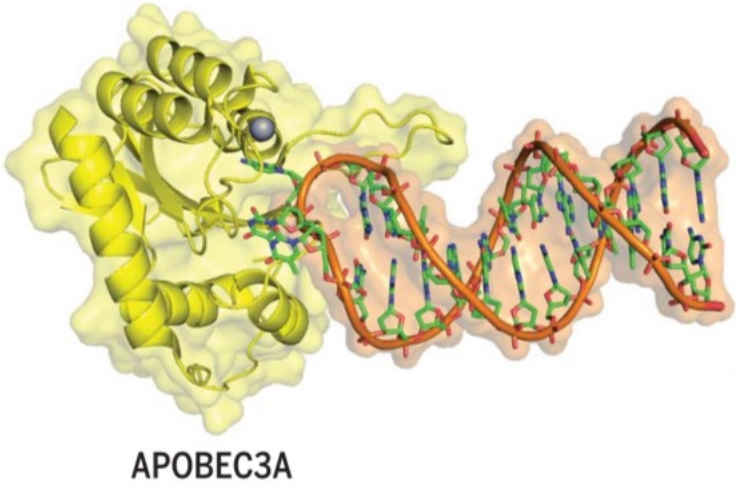
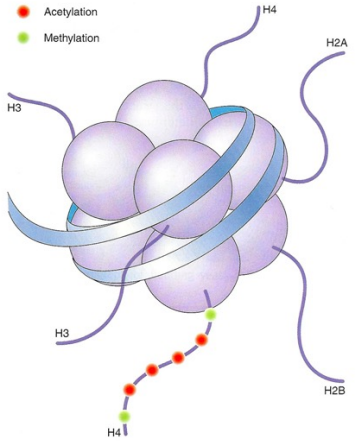


Buisson *et al.* 2019





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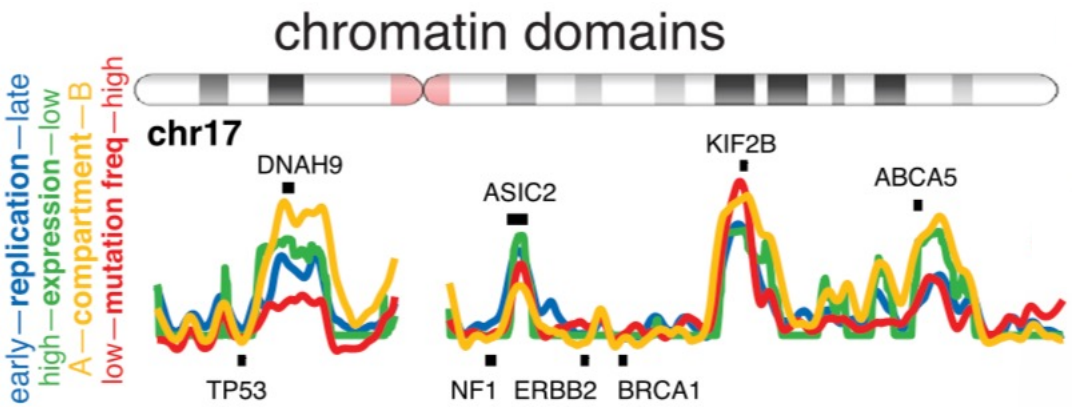
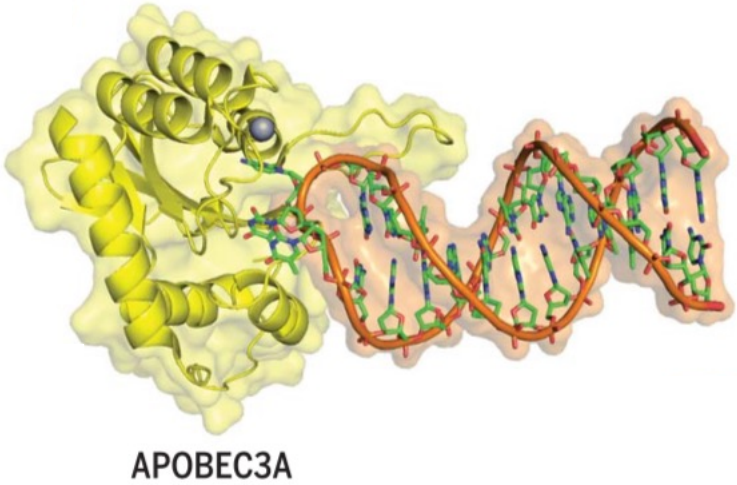
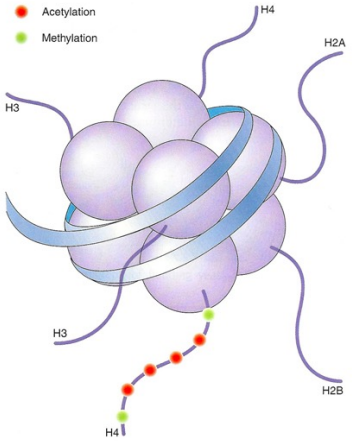
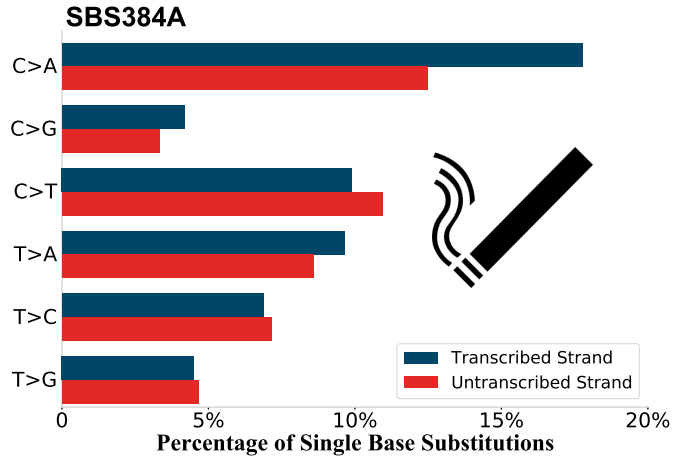


Buisson *et al.* 2019







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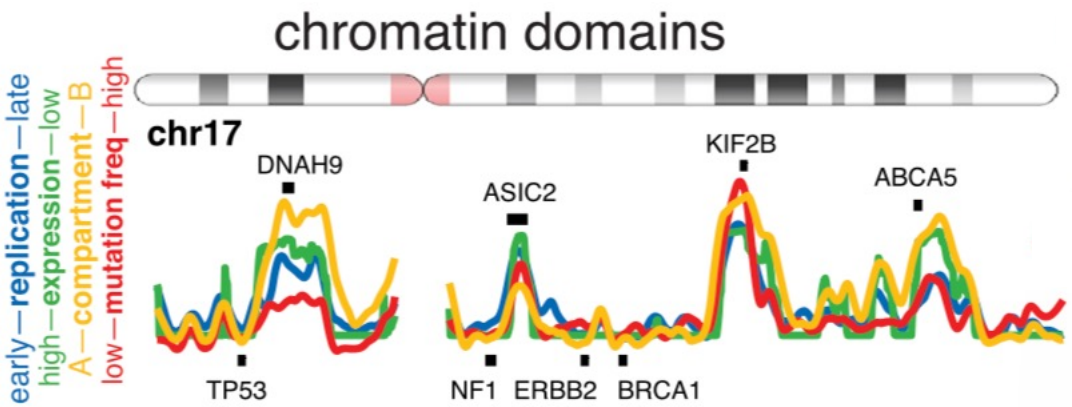

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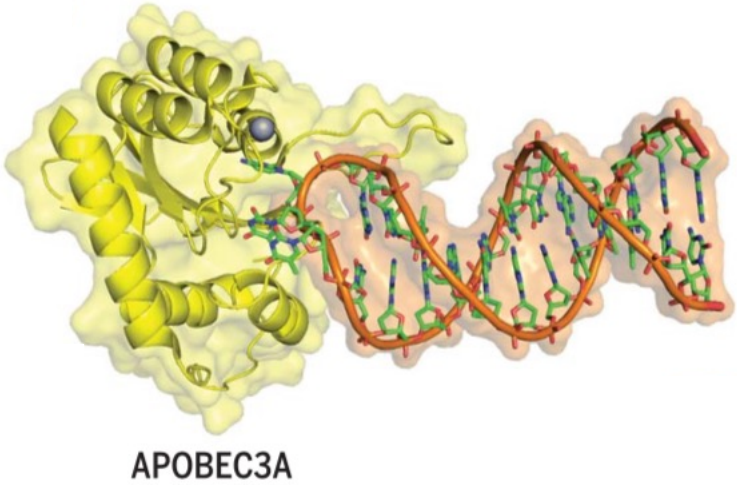
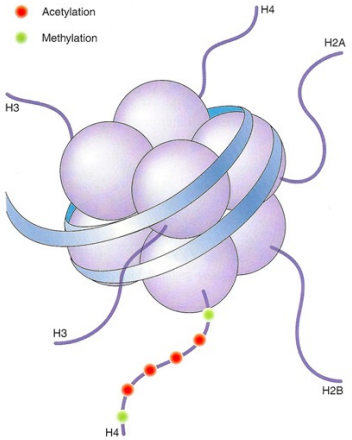
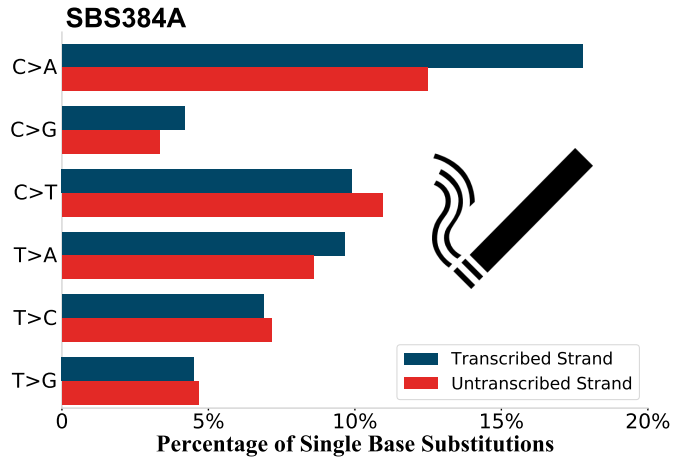
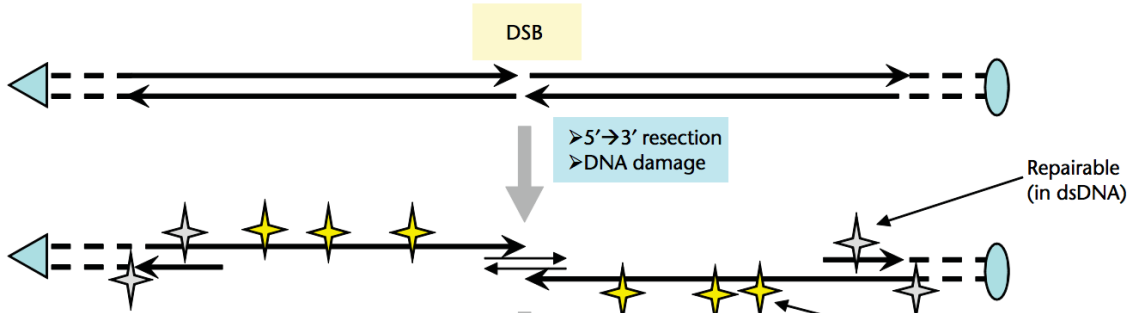
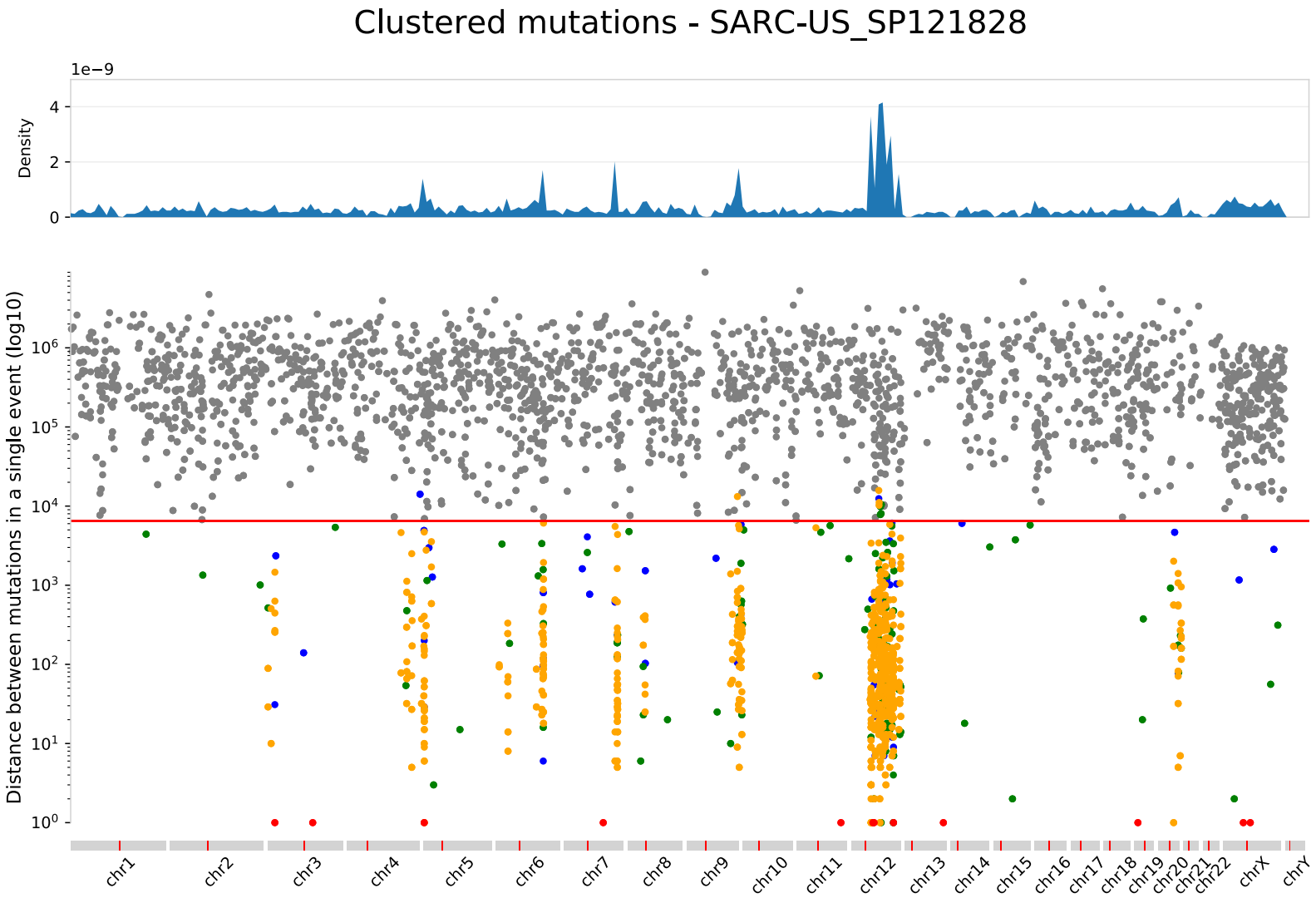








Classification of clustered mutations



Bergstrom *et al.*, Nature 2022

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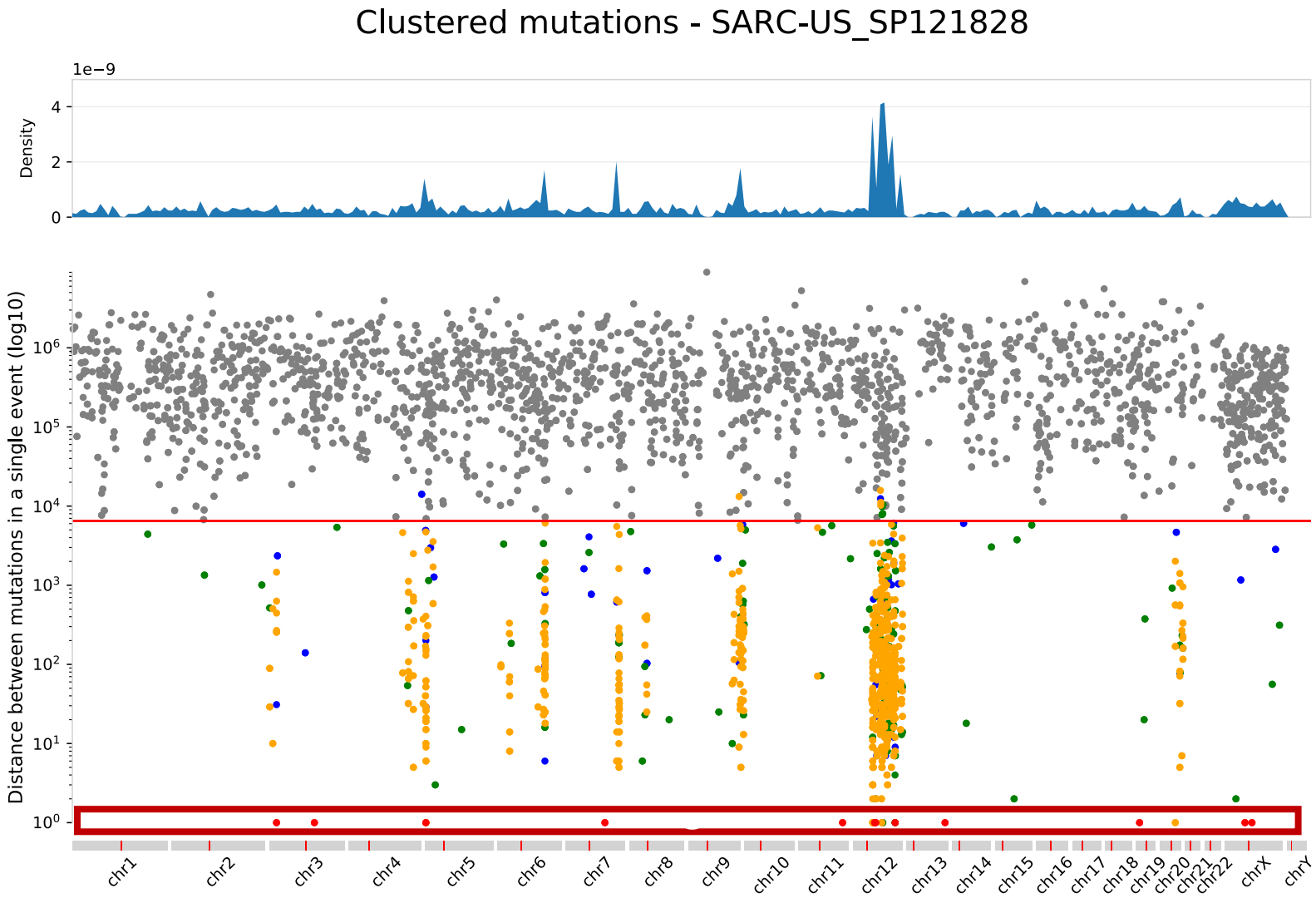

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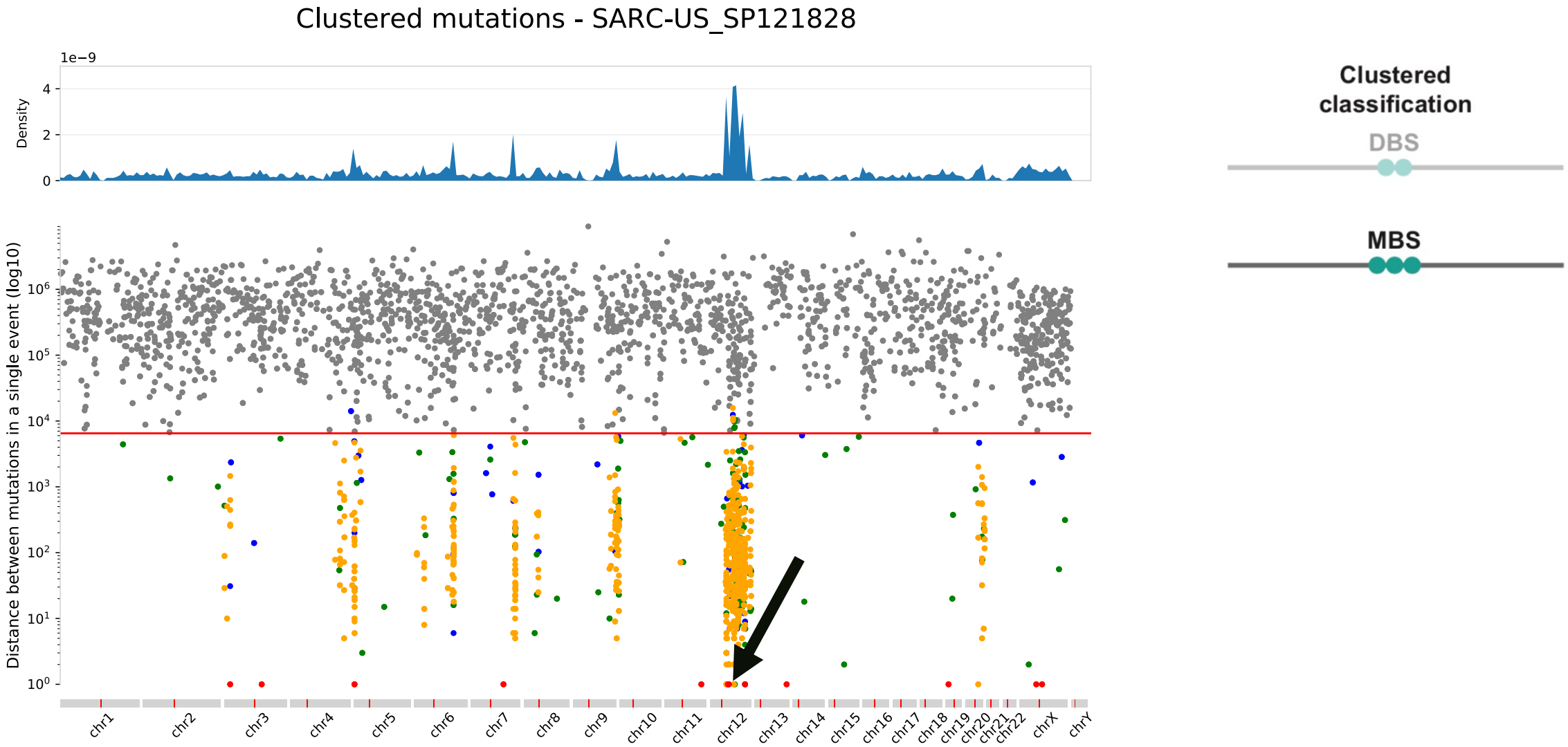

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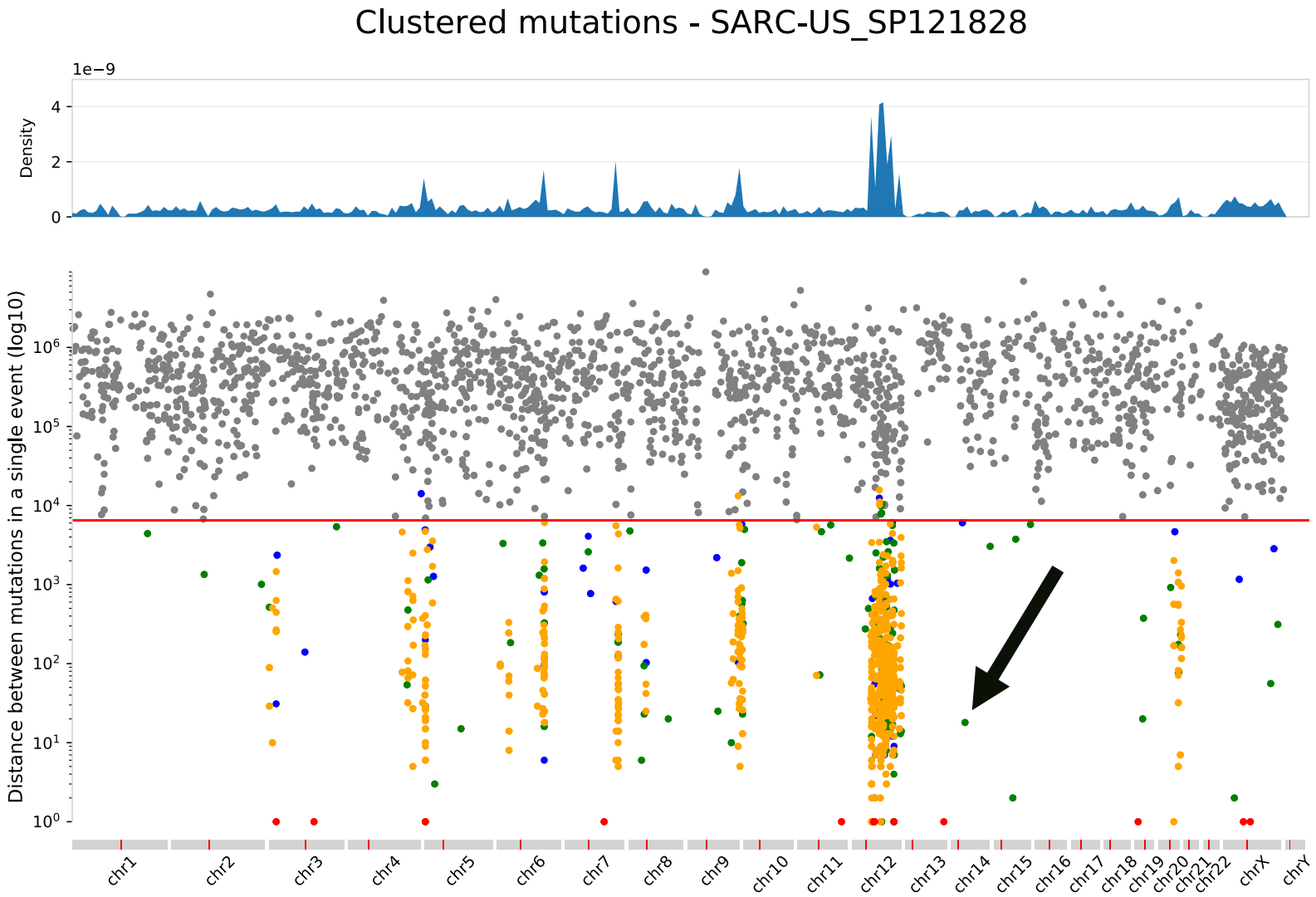

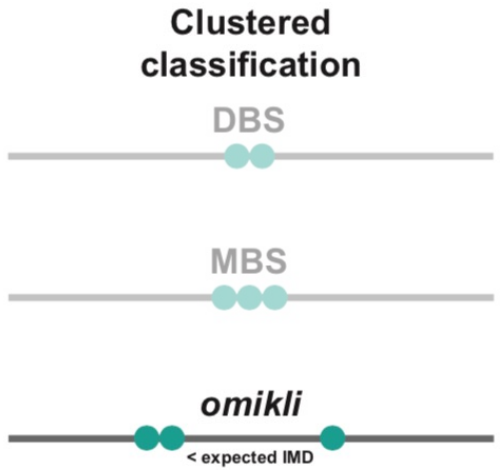

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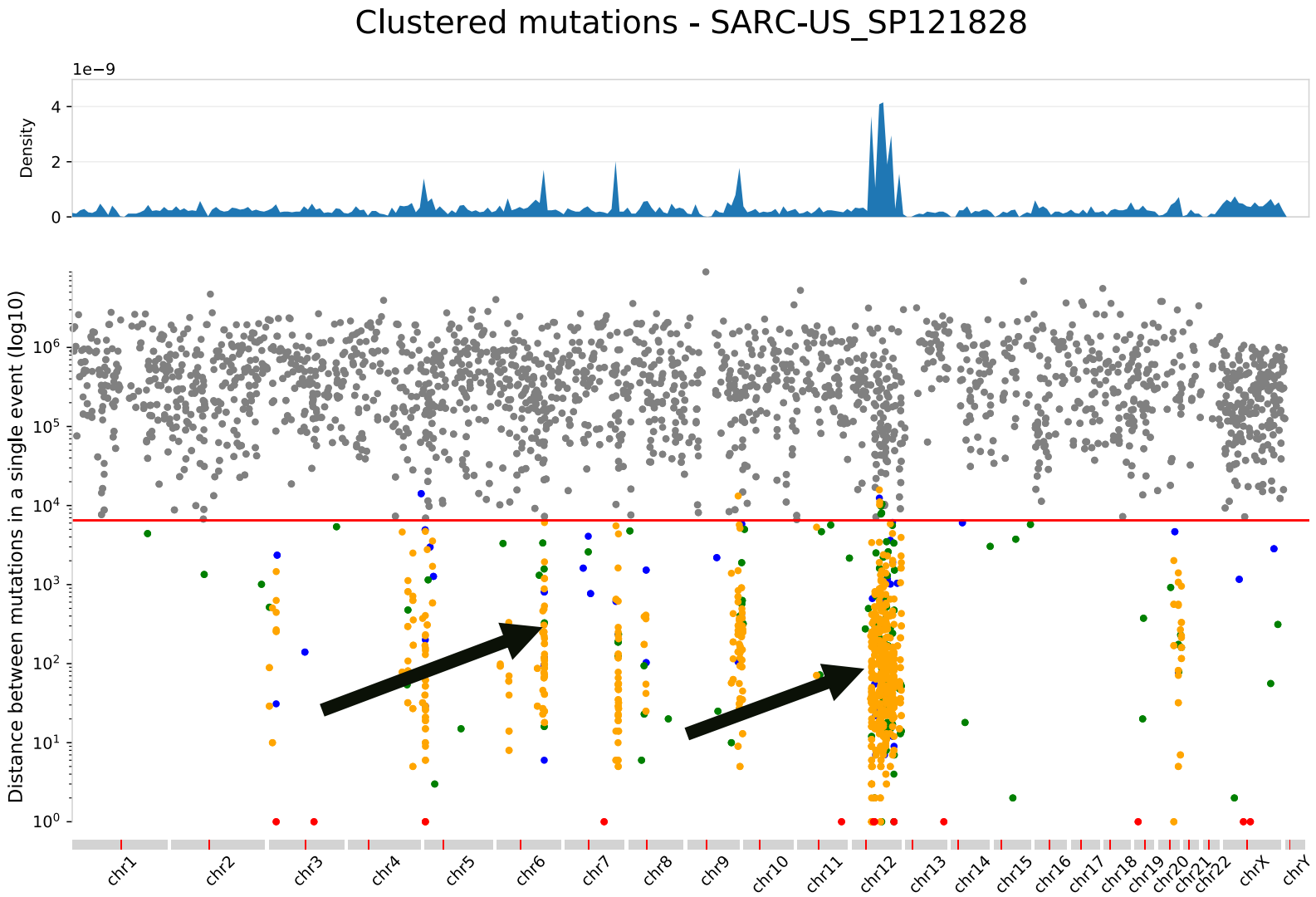

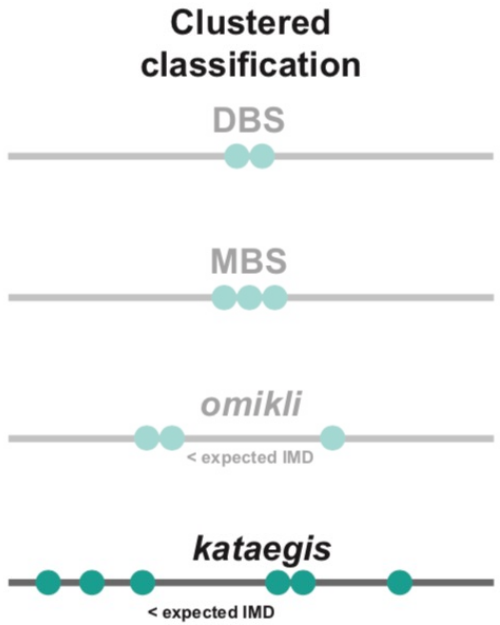

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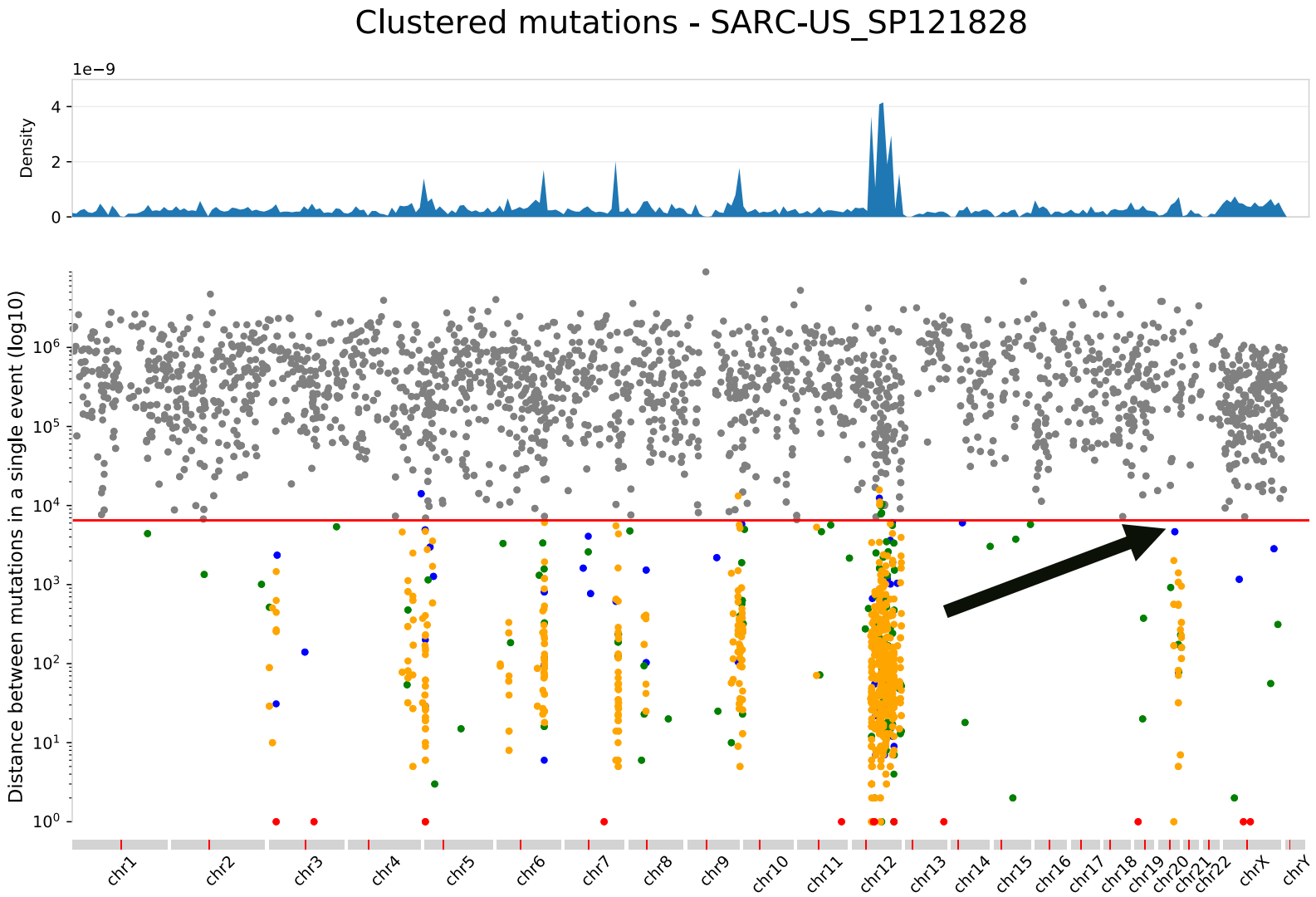
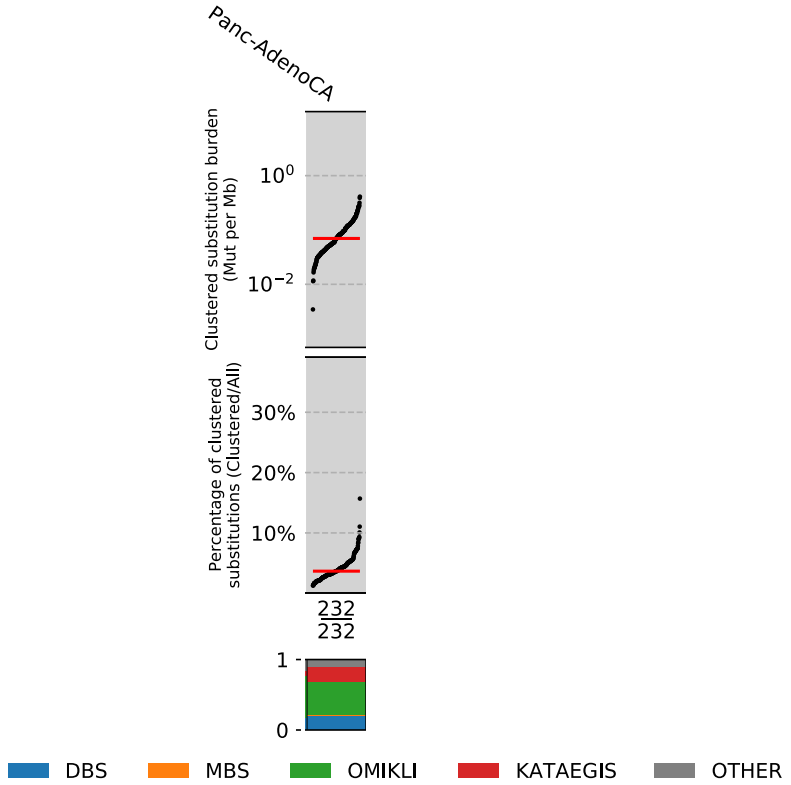


Bergstrom *et al.*, Nature 2022

The landscape of clustered mutations across human cancer



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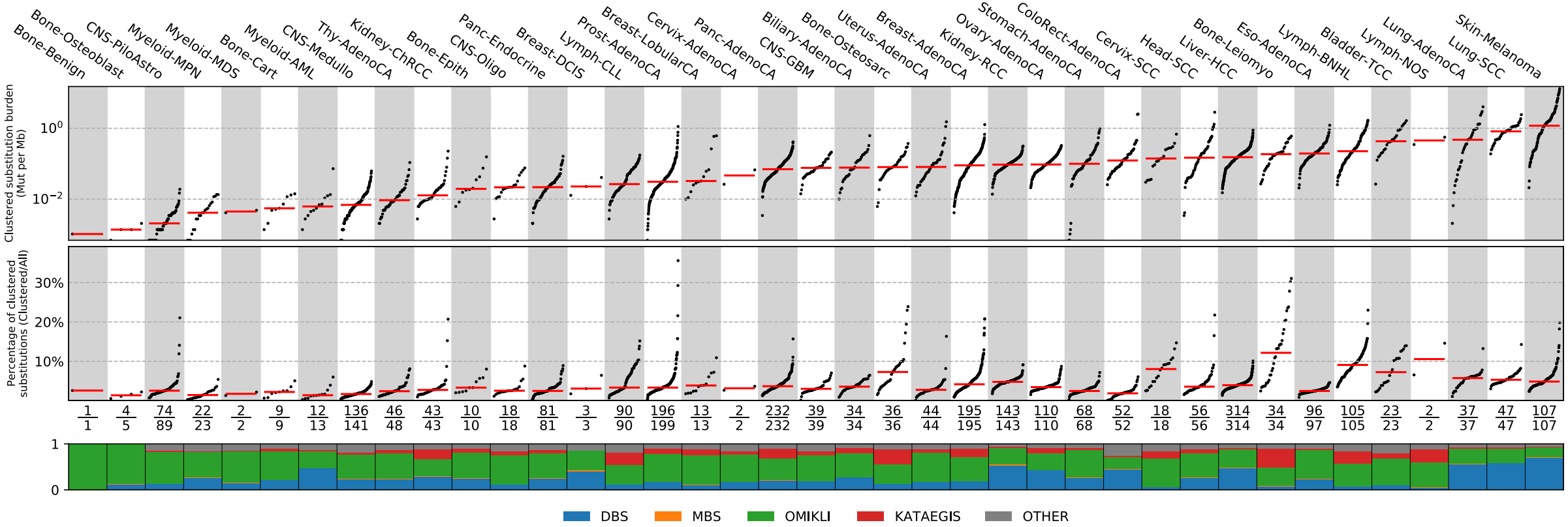

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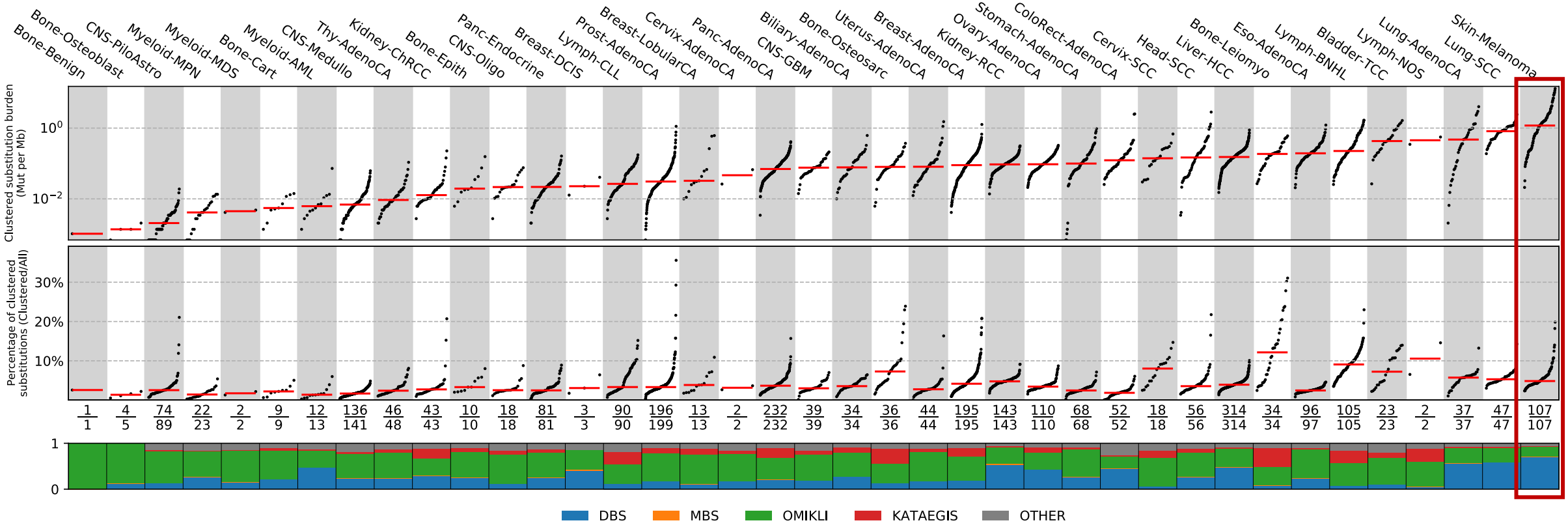

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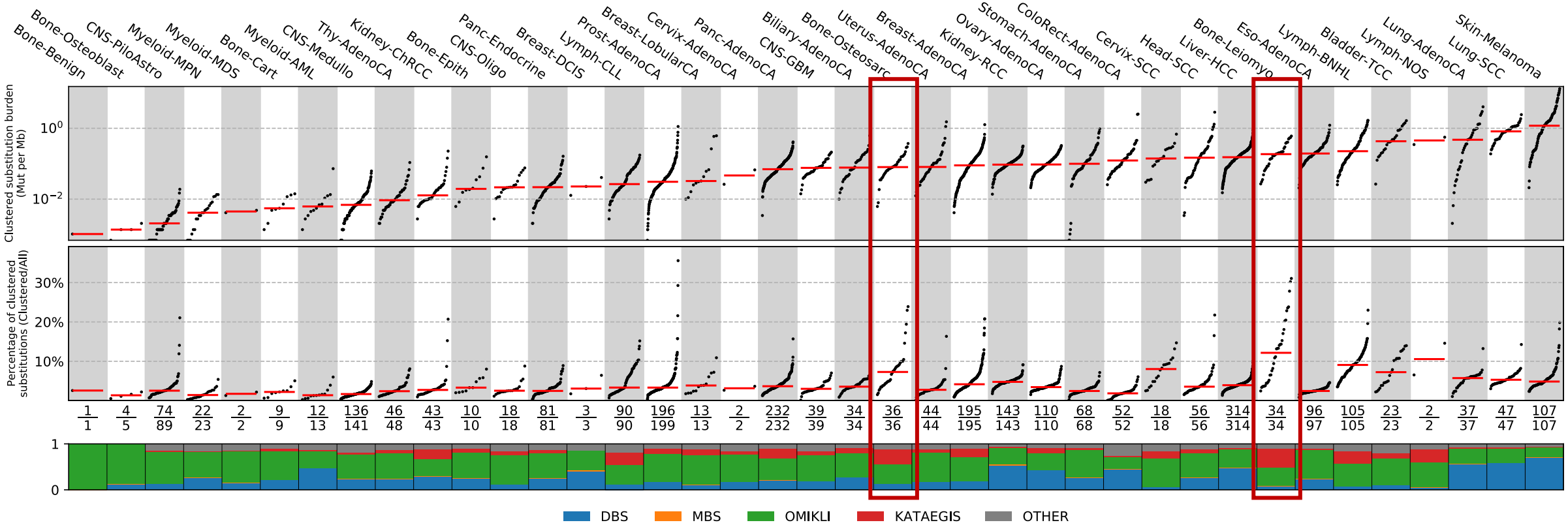
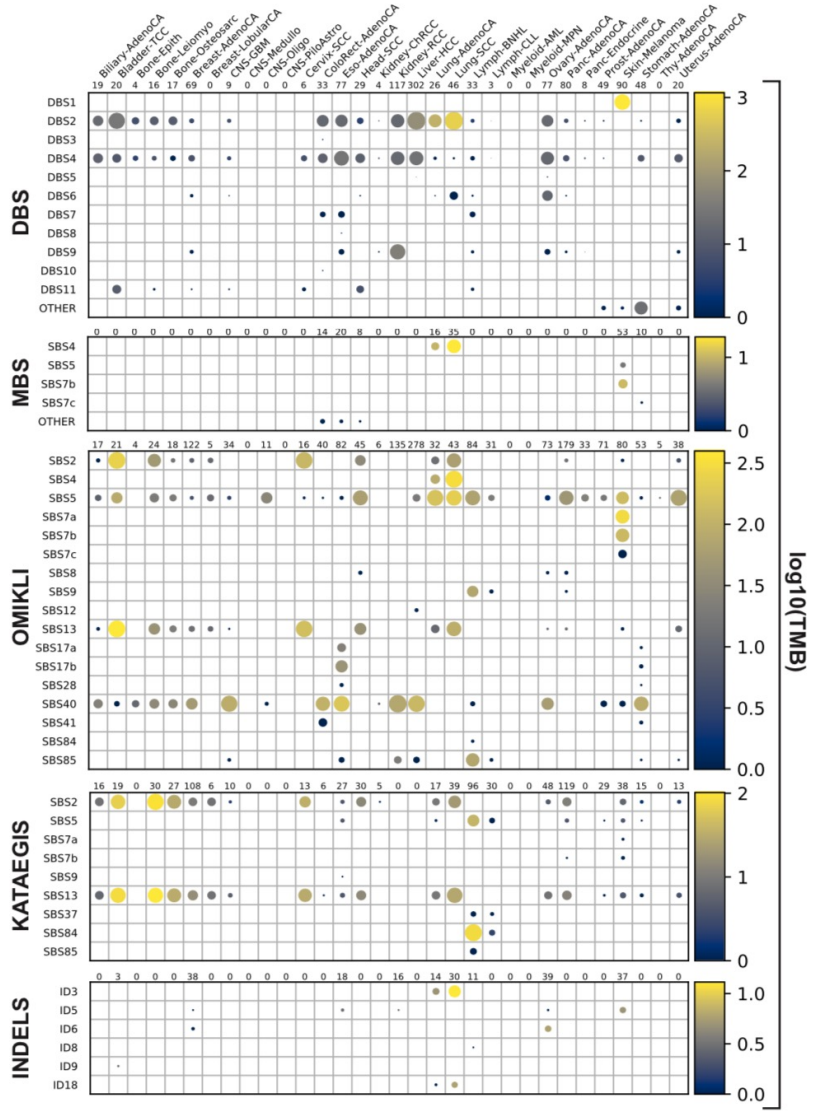


Bergstrom *et al.*, Nature 2022

Mutational processes underlying clustered events



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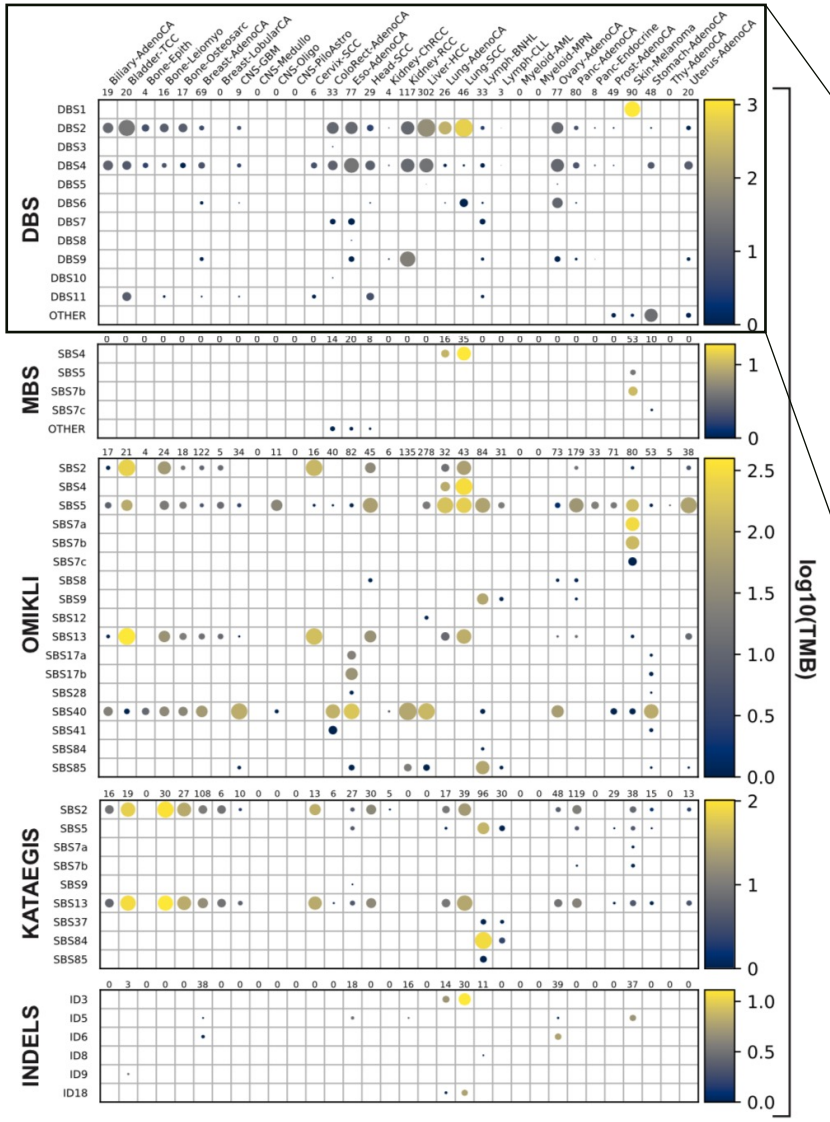

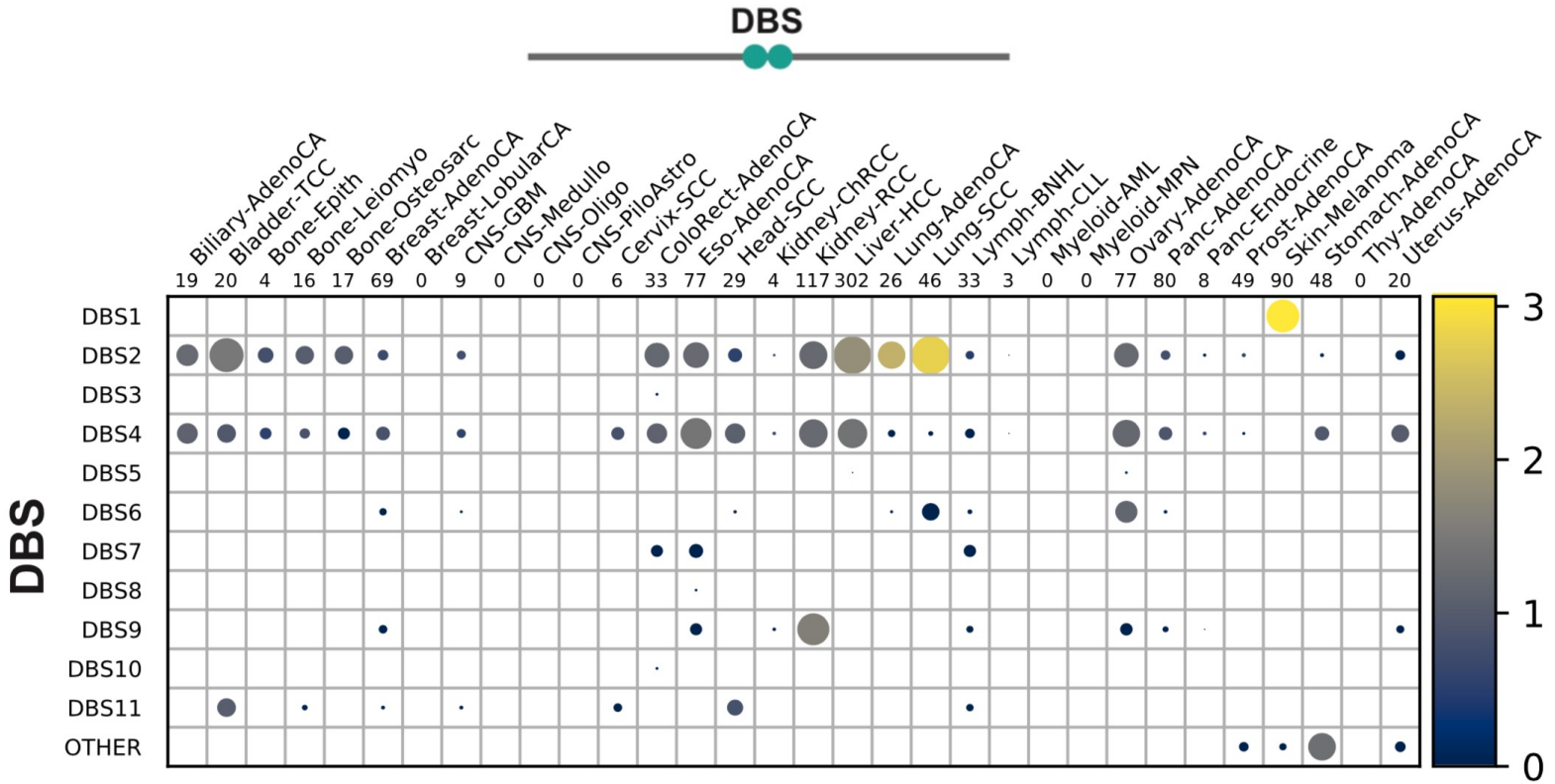

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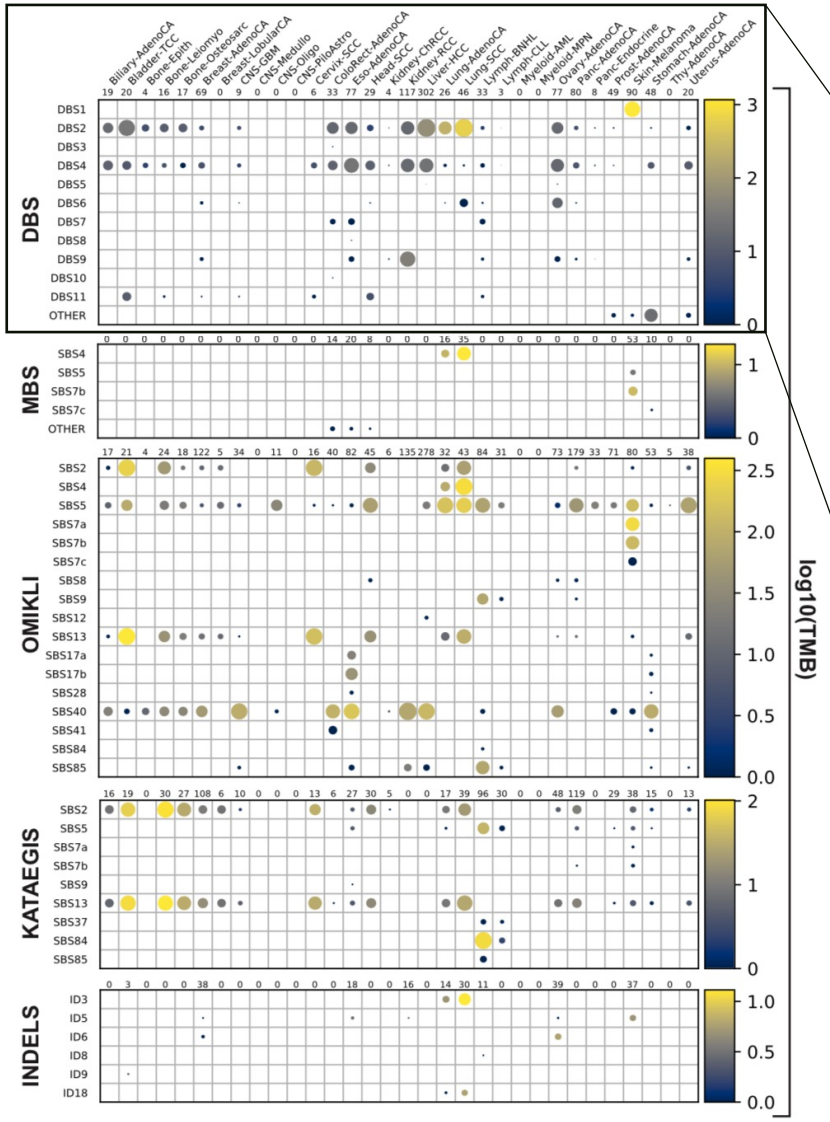

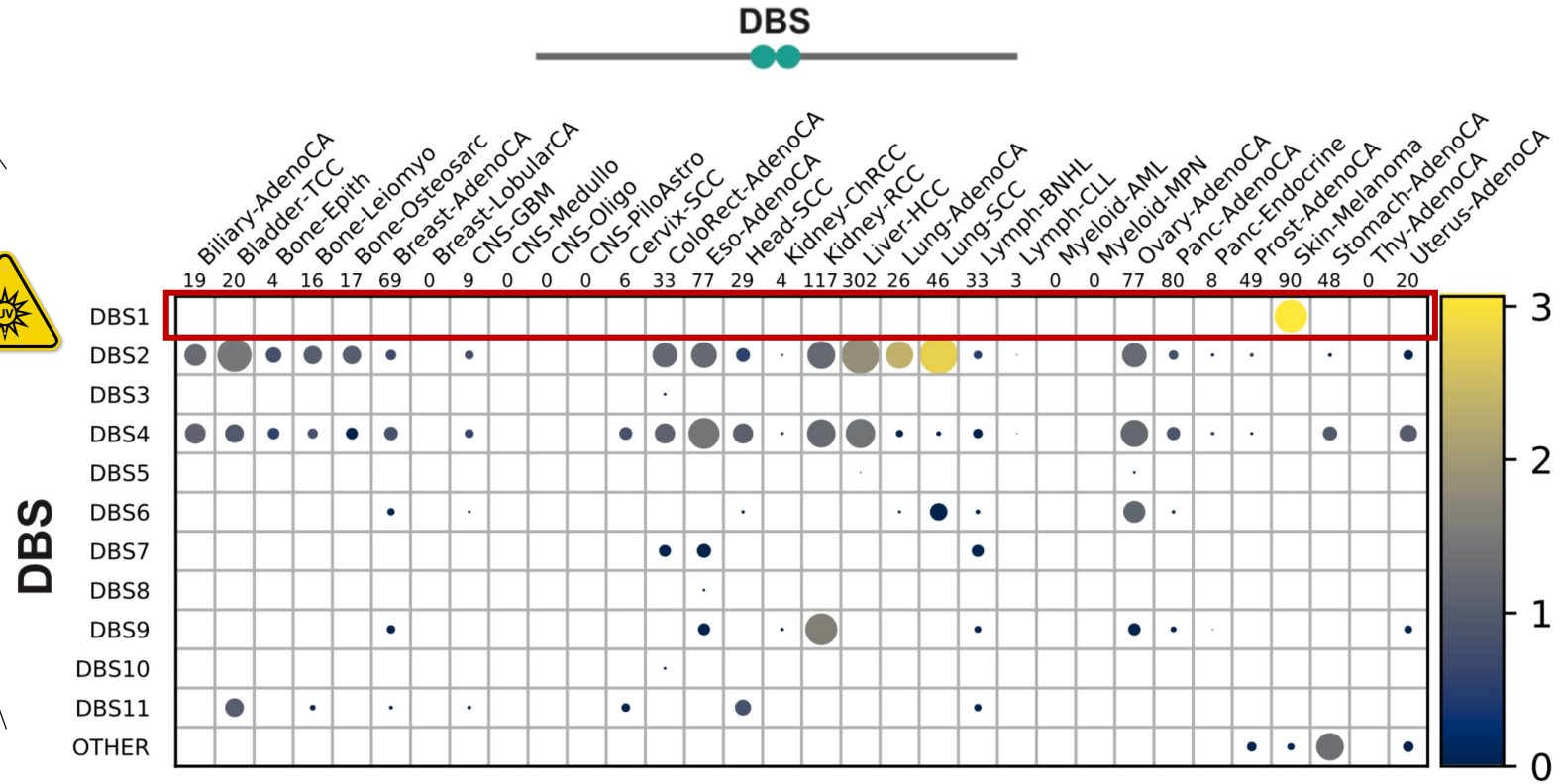

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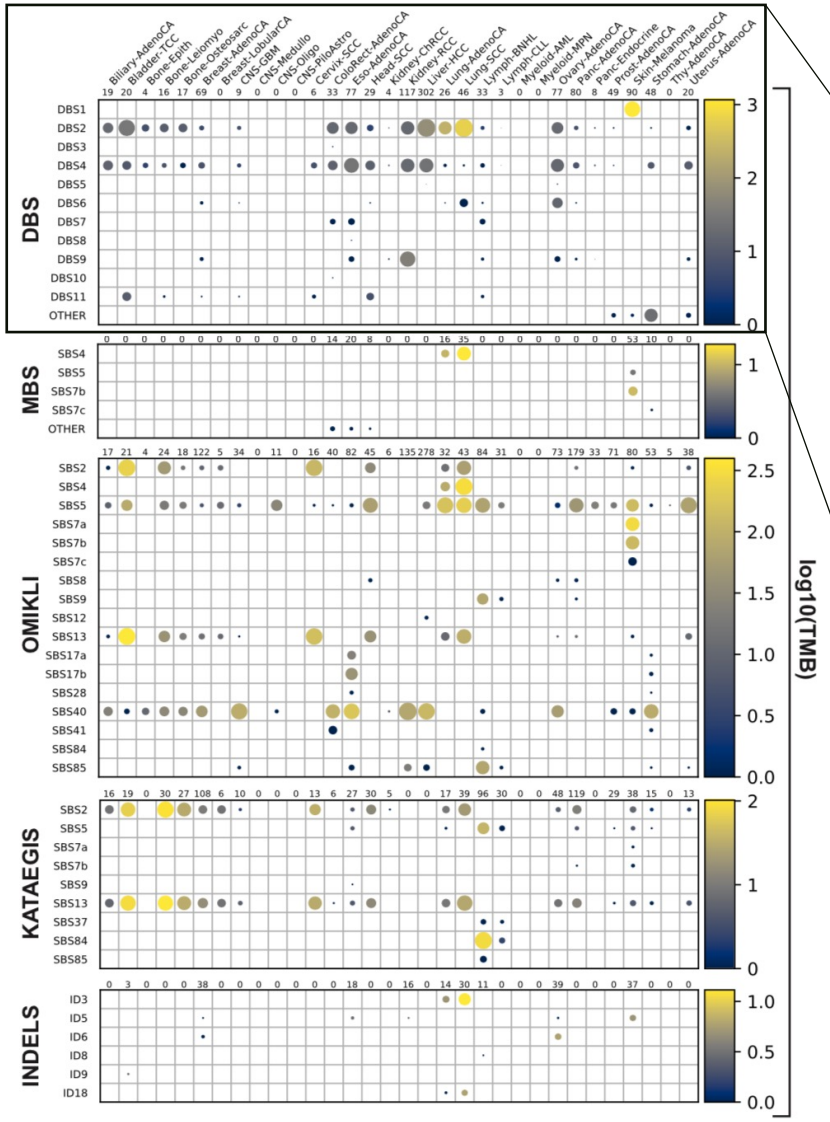

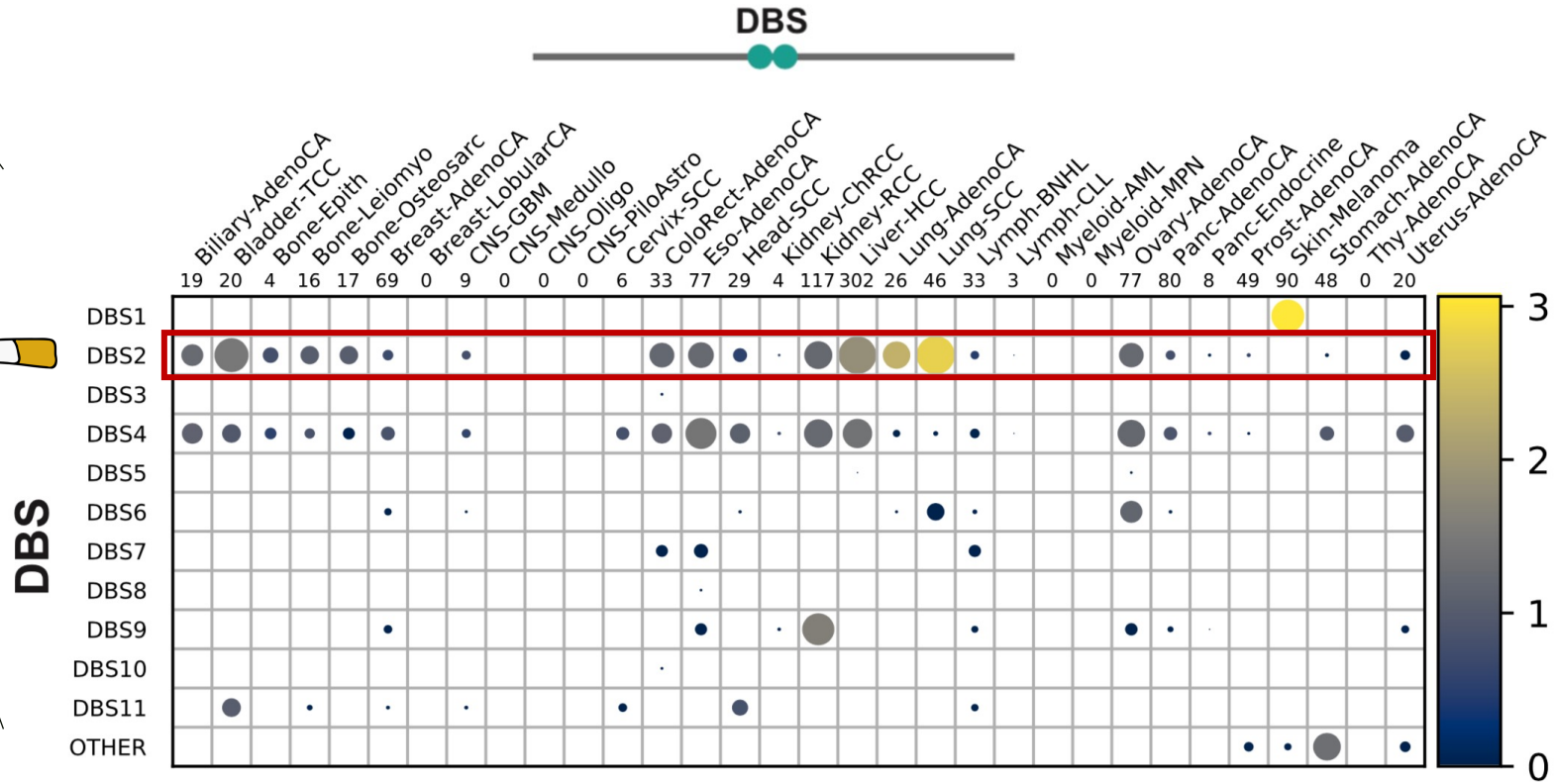

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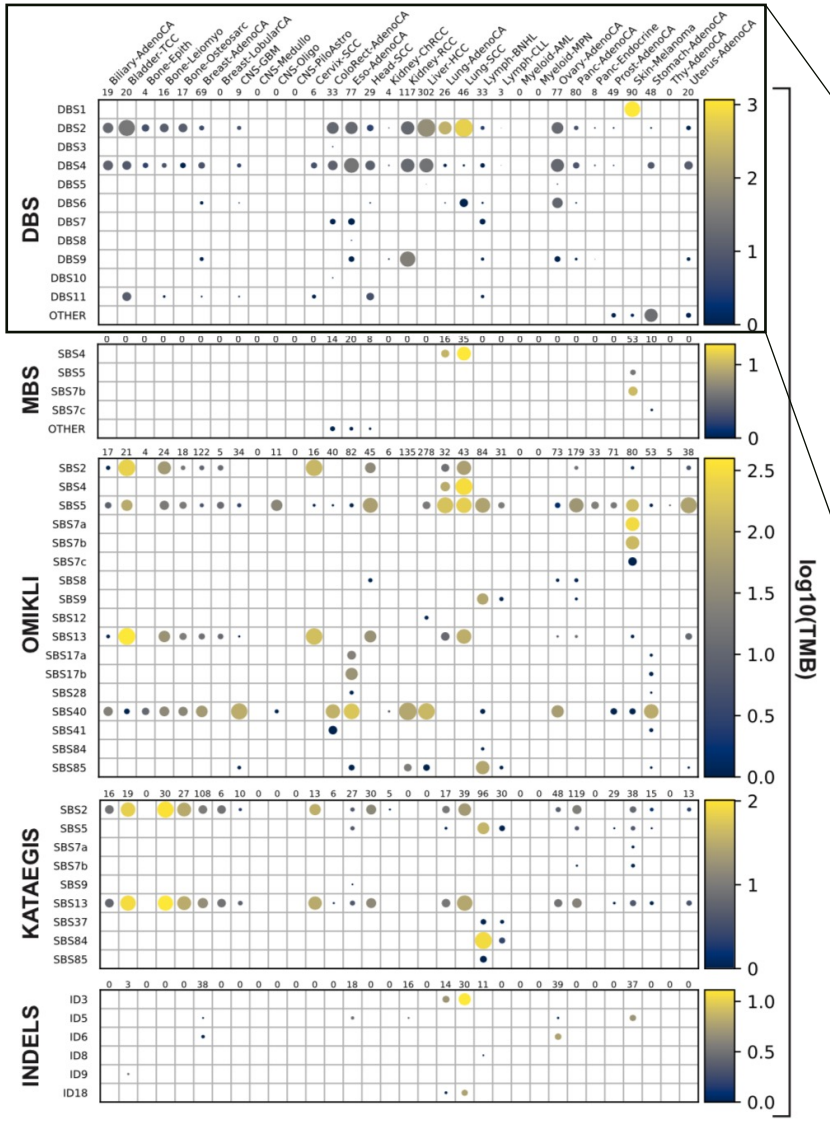

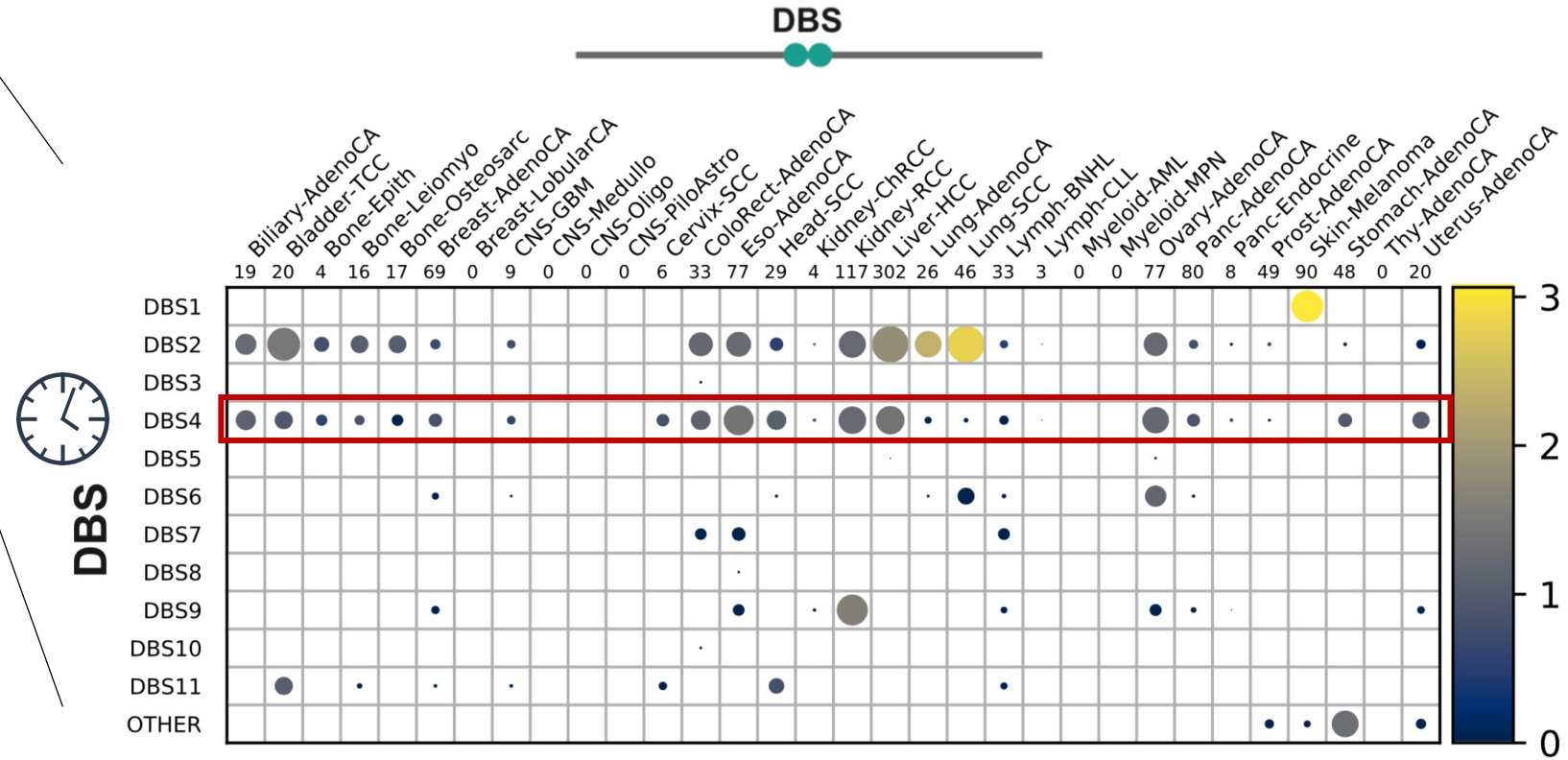

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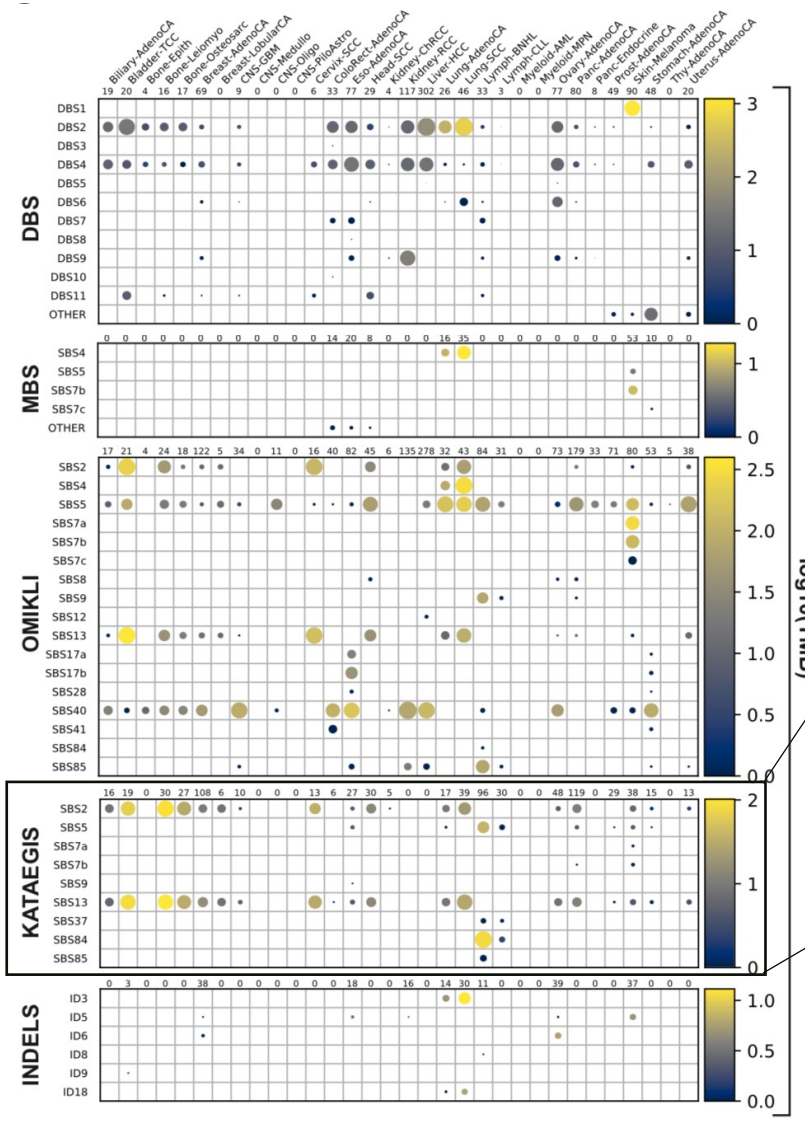

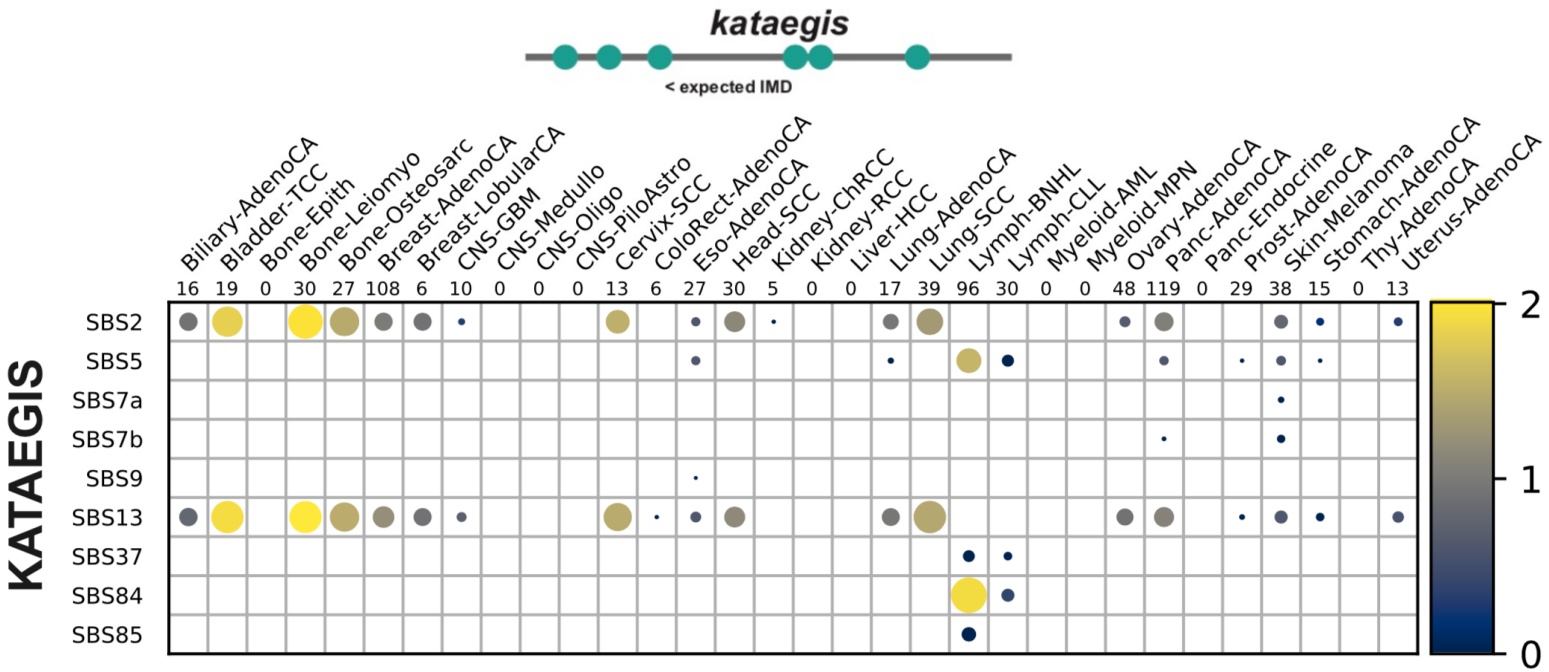

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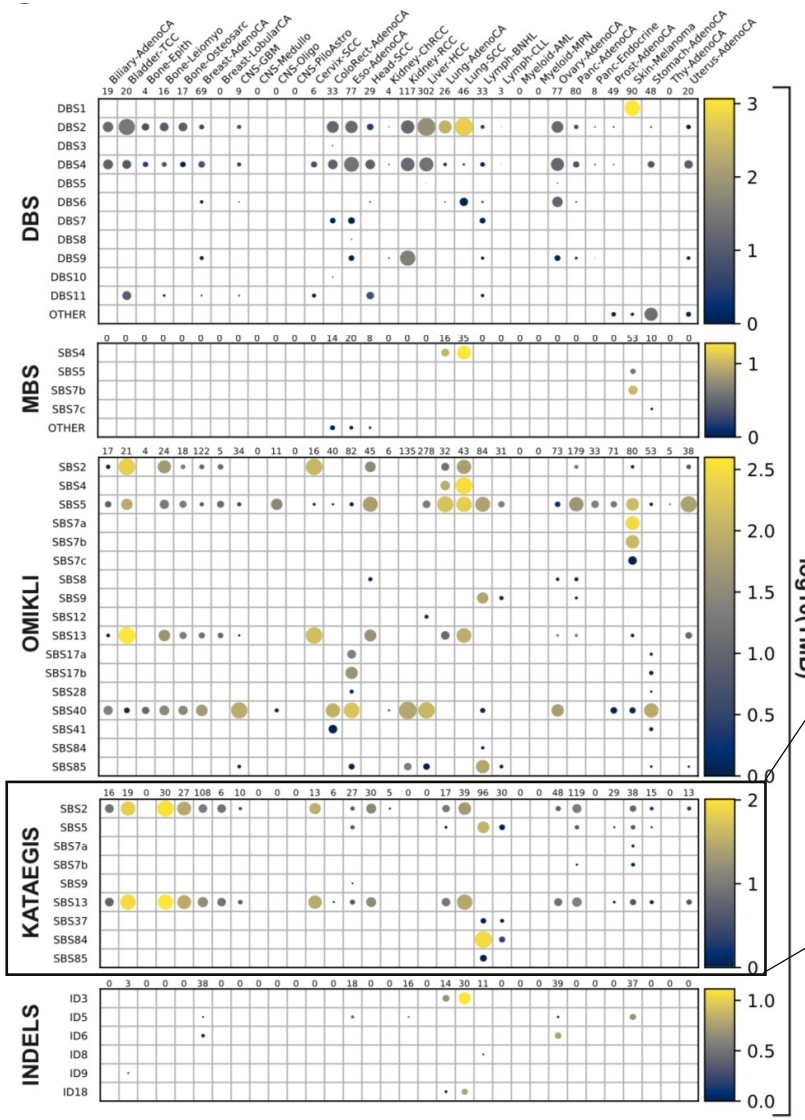

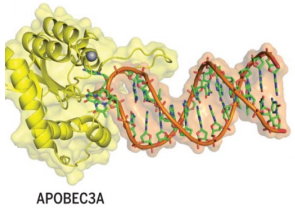

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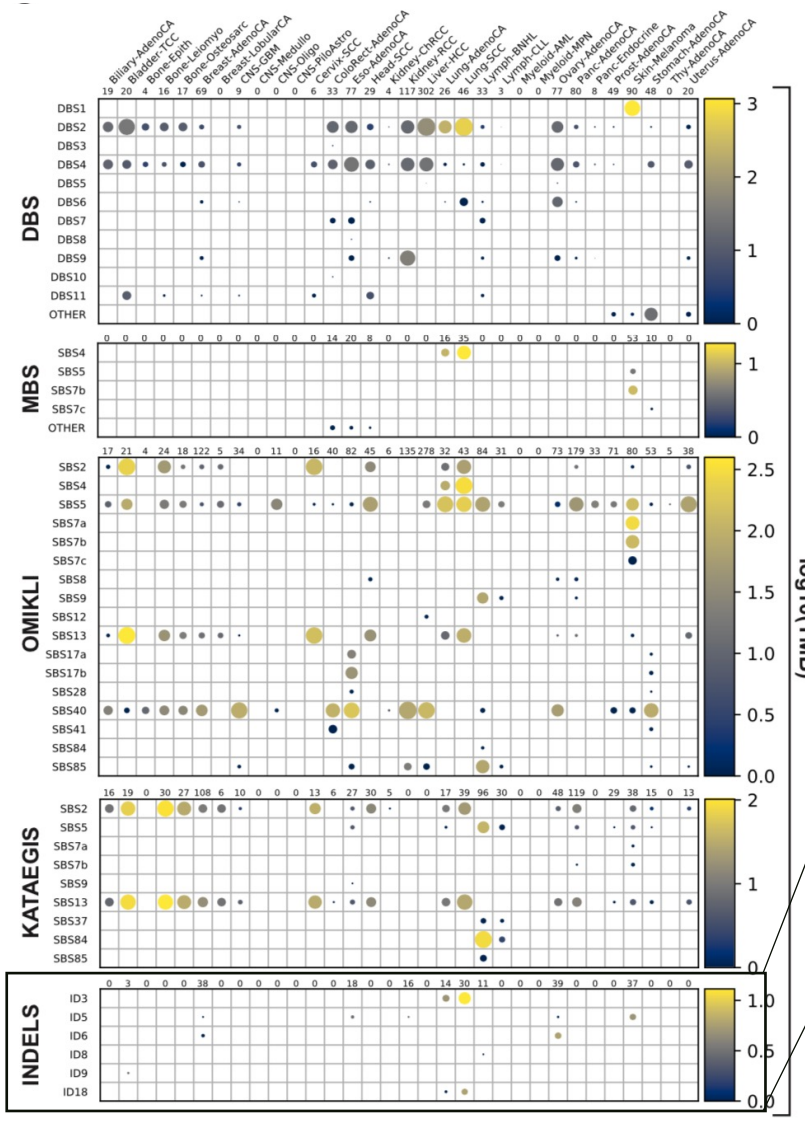

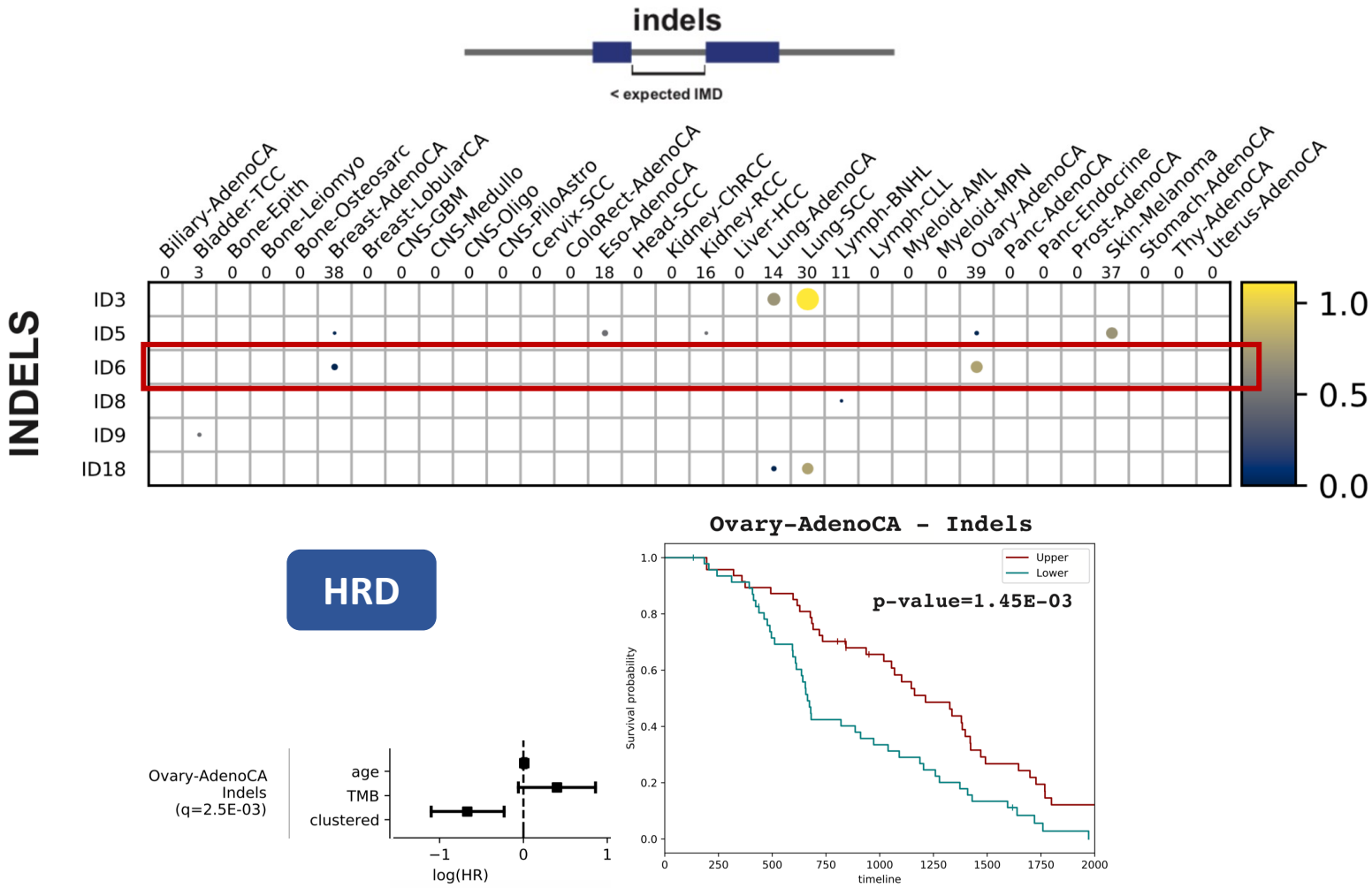

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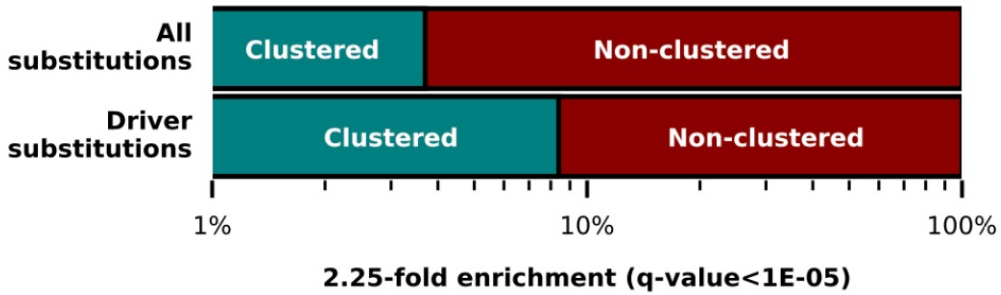
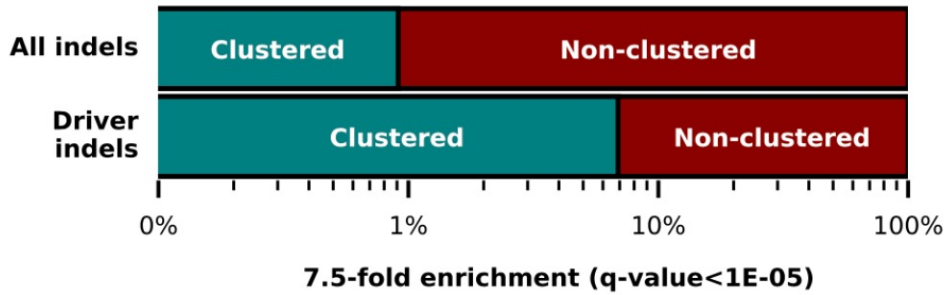
Panorama of clustered driver mutations in human cancer





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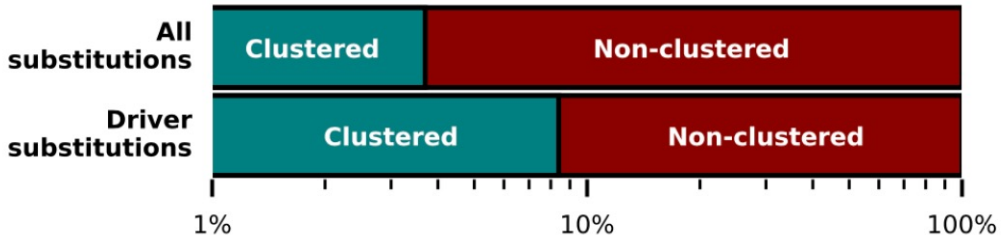
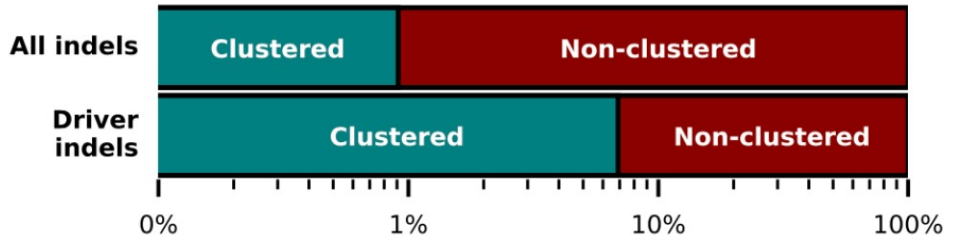
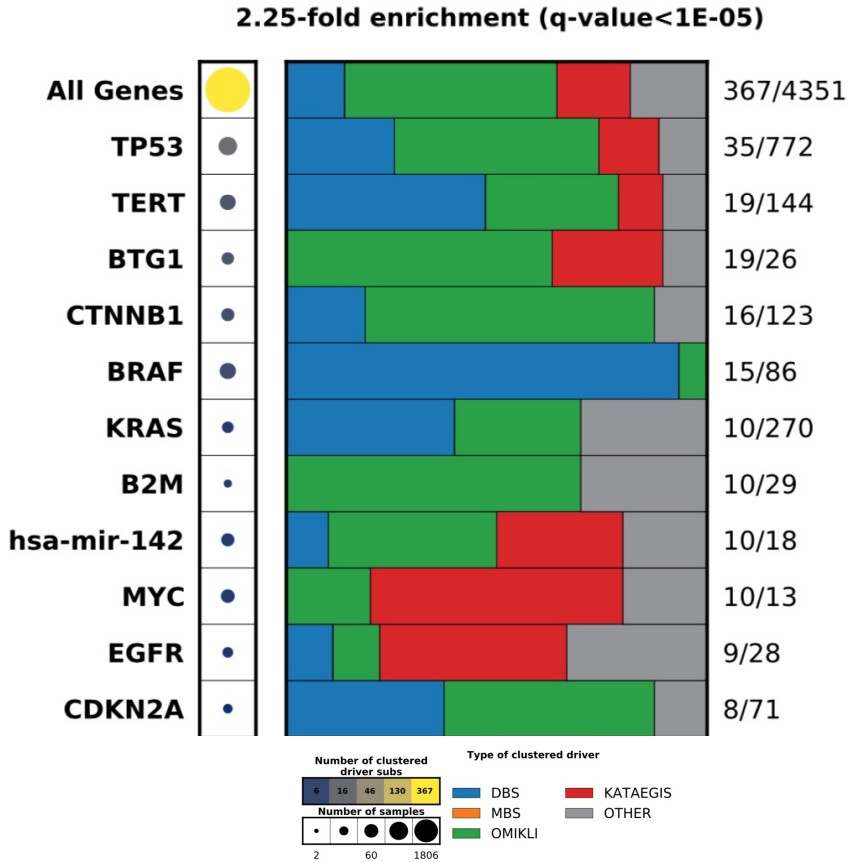
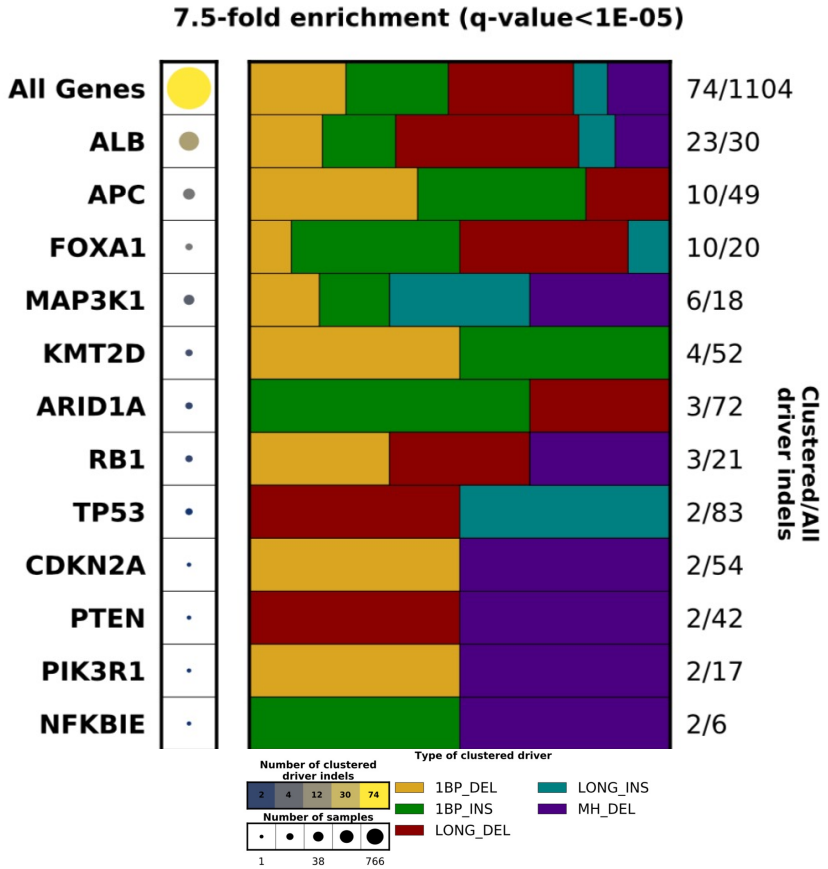


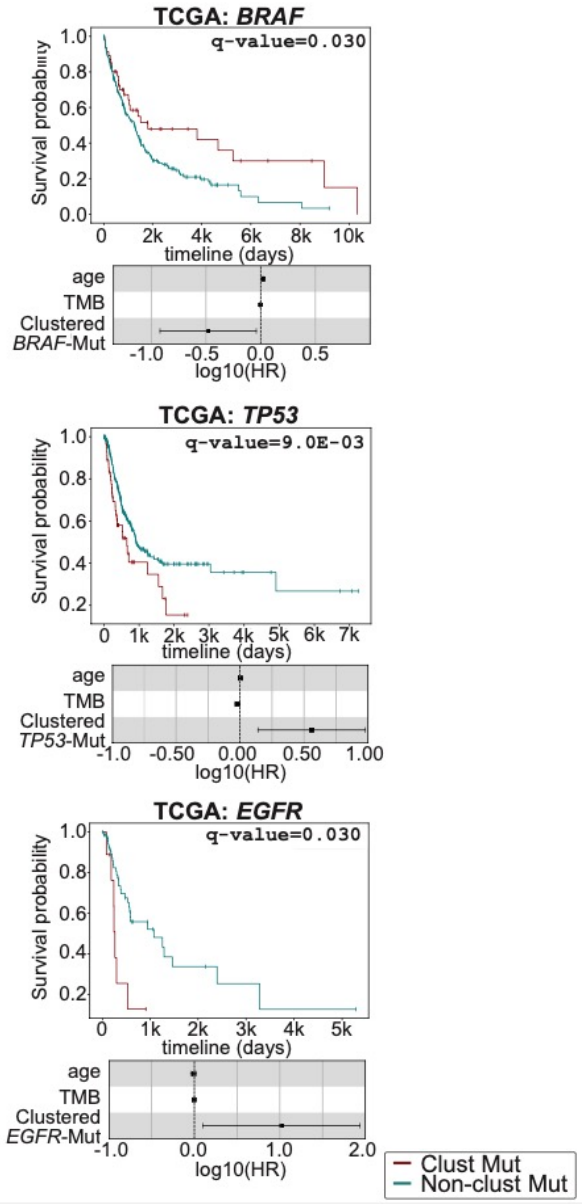






Bergstrom *et al.*, Nature 2022

Clustered mutations in driver genes serve as a prognostic biomarker



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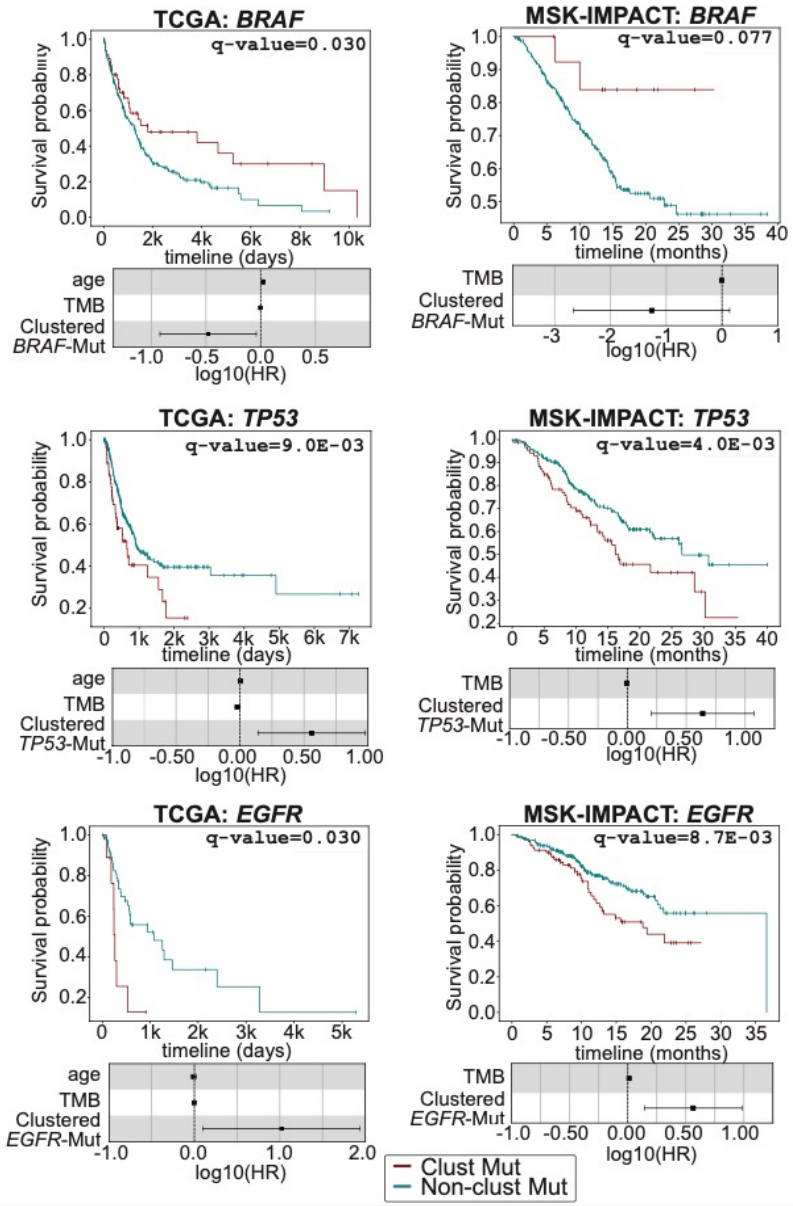
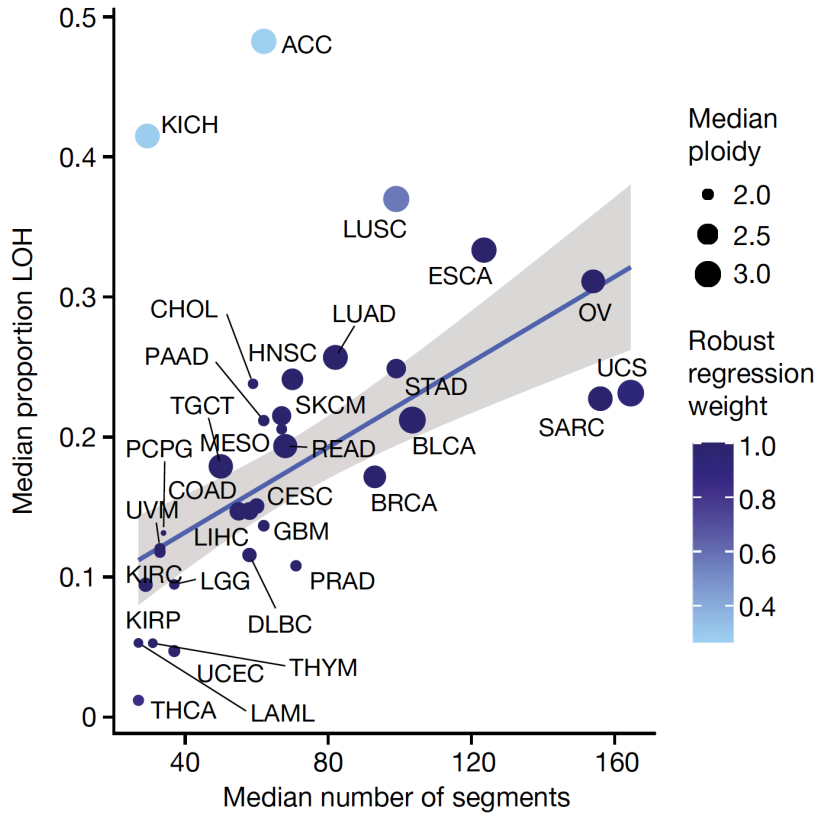


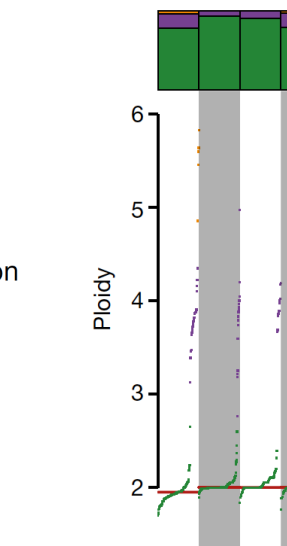
Bergstrom *et al.,* Nature 2022

The repertoire of copy-number signatures in human cancer

Chris Steele

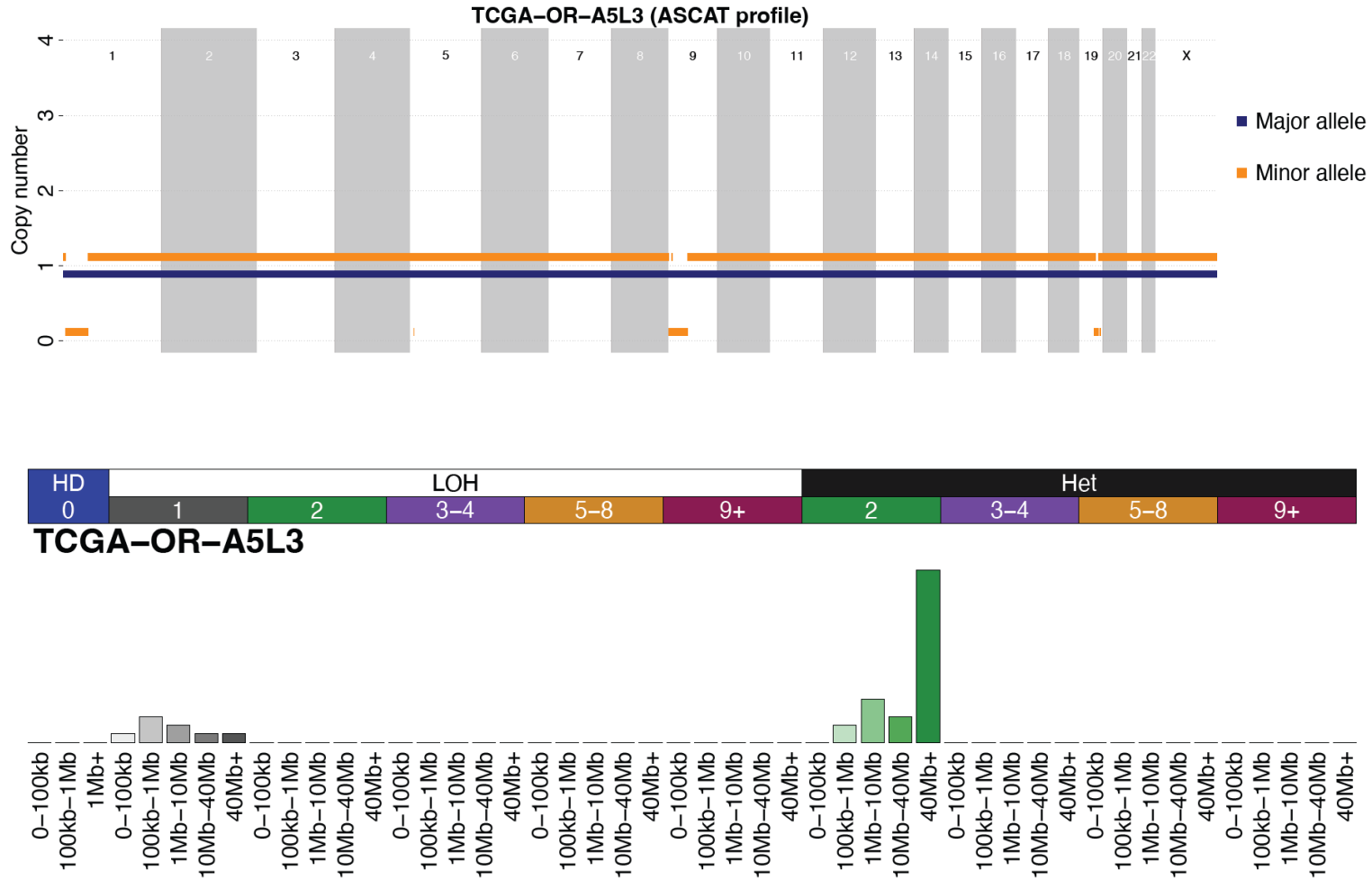
Global view of copy number changes in human cancer





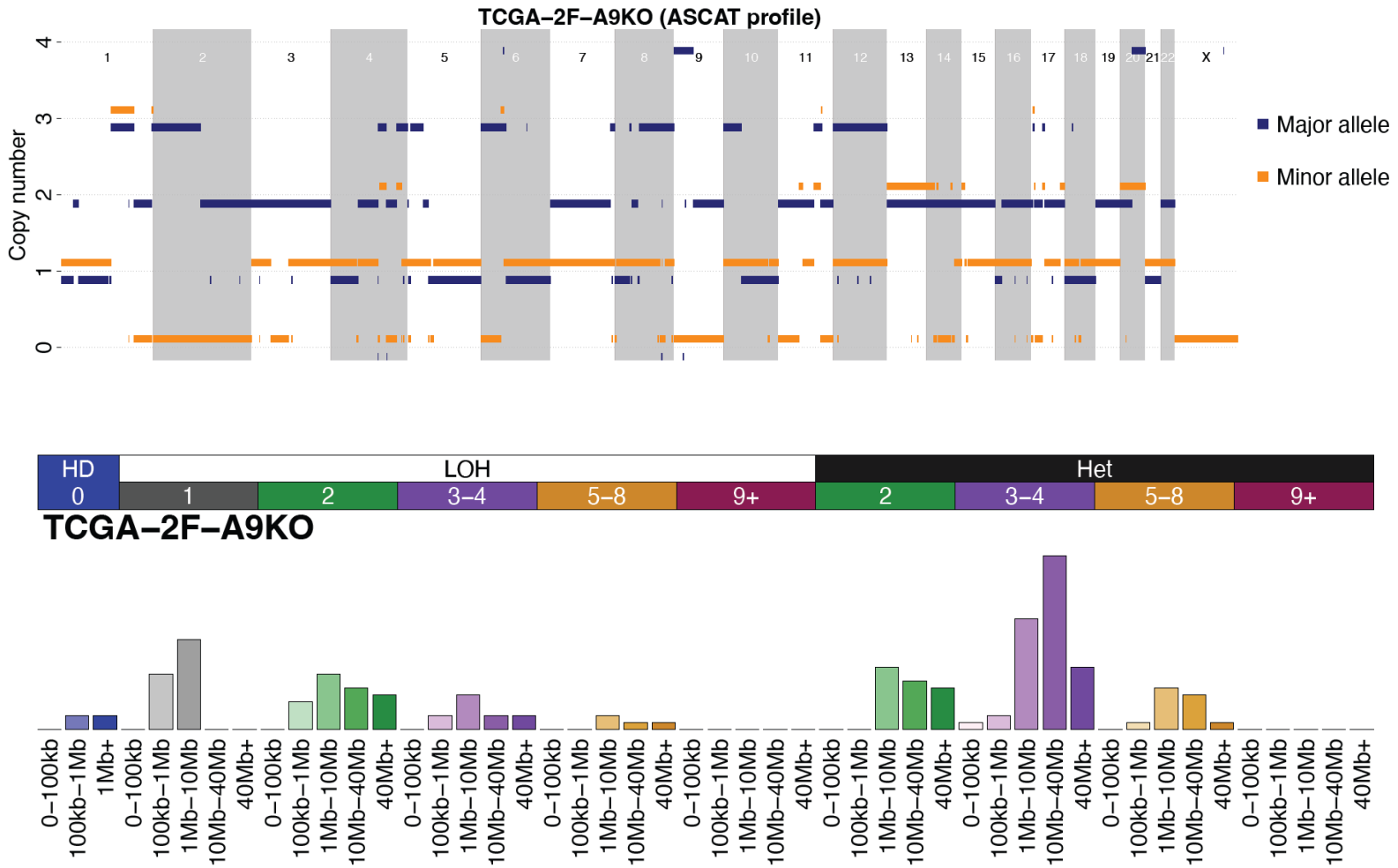
Steele *et al., Nature*, 2022

From copy-number profiles to summarized copy-number patterns (example 1)



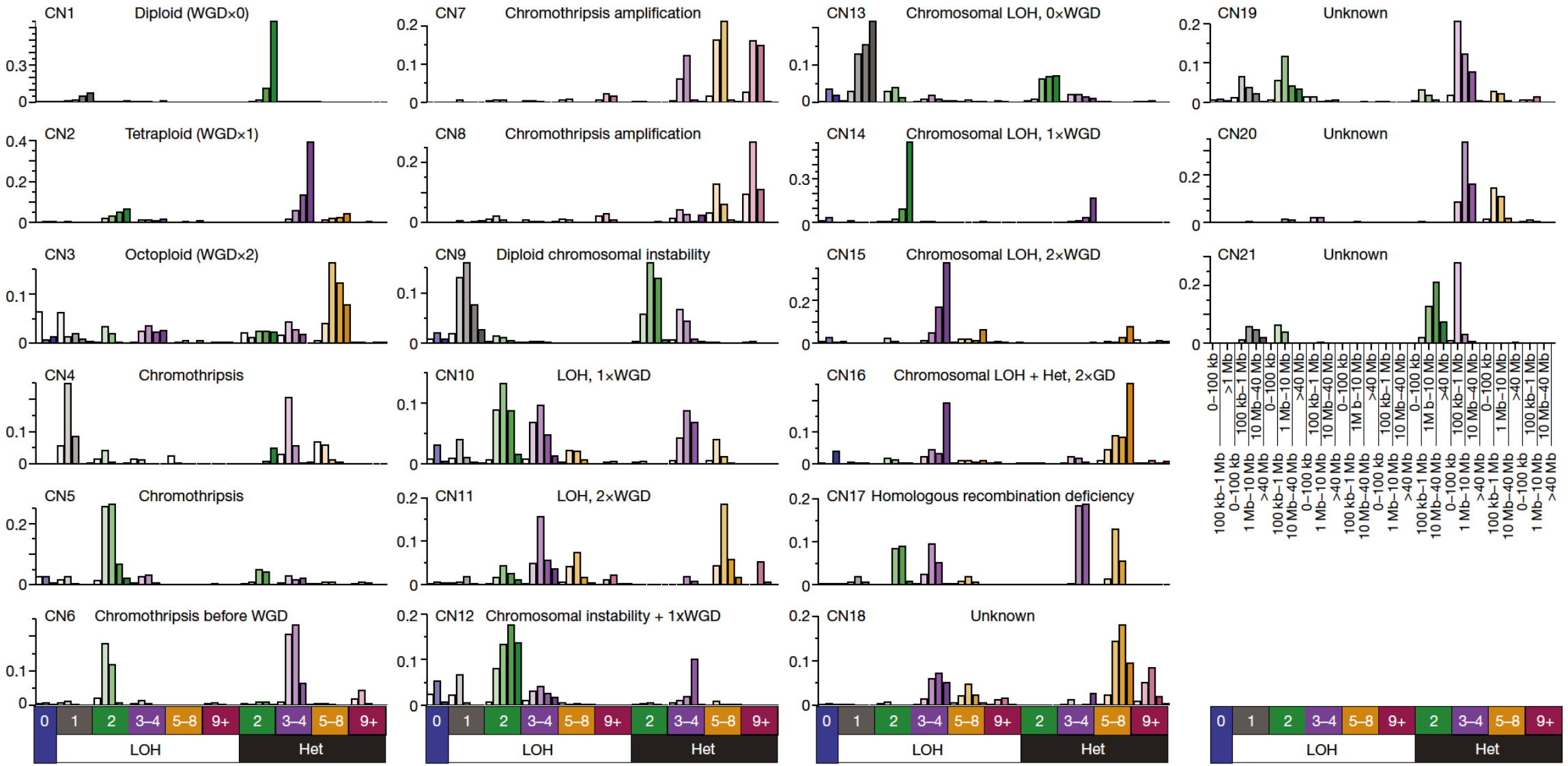
Steele *et al., Nature*, 2022

From copy-number profiles to summarized copy-number patterns (example 2)



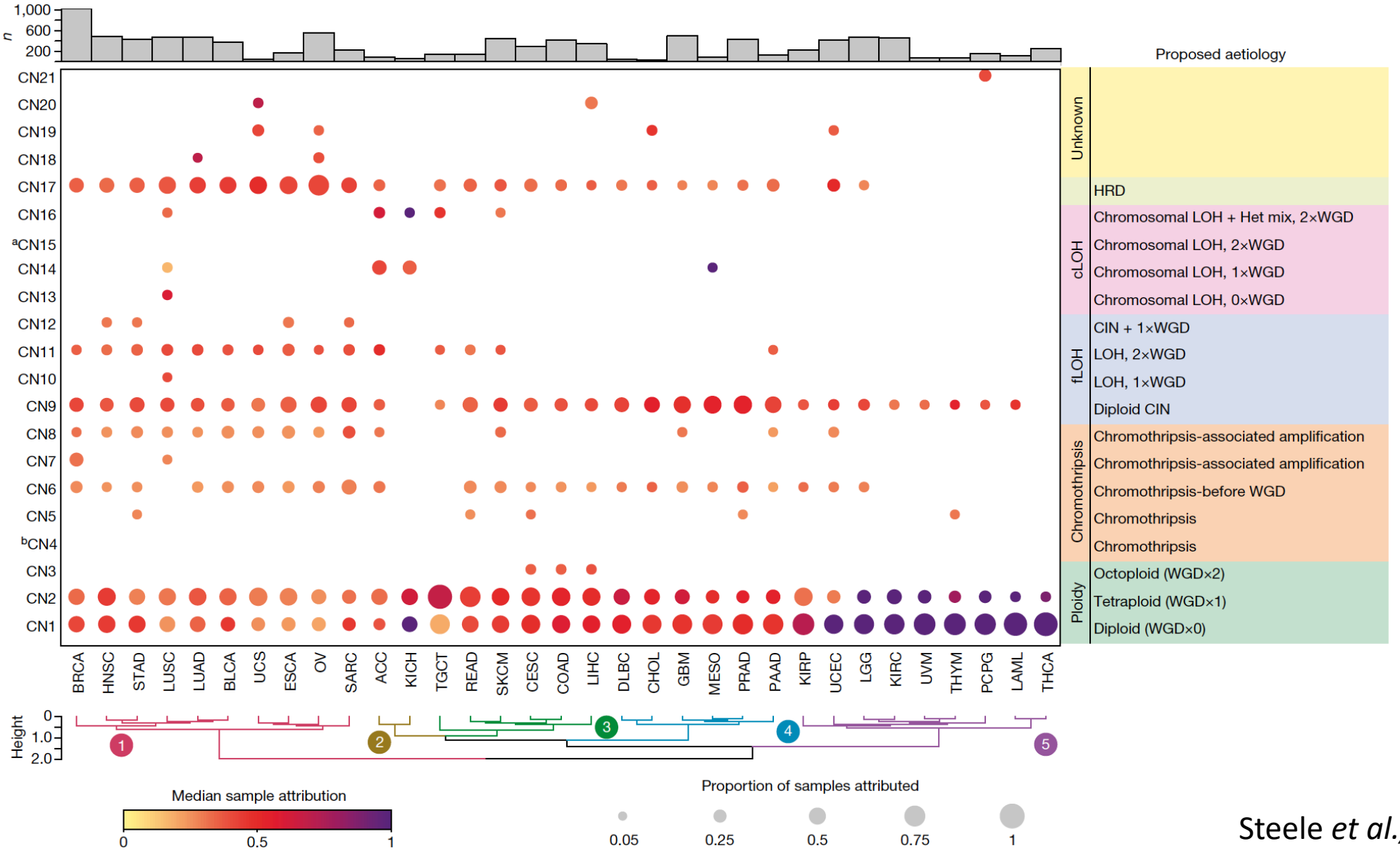
Steele *et al., Nature*, 2022

From copy-number profiles to copy-number mutational signatures



Steele *et al., Nature*, 2022

Copy-number mutational signatures across human and their etiologies



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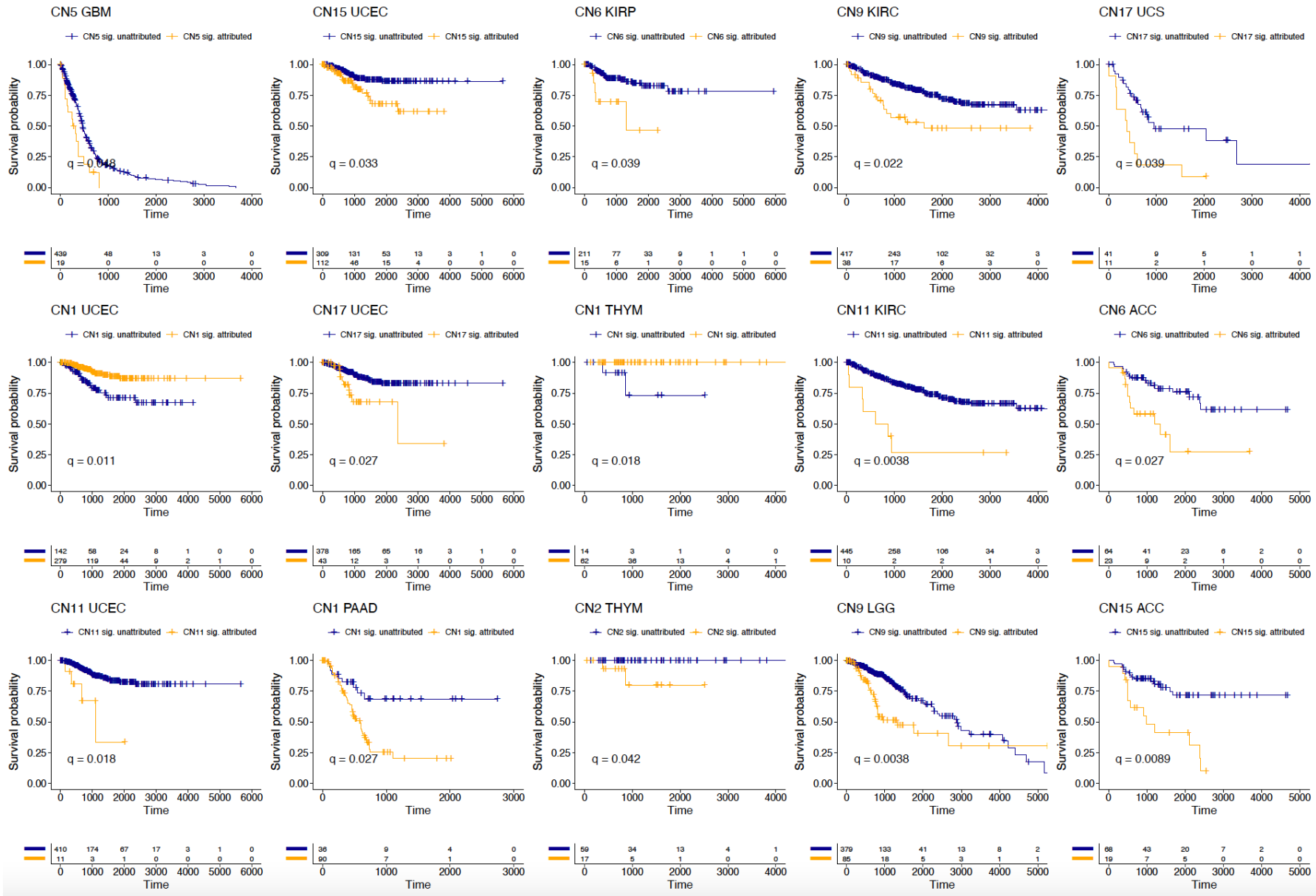
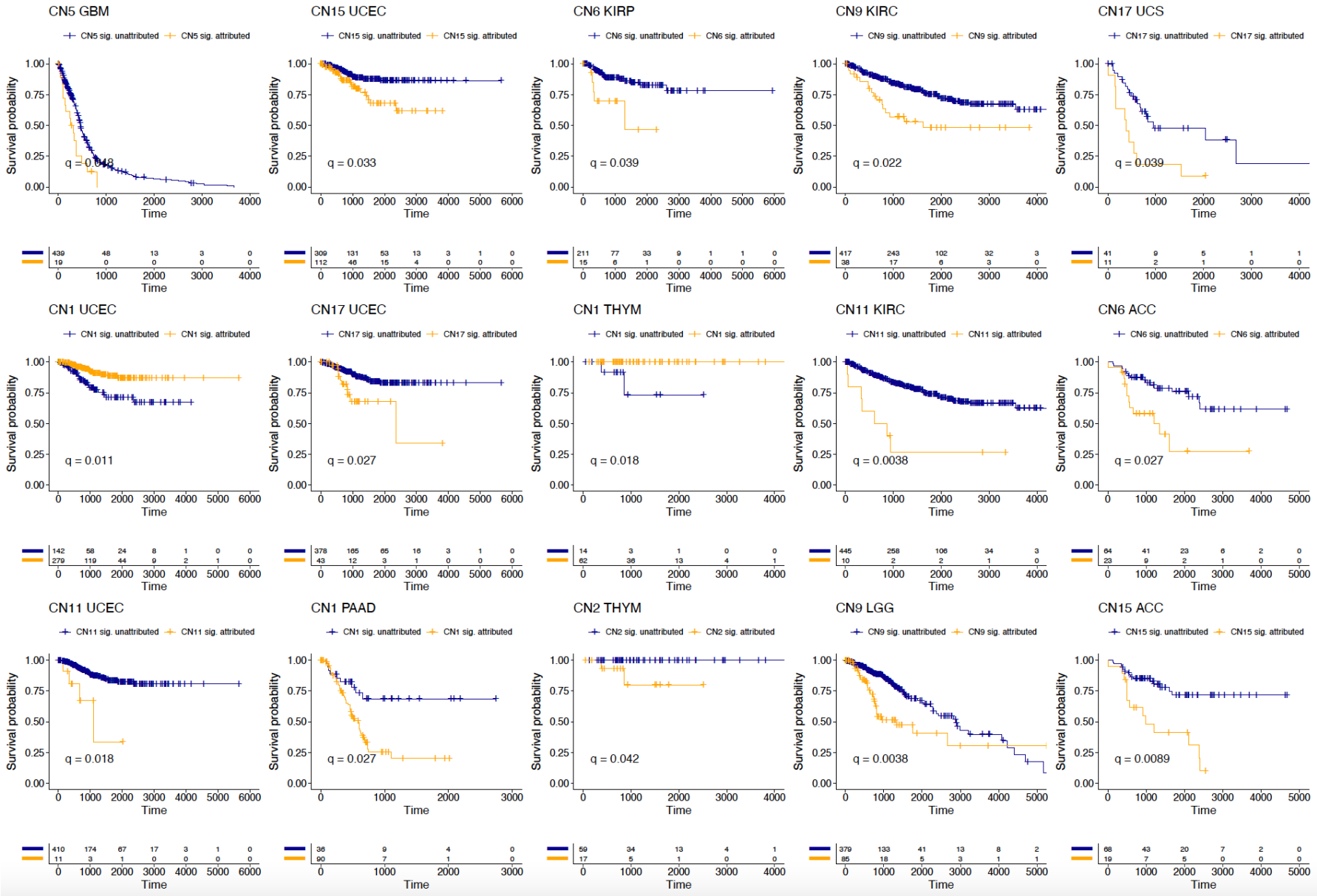
Clinical utility of copy-number mutational signatures as prognostic biomarkers



Steele *et al., Nature*, 2022

Clinical utility of copy-number mutational signatures as prognostic biomarkers



In contrast to other types of mutational signatures can be robustly detected from multiple platforms:

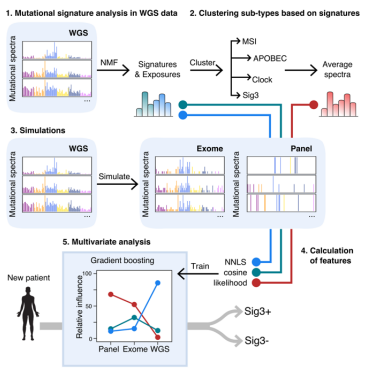
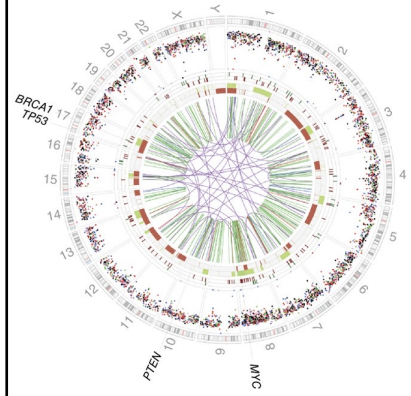
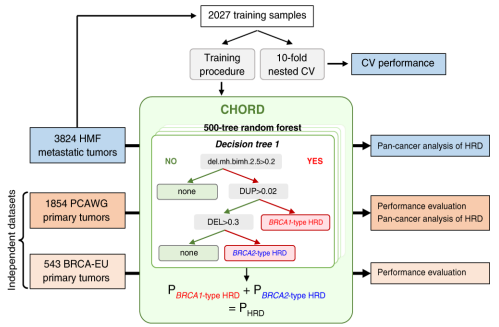
- Whole-genome sequencing
- Whole-exome sequencing
- Reduced-representation bisulfite sequencing
- Single-cell DNA sequencing
- SNP6 microarrays

Steele *et al., Nature*, 2022

A novel machine learning approach for detecting homologous recombination deficiency

Ammal Abbasi

HRD Prediction tools that use mutational signatures or mutational patterns

Tools	 SigMA Gulhan, D. *et al. Nat Genet* (2019)	 HRDetect Davies, H. *et al. Nat Med* (2017)	 CHORD Nguyen, L. *et al. Nat Commun* (2020)
Features	SBS3	SBS3, SBS8, Microhomology-mediated deletions, RS3, RS5	SBS, ID, and SV mutational patterns
Sequencing Platform	WGS, WES, Panels	WGS	WGS
Advantages & Limitations	Method can be applied to WGS, WES, and panel data. SBS3 is flat and method can be used only for highly mutated panels (~15% breast cancers).	Whole-genome sequencing is expensive approach especially at high-coverage. In many cases it requires fresh cancer tissues, and it is not commonly used in clinical practice. HRDetect & CHORD can detect ~50% more samples that will respond to PARPi when compared myChoice CDx.	

Training iHRD with breast cancer samples

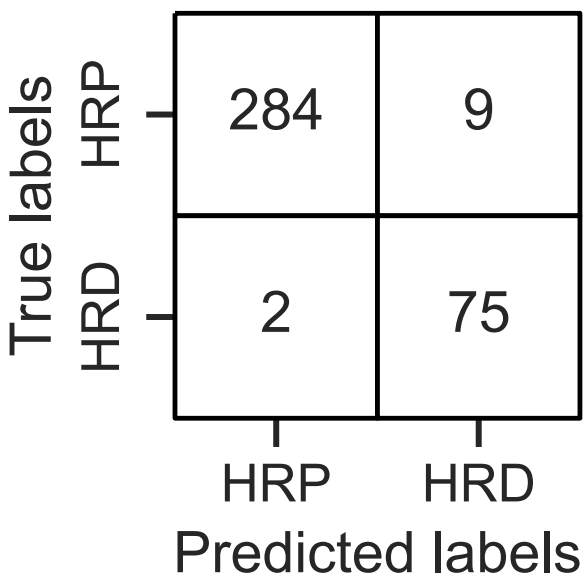
Training dataset: 234 genomically quiescent **whole-genome sequenced breast cancer samples** used as homologous recombination proficient (HRP). 77 BRCA1 or BRCA2 deficient **whole-genome sequenced breast cancer samples** used as homologous recombination deficient (HRD).

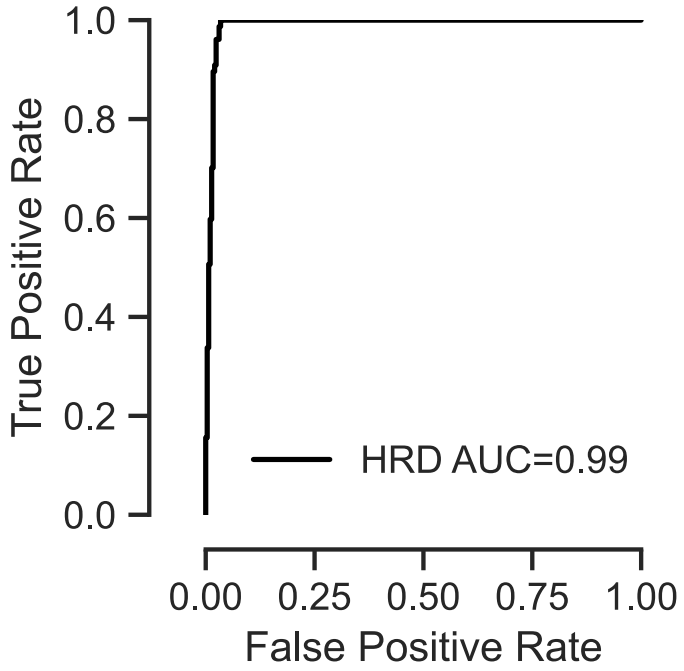
Testing dataset (WGS): 370 whole-genome sequenced breast cancer samples (77 HRD & 293 HRP).

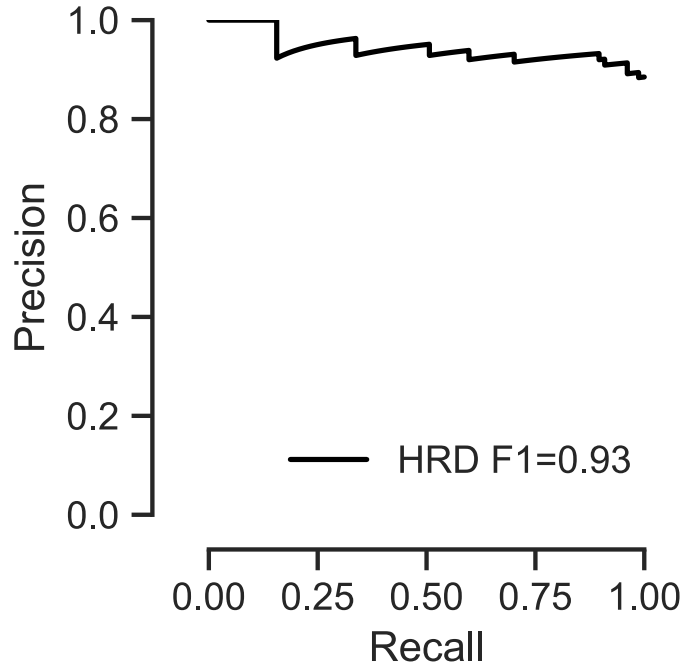
Independent validation dataset (WGS): 237 whole-genome sequenced triple-negative breast cancer samples (95 HRD & 142 HRP).

Independent validation dataset (WES): TCGA breast and ovarian whole-exome sequenced samples with consensus HRD and HRP status.

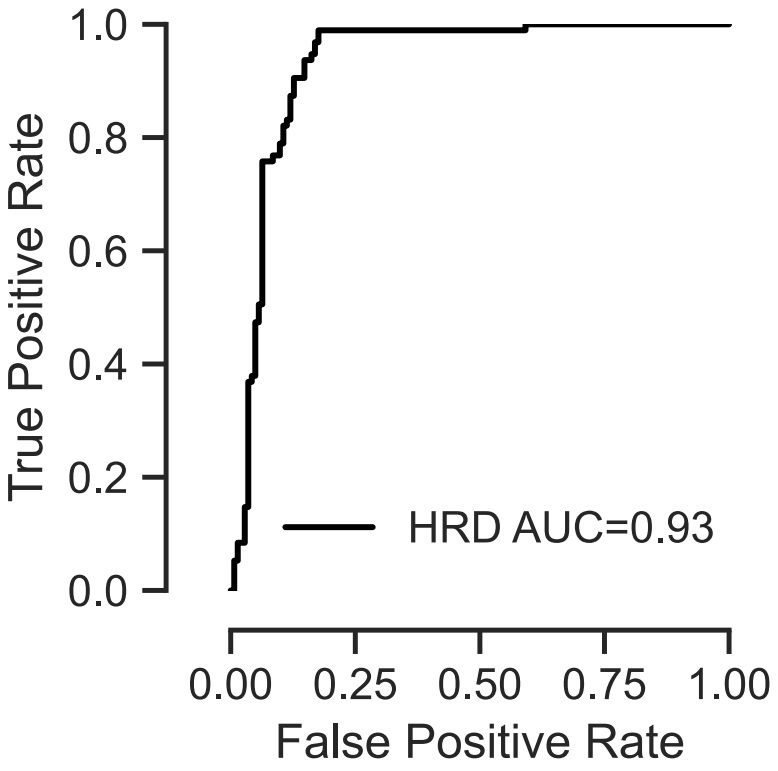
Classifier performance on test dataset (370 WGS samples)

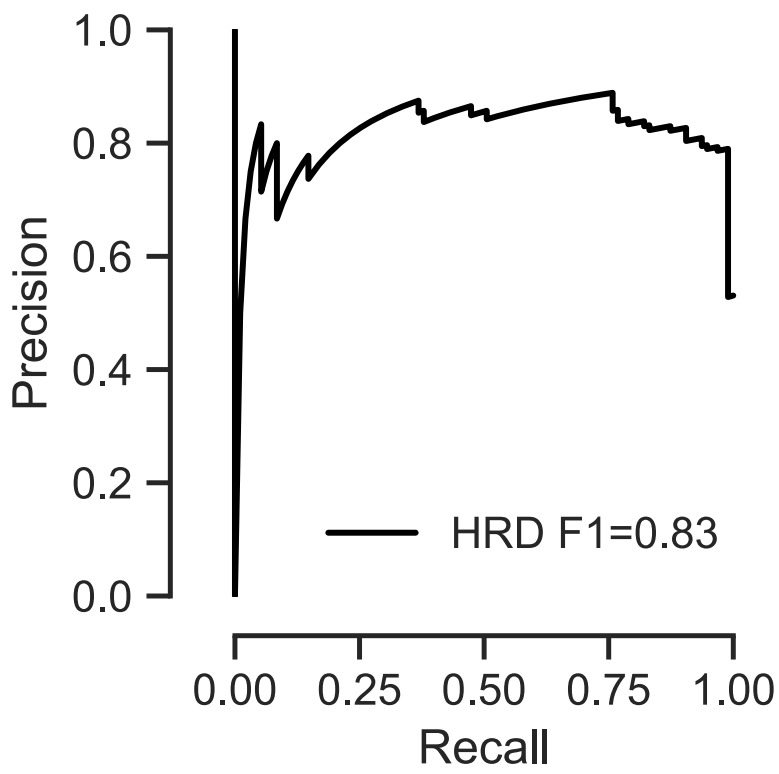




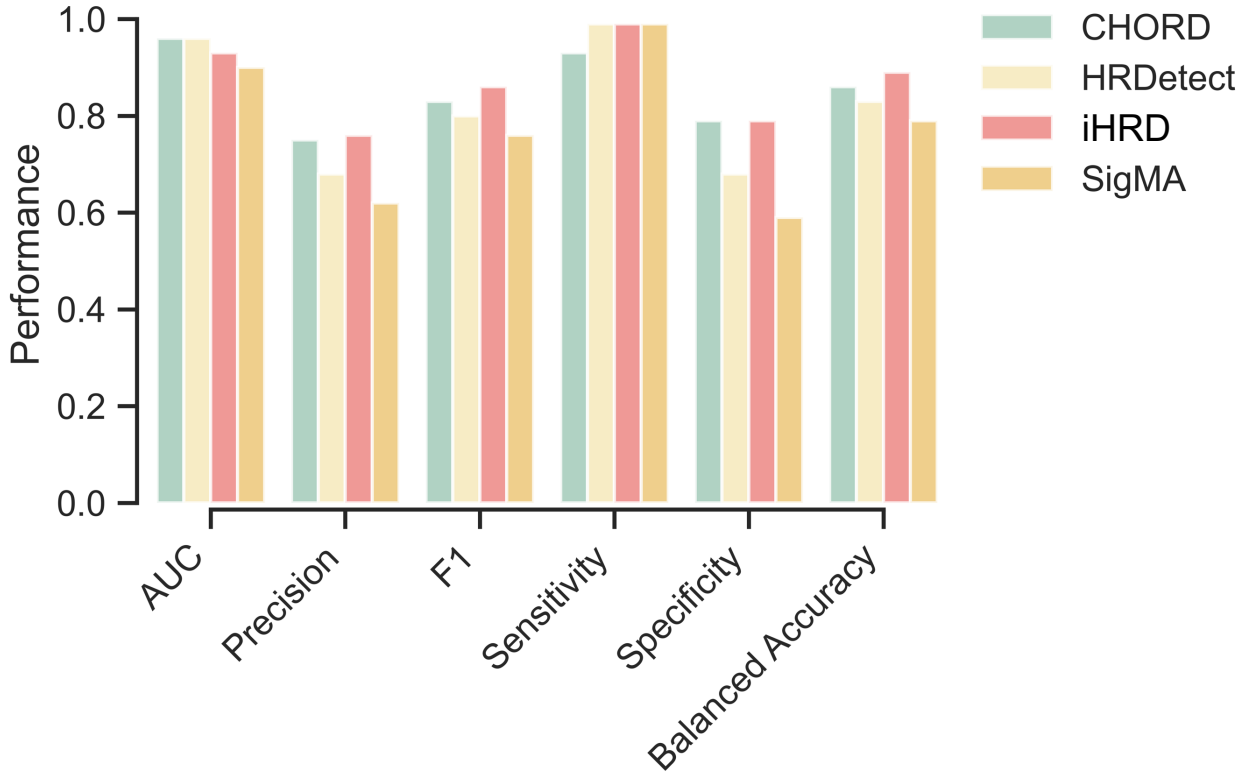


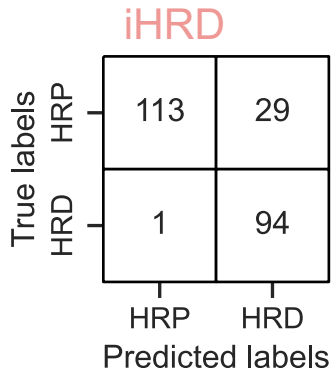
Classifier performance on validation dataset (237 WGS TNBC)

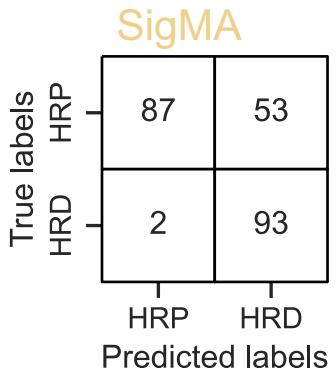


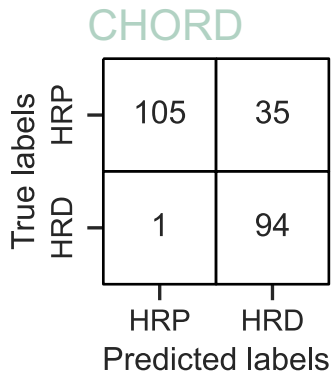


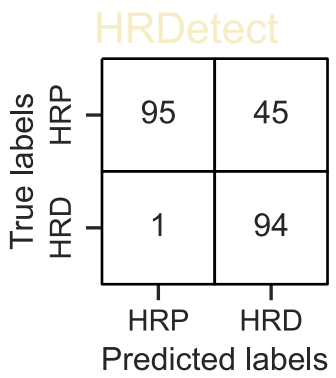
Model performance on validation WGS dataset across HRD genomic tools



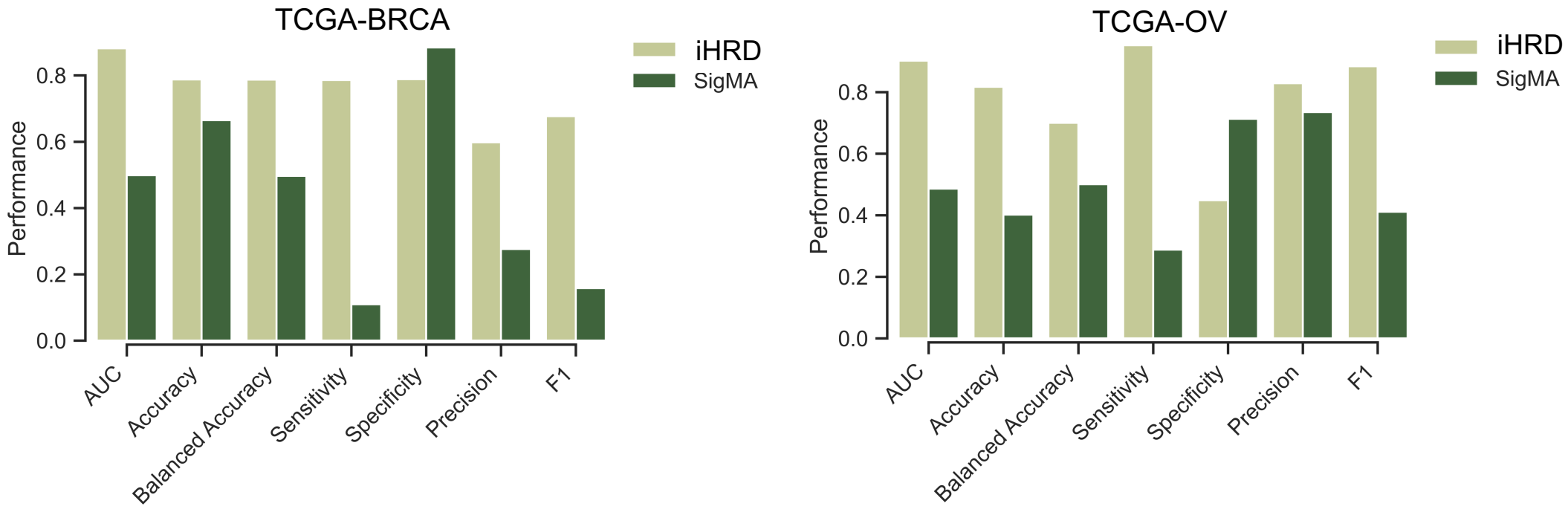








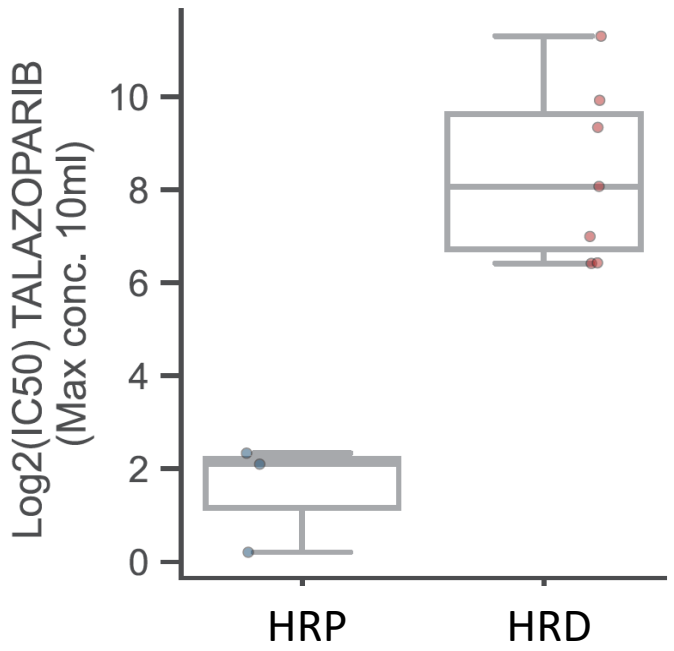
Model performance on validation WES dataset across HRD genomic tools



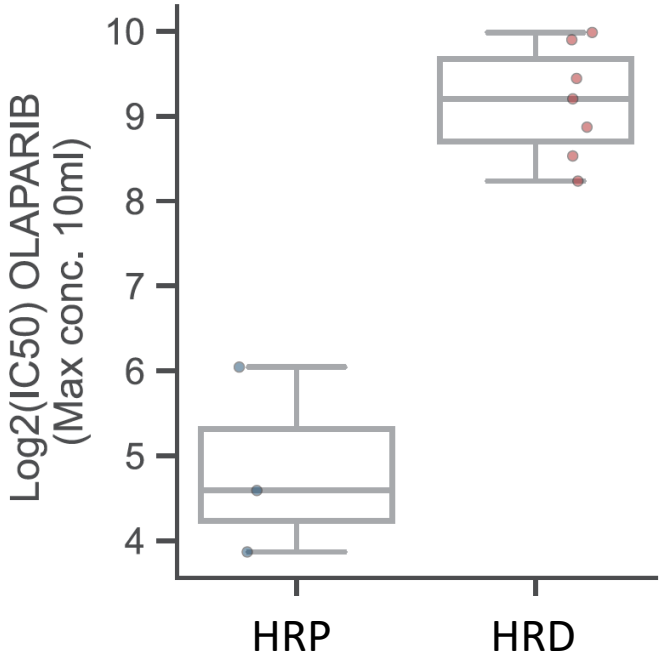
iHRD uses model trained on whole-genome sequenced breast cancers.
SigMA uses tissue-specific models trained on whole-exome sequencing data.

Applying iHRD to exome sequenced cell lines with PARPi response

Talazoparib

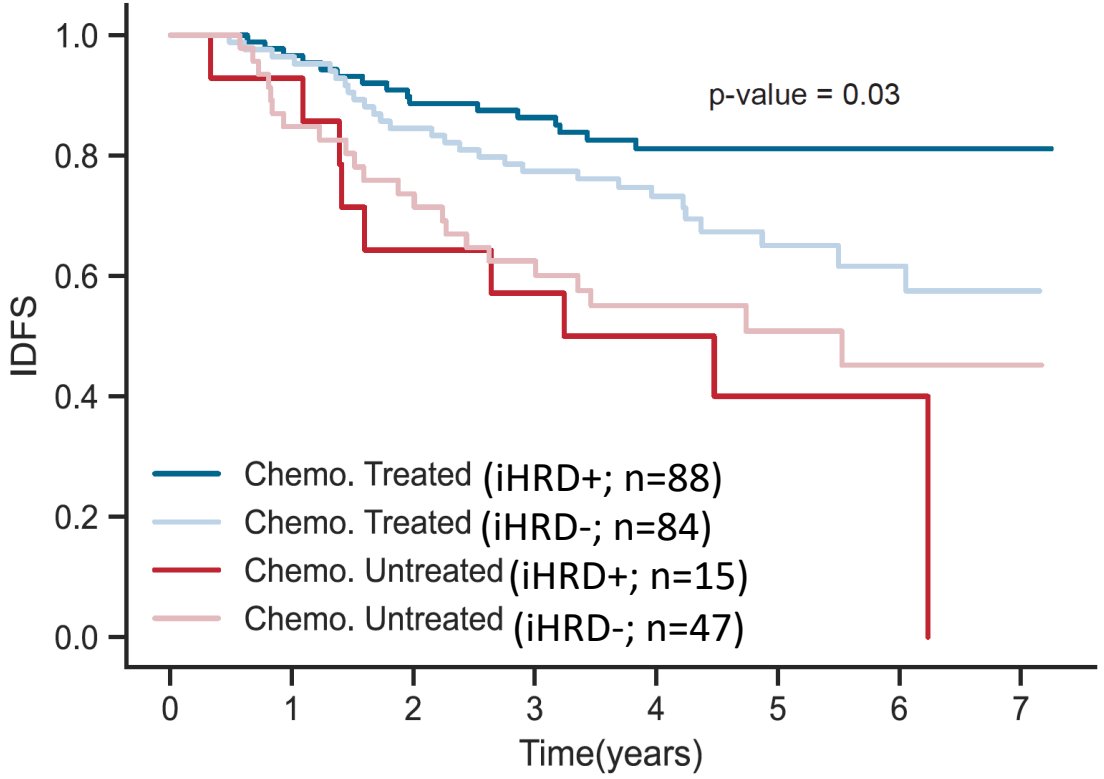


Olaparib

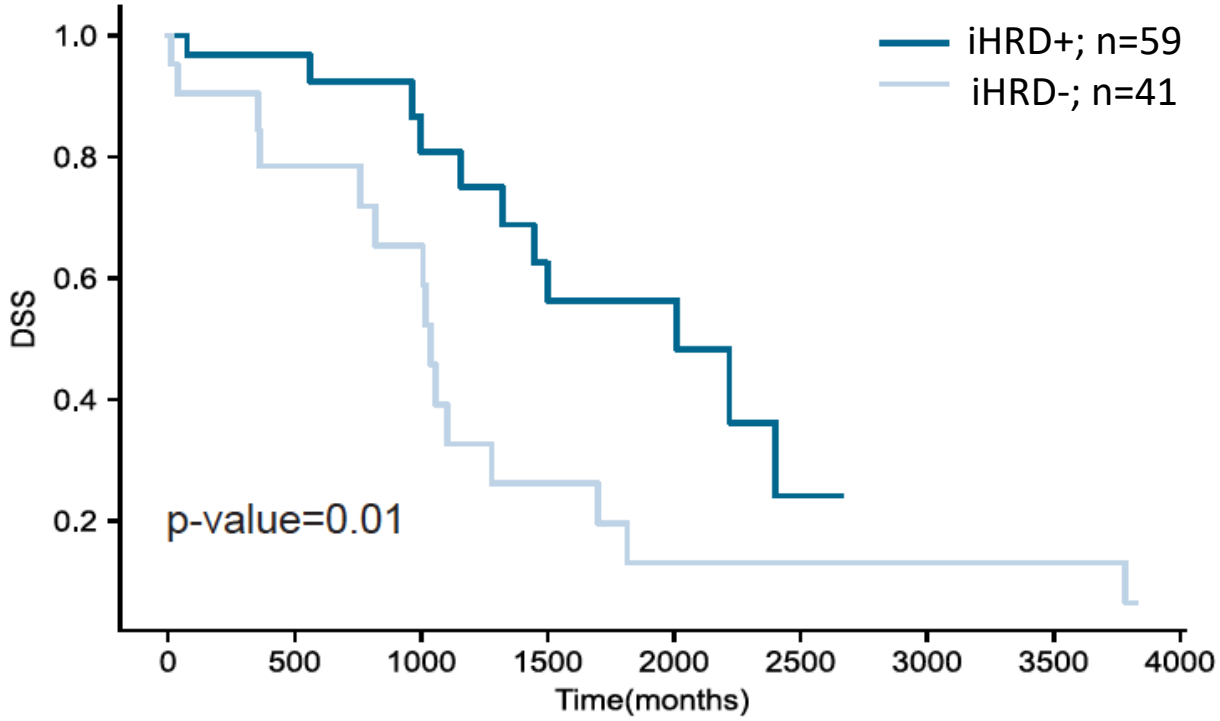


Applying iHRD to exome sequenced retrospective clinical cohorts

Breast Cancers & Platinum Therapy



Ovarian Cancers & Platinum Therapy



Ongoing iHRD work

- Applying to a breast cancer clinical cohort with known response to PARPi
- Applying to a prostate cancer clinical cohort with known response to PARPi
- Applying to a uterine sarcoma clinical cohort with known response to PARPi
- Working on extending its applicability to panel sequencing data

UC San Diego
Moores Cancer Center

DELIVERING
DISCOVERIES

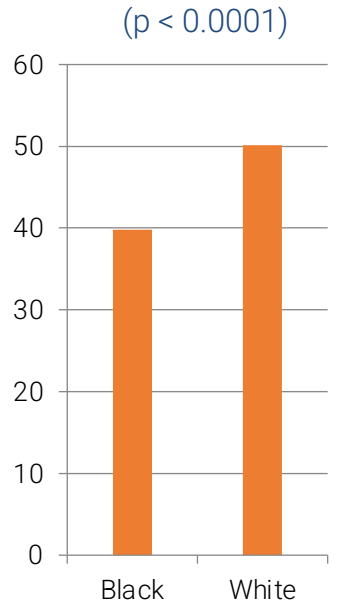
Beyond genomics: Utilizing AI for addressing inequalities of cancer diagnosis

Erik Bergstrom

- NGS profiling is not available to all patients in the US and access outside the US is very limited

- Adoption of proven companion diagnostics is low due to cost:
  - Lung cancer biomarkers testing was first approved by the FDA in 2004
  - Recent data show that NGS testing rates in the US for the 5 SOC biomarkers is <50% overall.

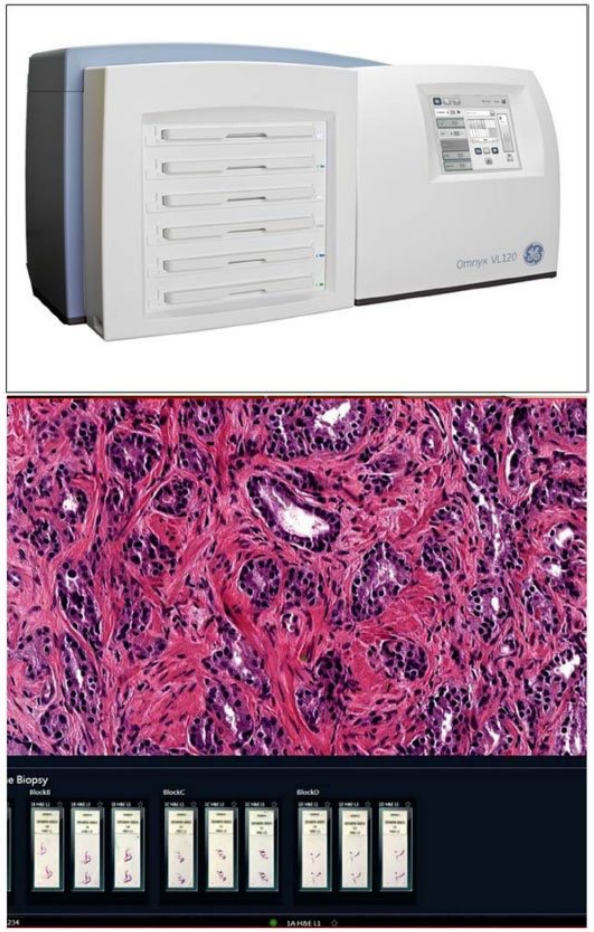
Roberts, N *et al* on behalf of the MYLUNG Consortium™ Collaborators: The US Oncology Network & Sponsors. ASCO Meeting, June 2021

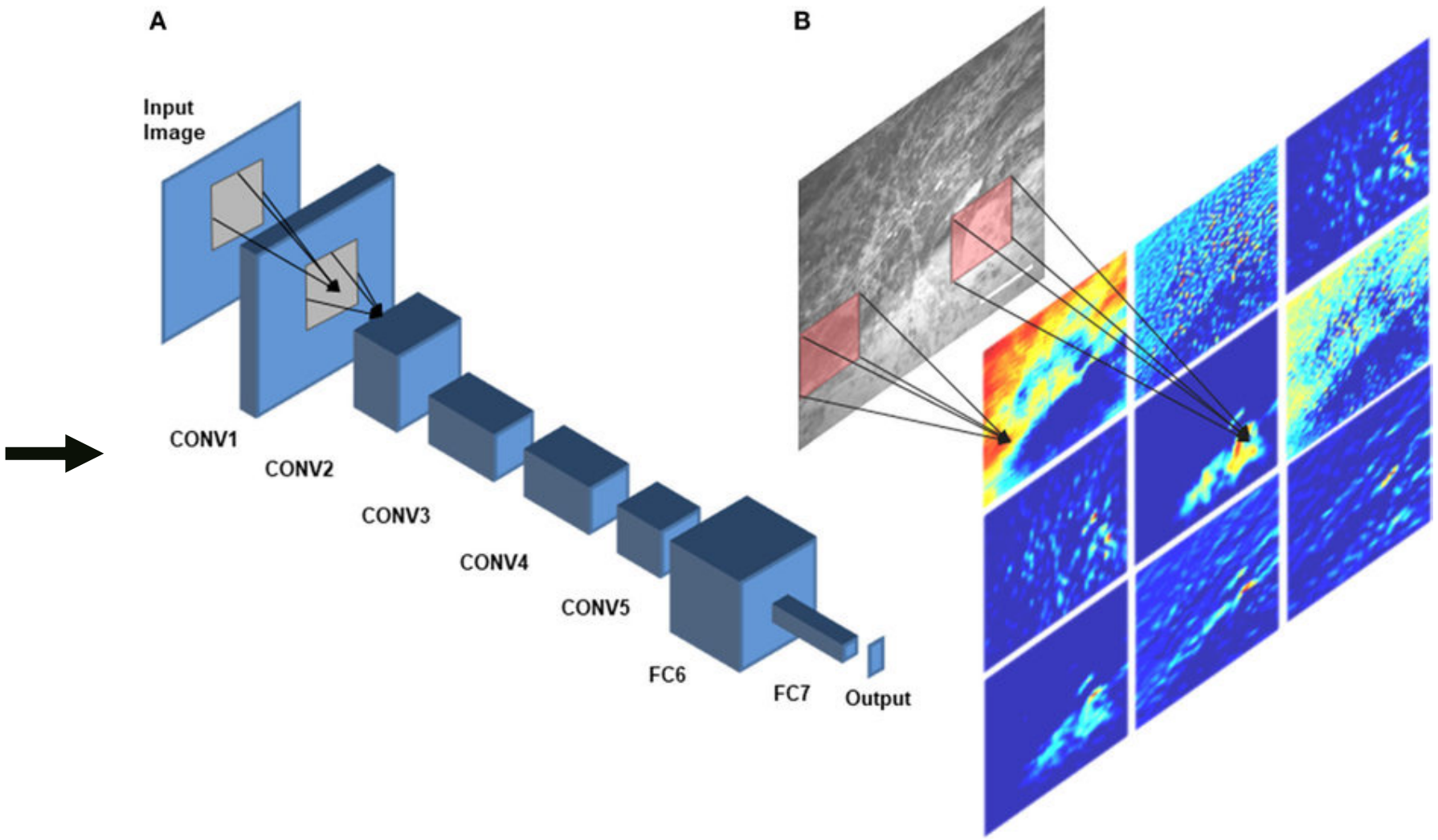


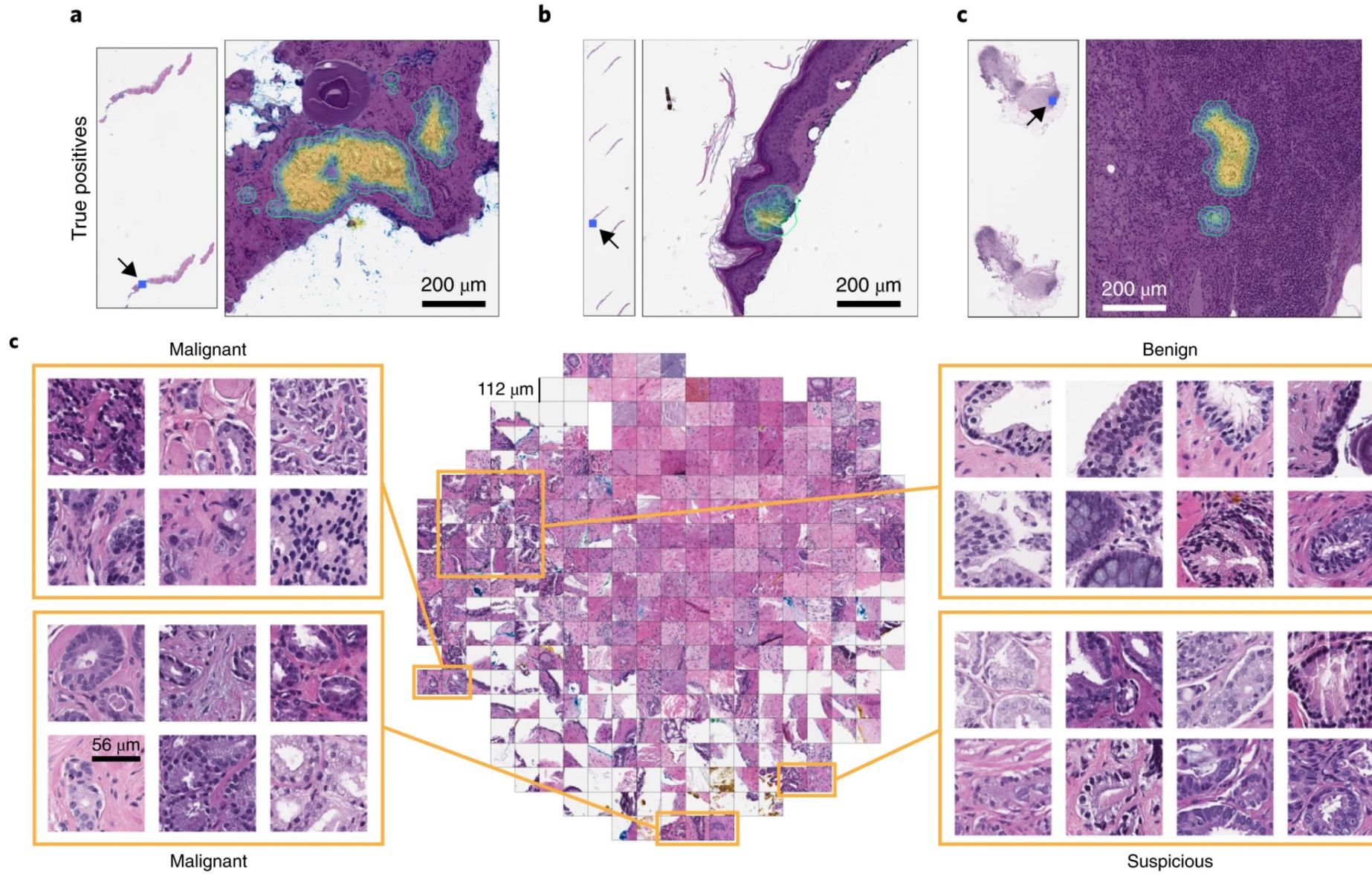
Bruno et al.; Roberts et al., **Lung Cancer, *ASCO*, June 2021

Convolutional neural network to automatically extract image features

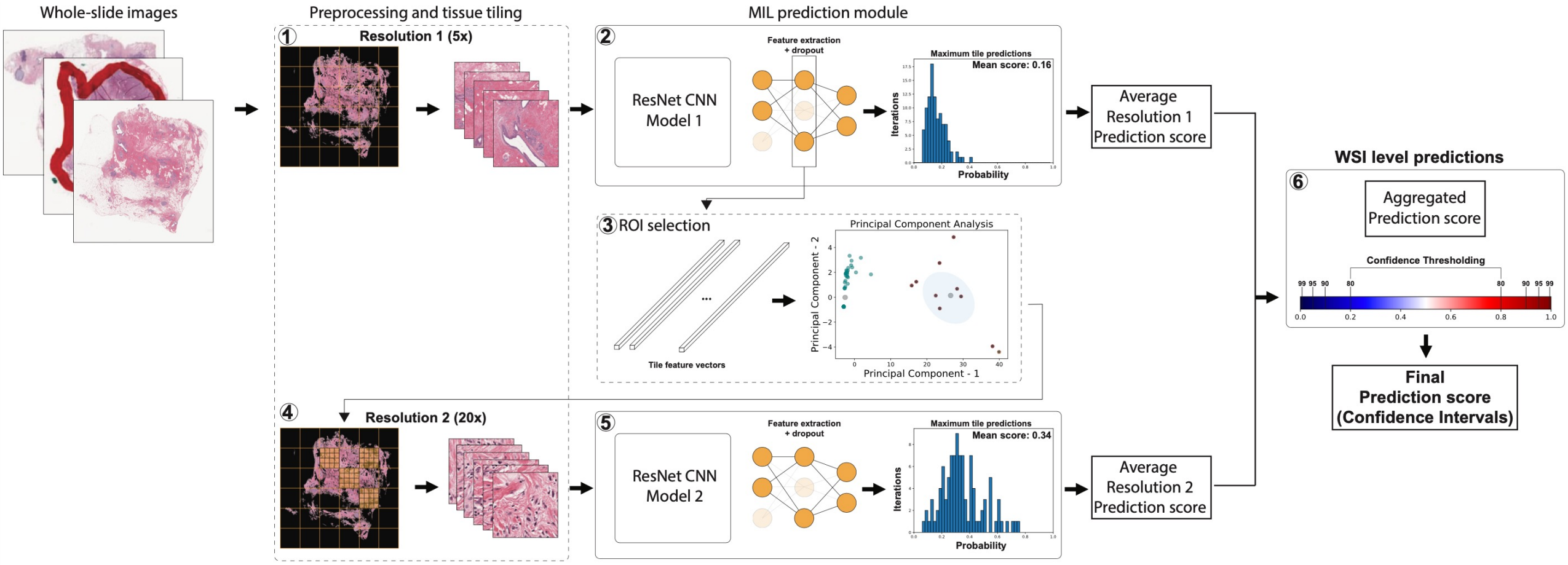
FFPE and frozen





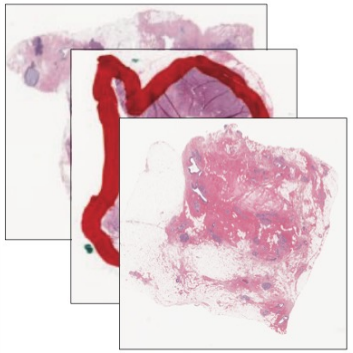

a
b
c
True positives
200 µm
200 µm
200 µm
c
Malignant
112 µm
Benign
56 µm
Malignant
Suspicious

Convolutional neural network to detect biomarkers from histopathological slides

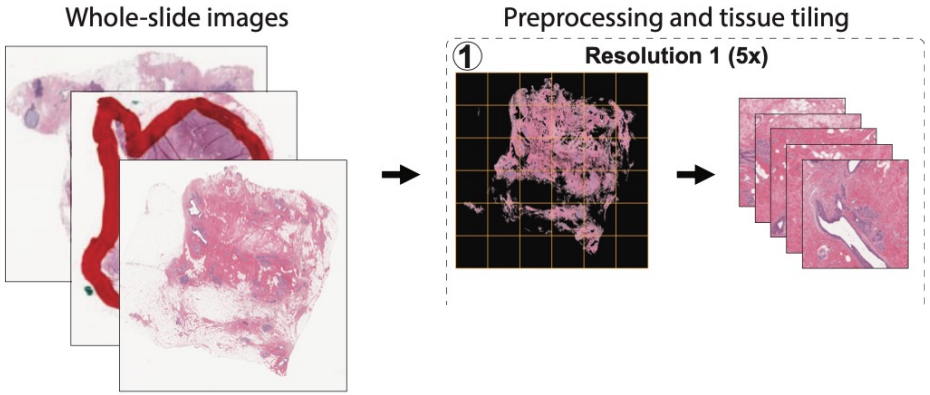


Convolutional neural network to detect biomarkers from histopathological slides

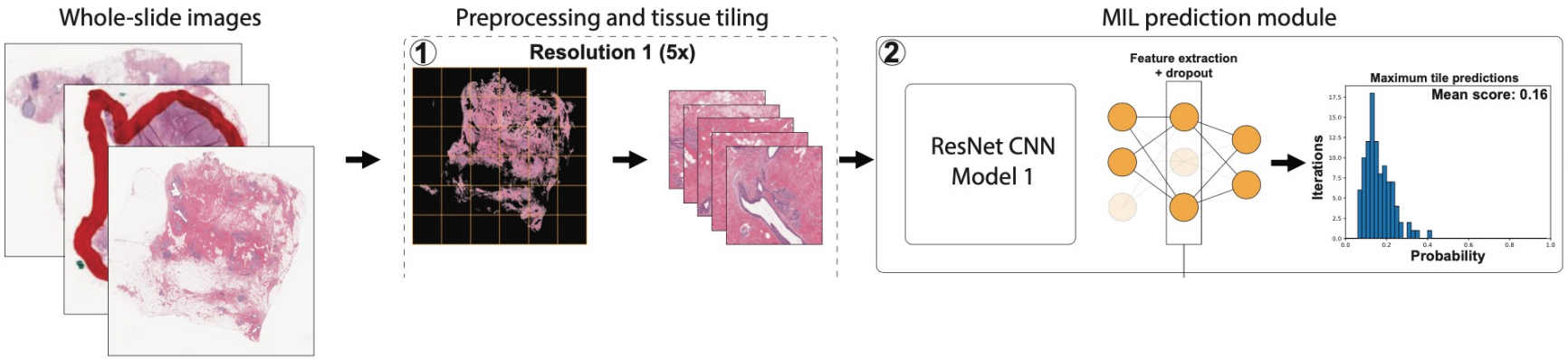
Whole-slide images



Convolutional neural network to detect biomarkers from histopathological slides



Convolutional neural network to detect biomarkers from histopathological slides



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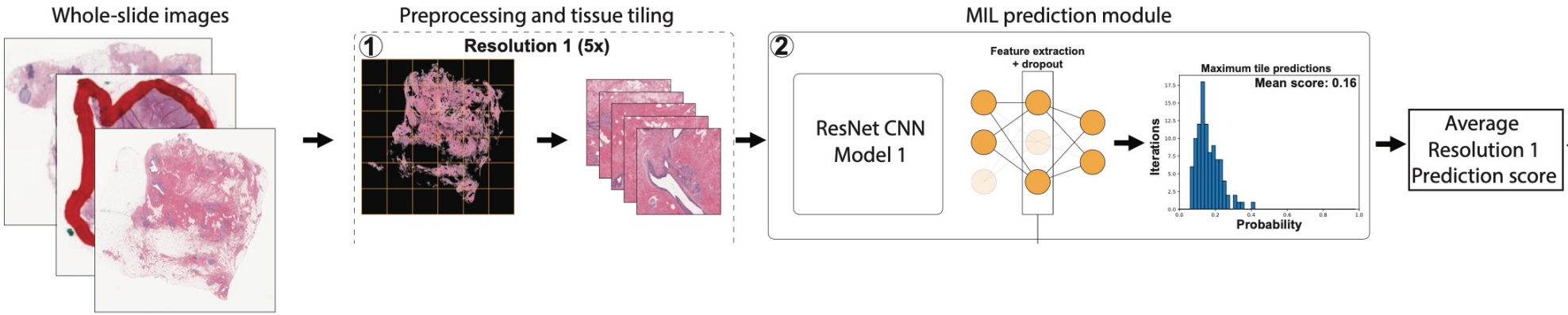

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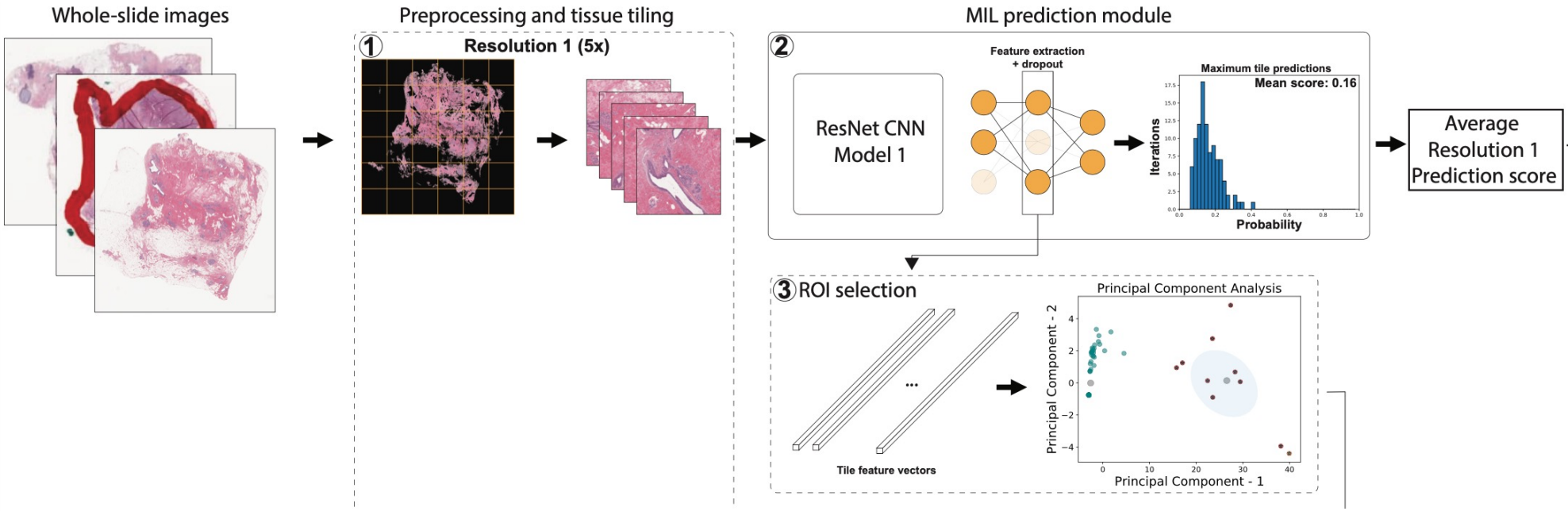
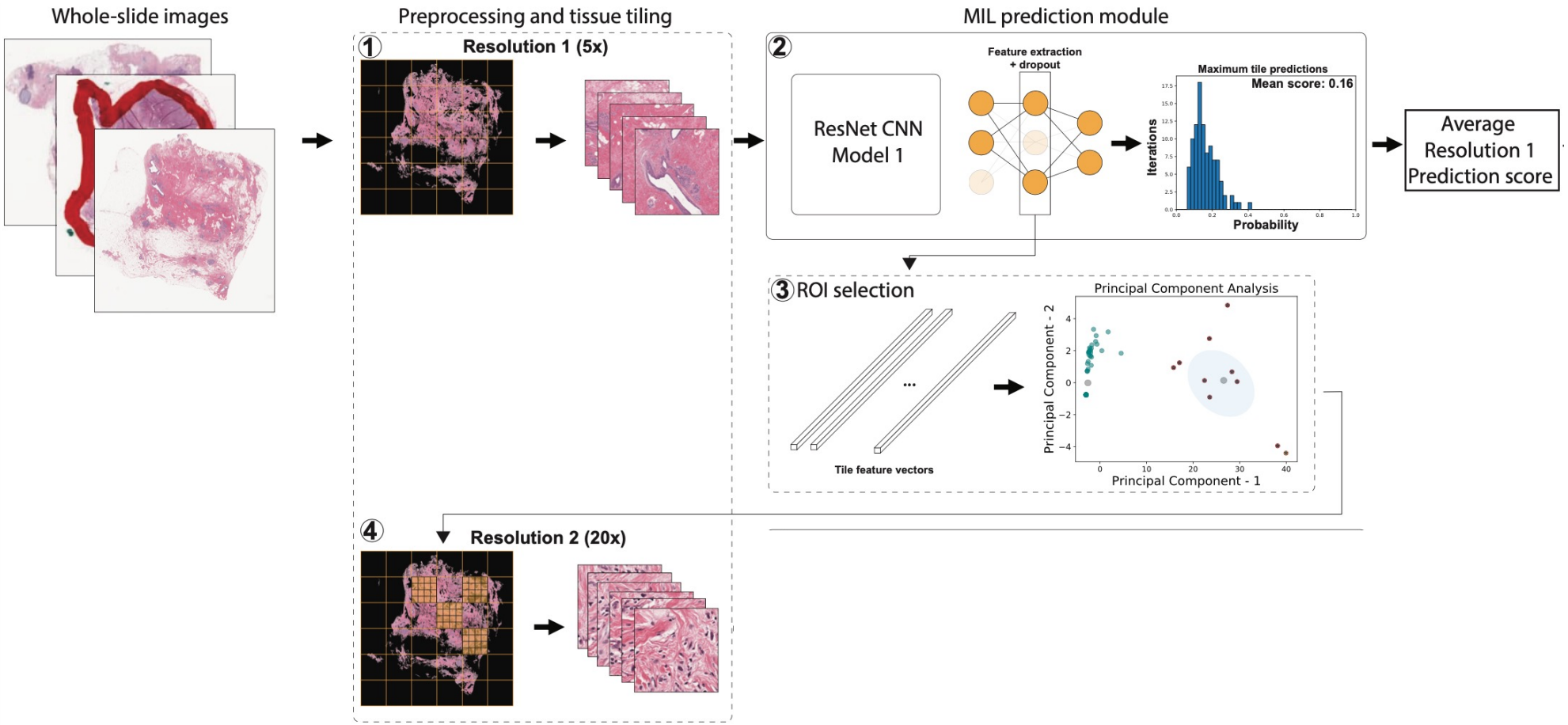
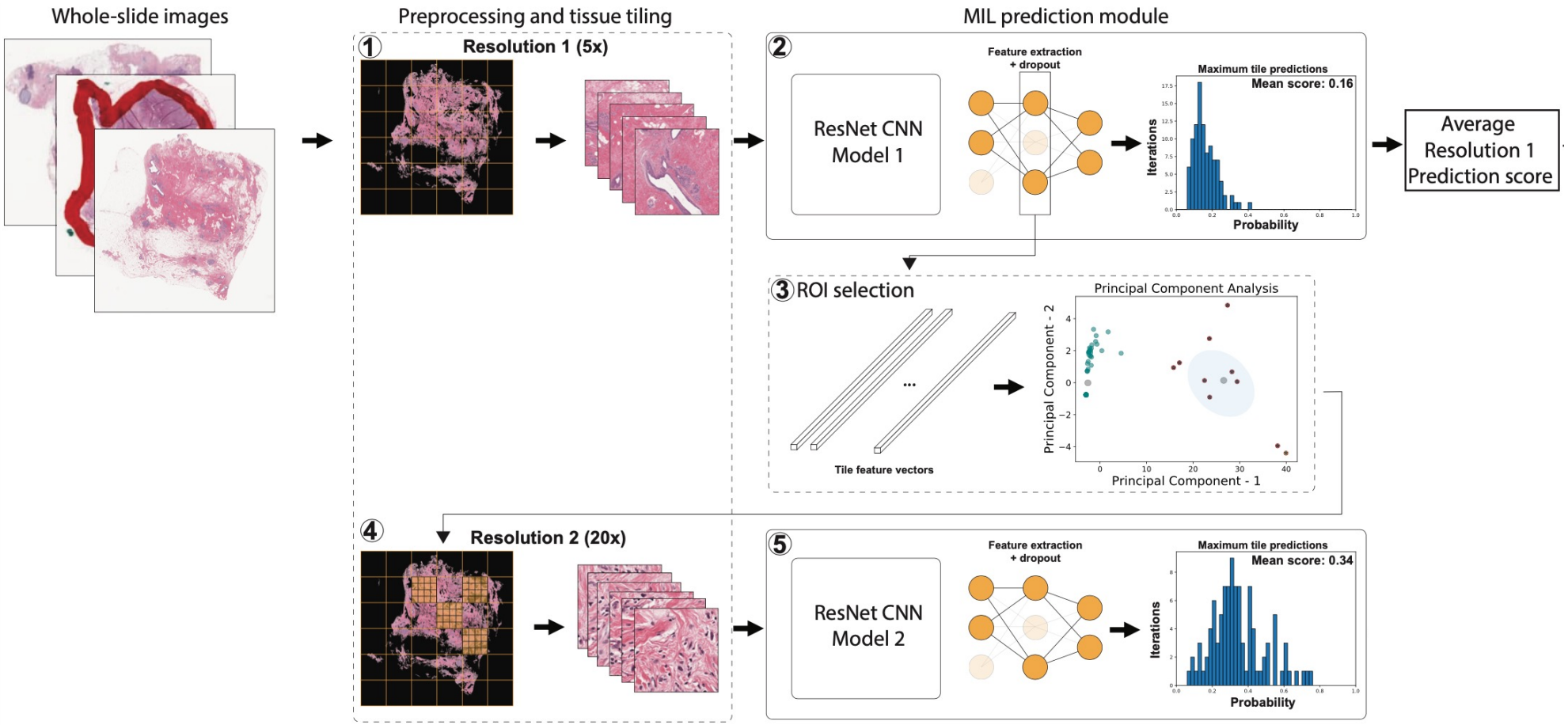


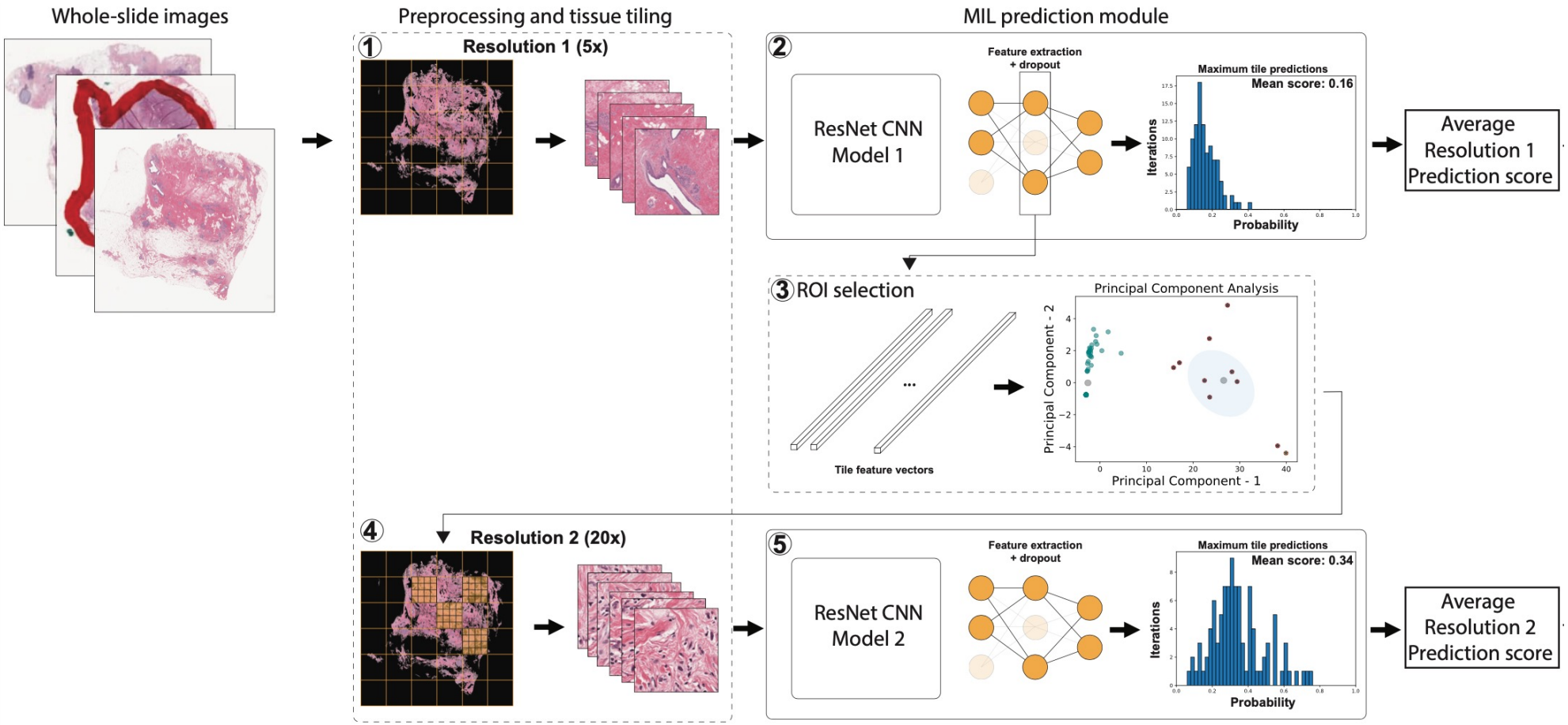
Convolutional neural network to detect biomarkers from histopathological slides



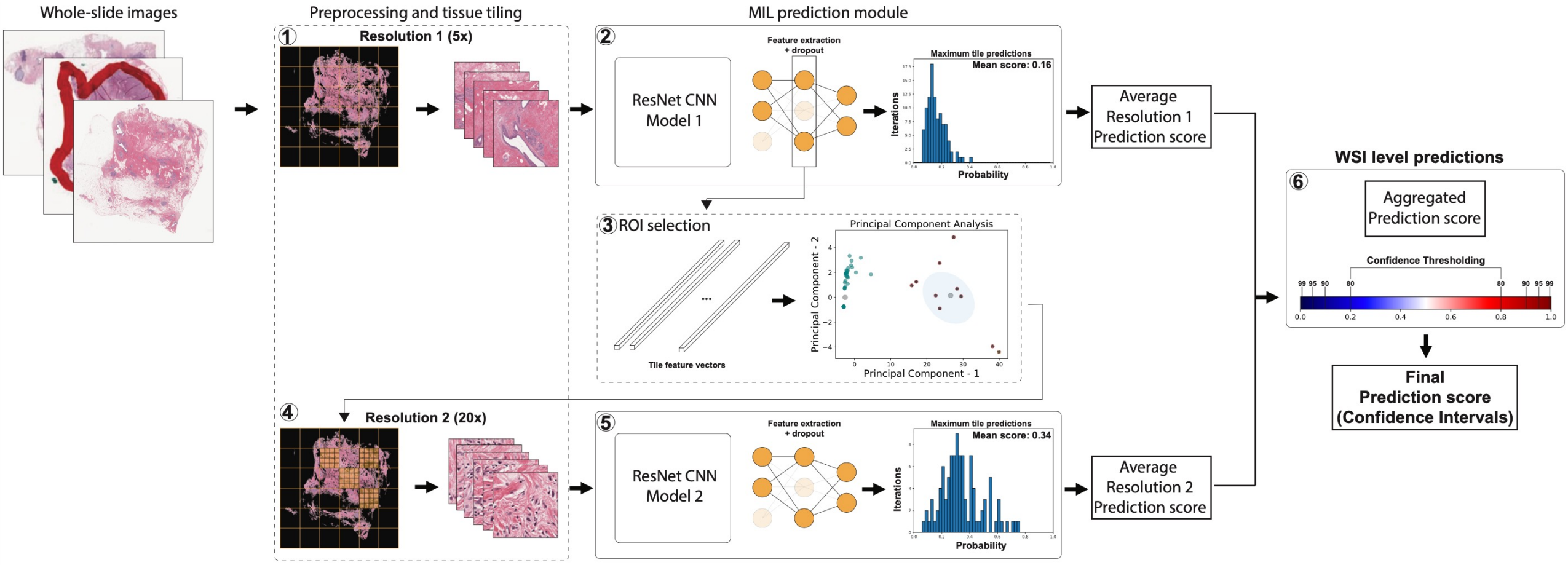
Convolutional neural network to detect biomarkers from histopathological slides



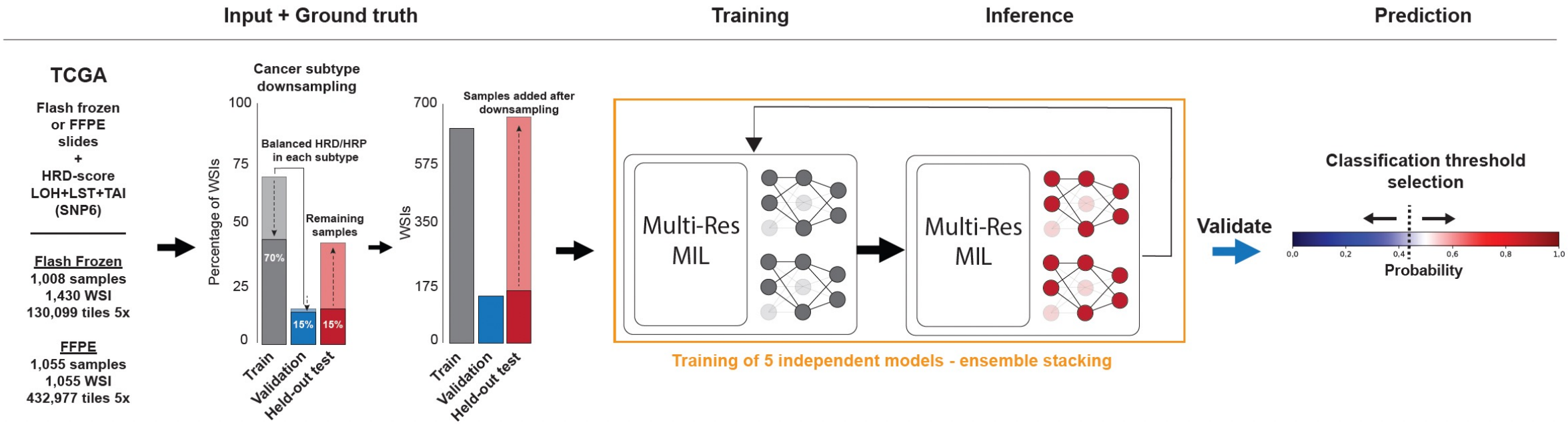
Convolutional neural network to detect biomarkers from histopathological slides



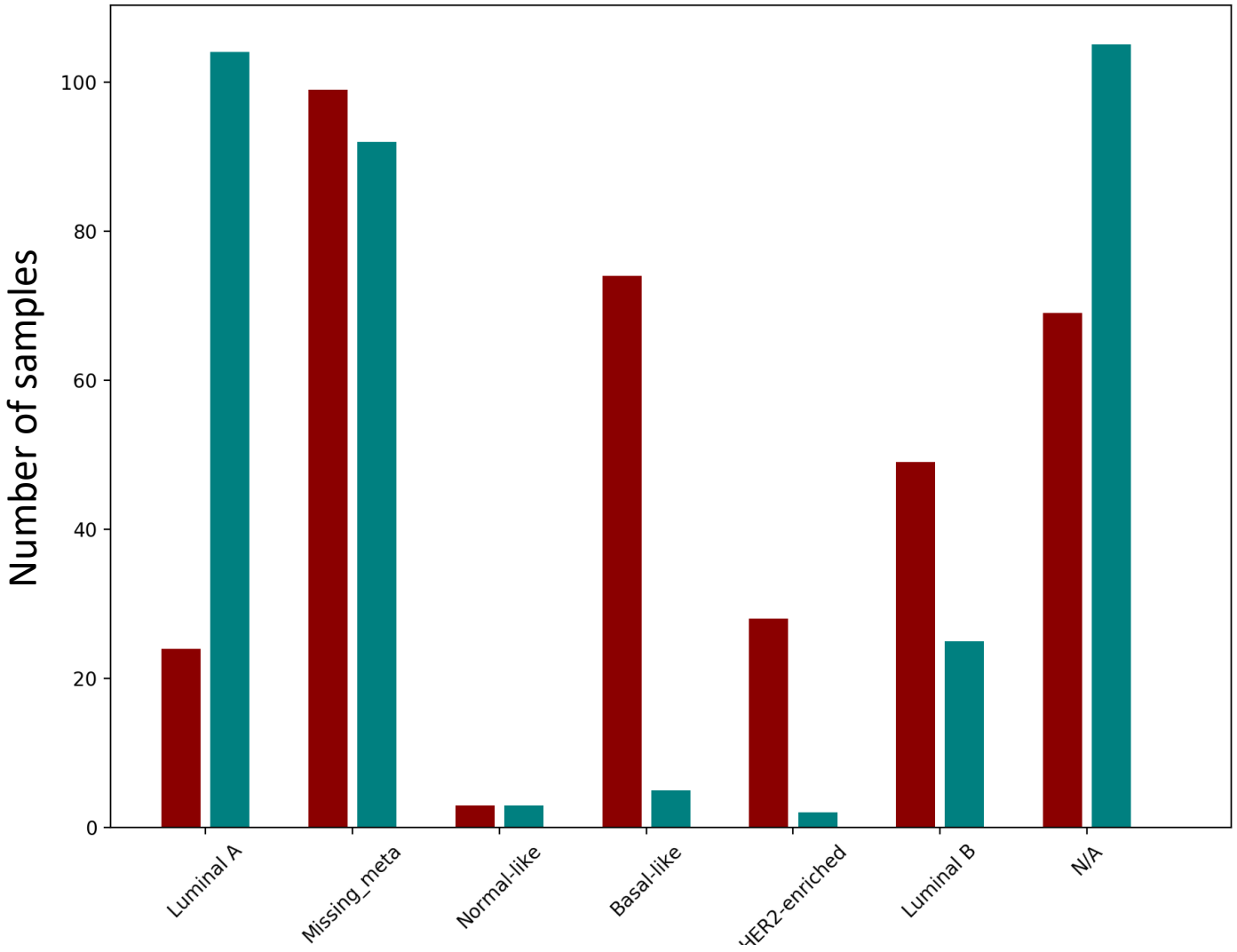
Convolutional neural network to detect biomarkers from histopathological slides



Training a DeepHRD prediction model for detecting HRD from digital H&E slides

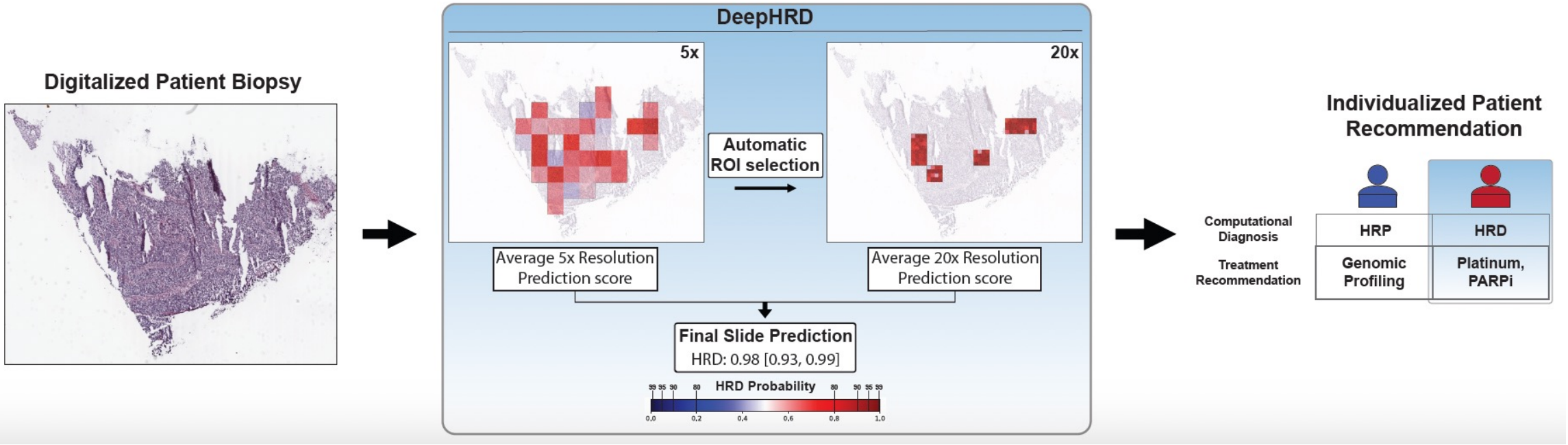


Training a DeepHRD prediction model for detecting HRD from digital H&E slides

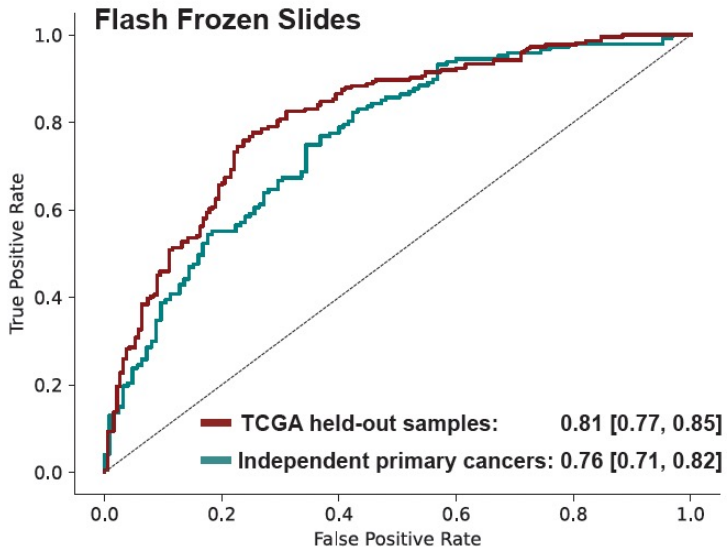


MYRIAD myChoice® CDx

Applying a trained DeepHRD model for predicting HRD from digital H&E slides



Comparing DeepHRD detection power to the score of a molecular test in primary breast cancer



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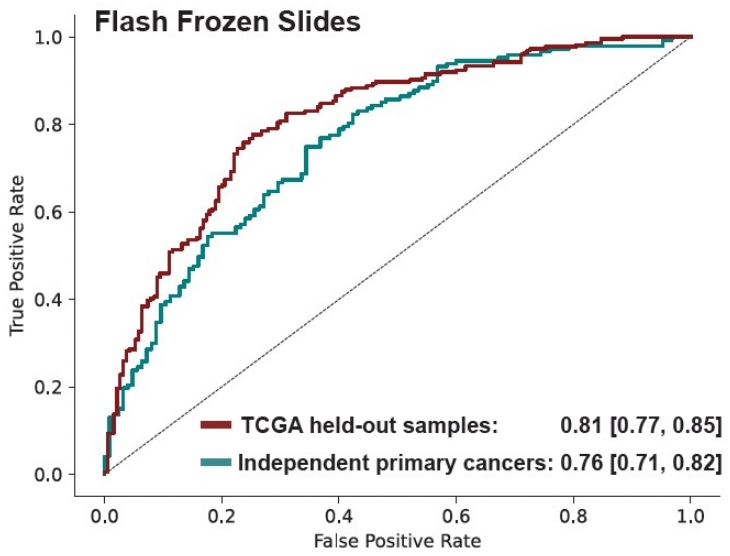
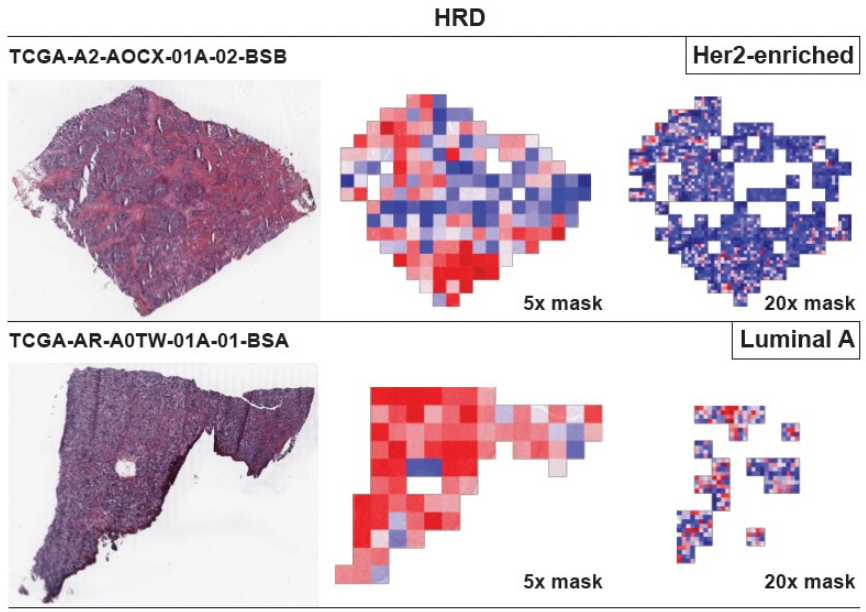
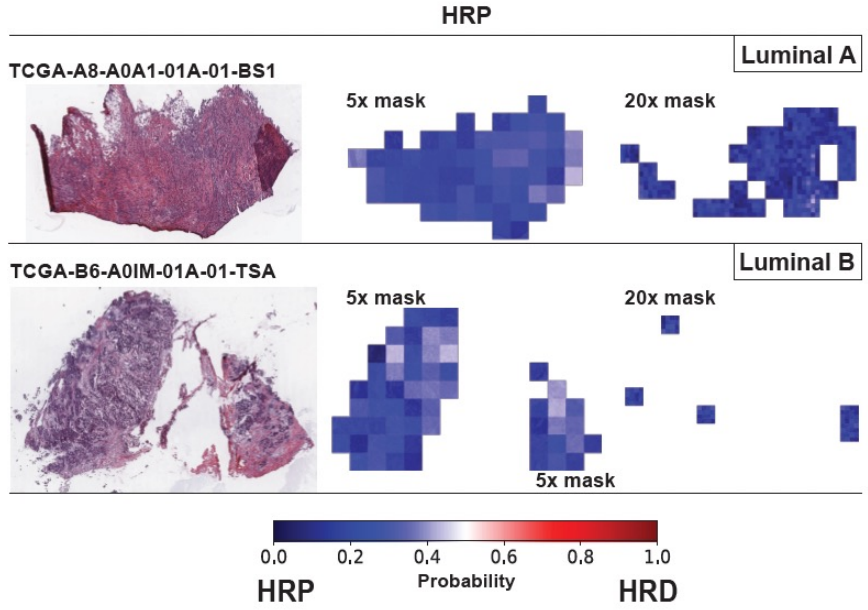
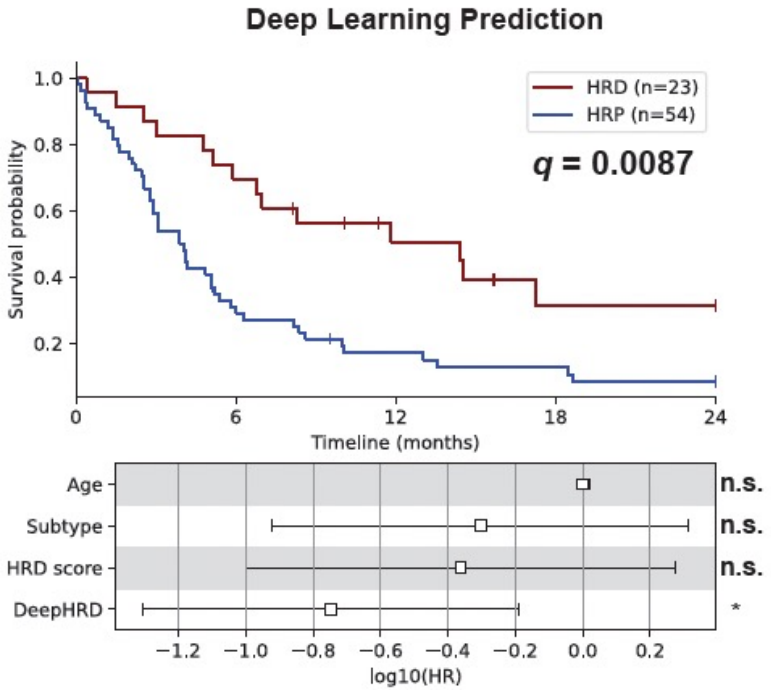






Predicting platinum response in metastatic breast cancer (MBC) with DeepHRD

Platinum-treated Metastatic Breast Cancers



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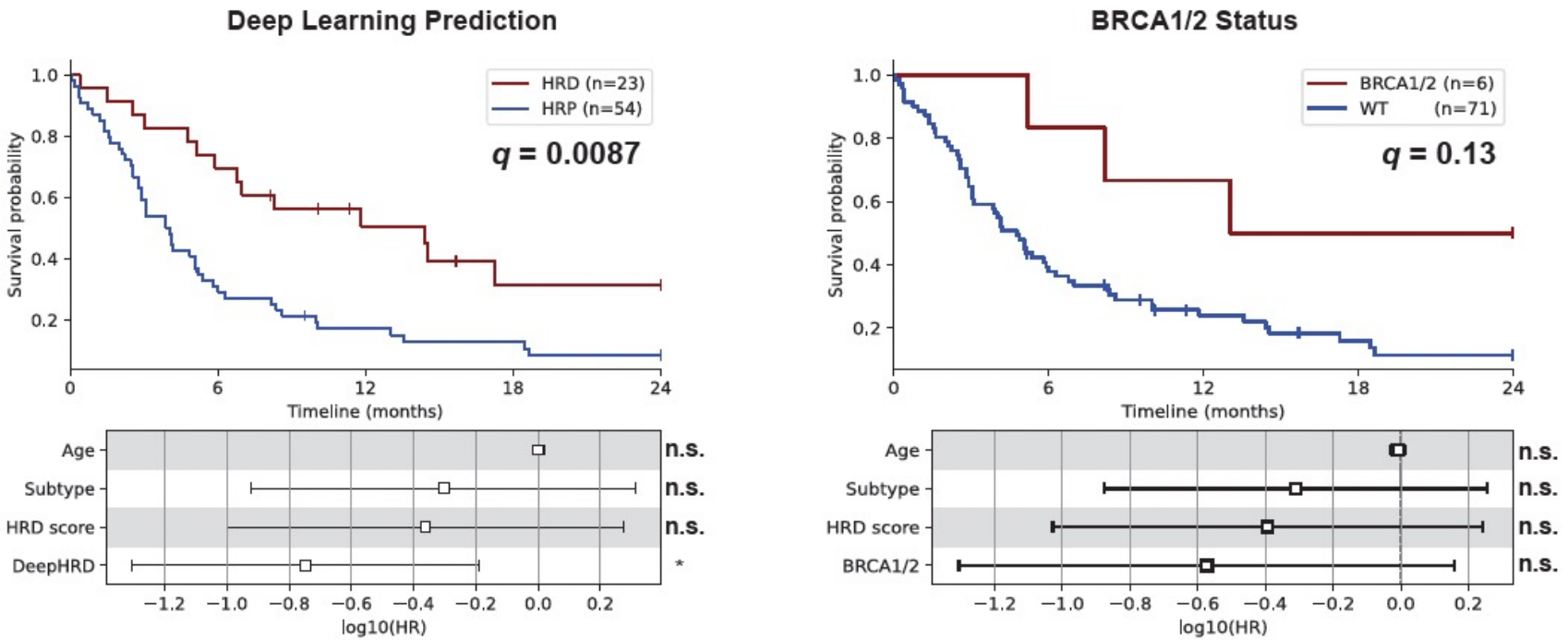
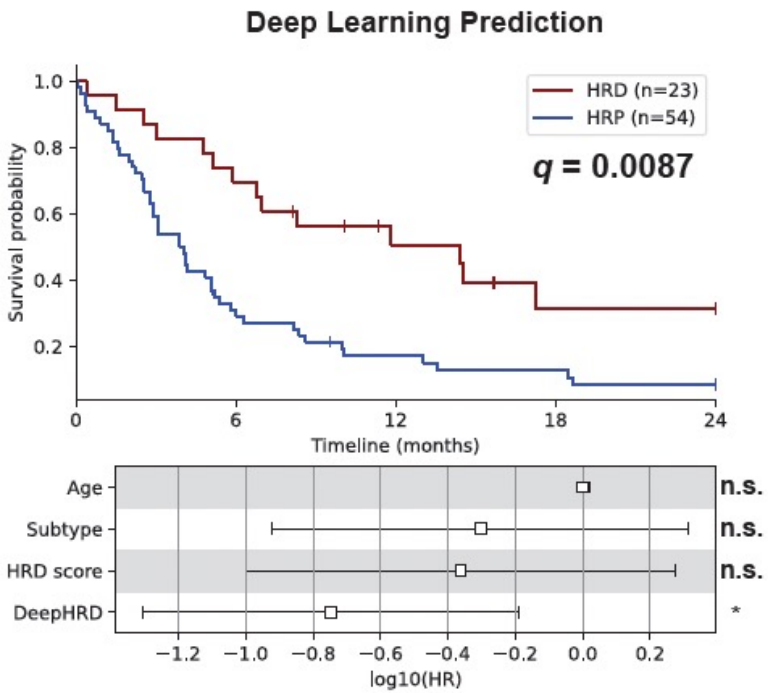
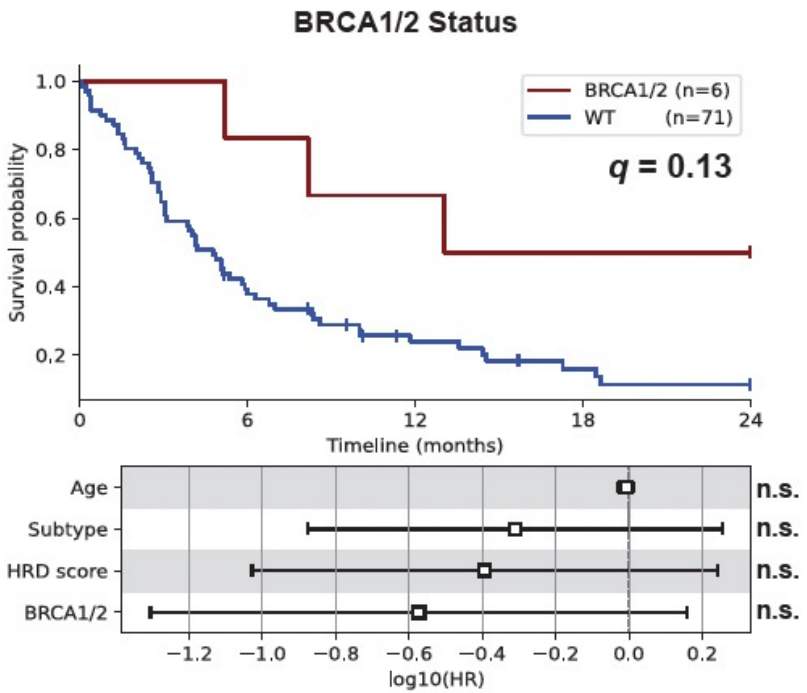
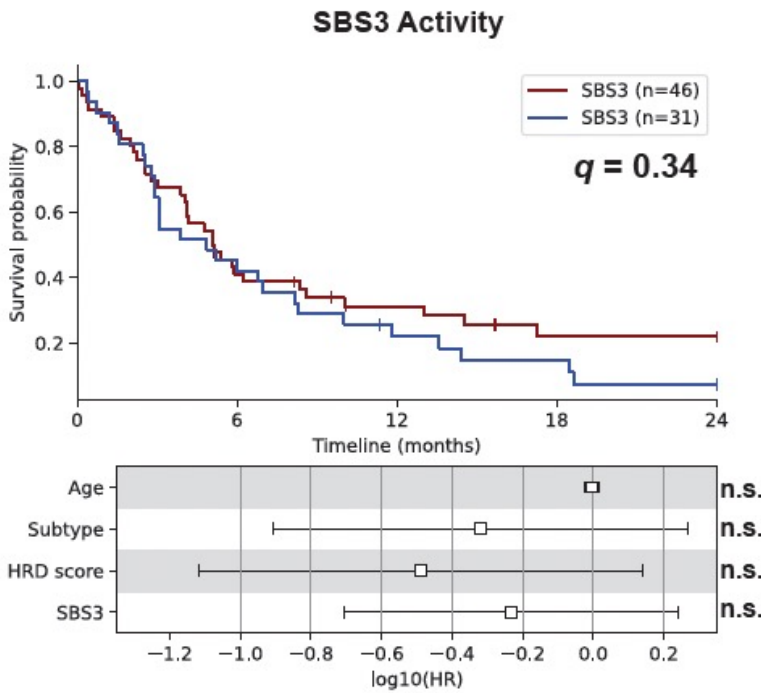


Predicting platinum response in metastatic breast cancer (MBC) with DeepHRD

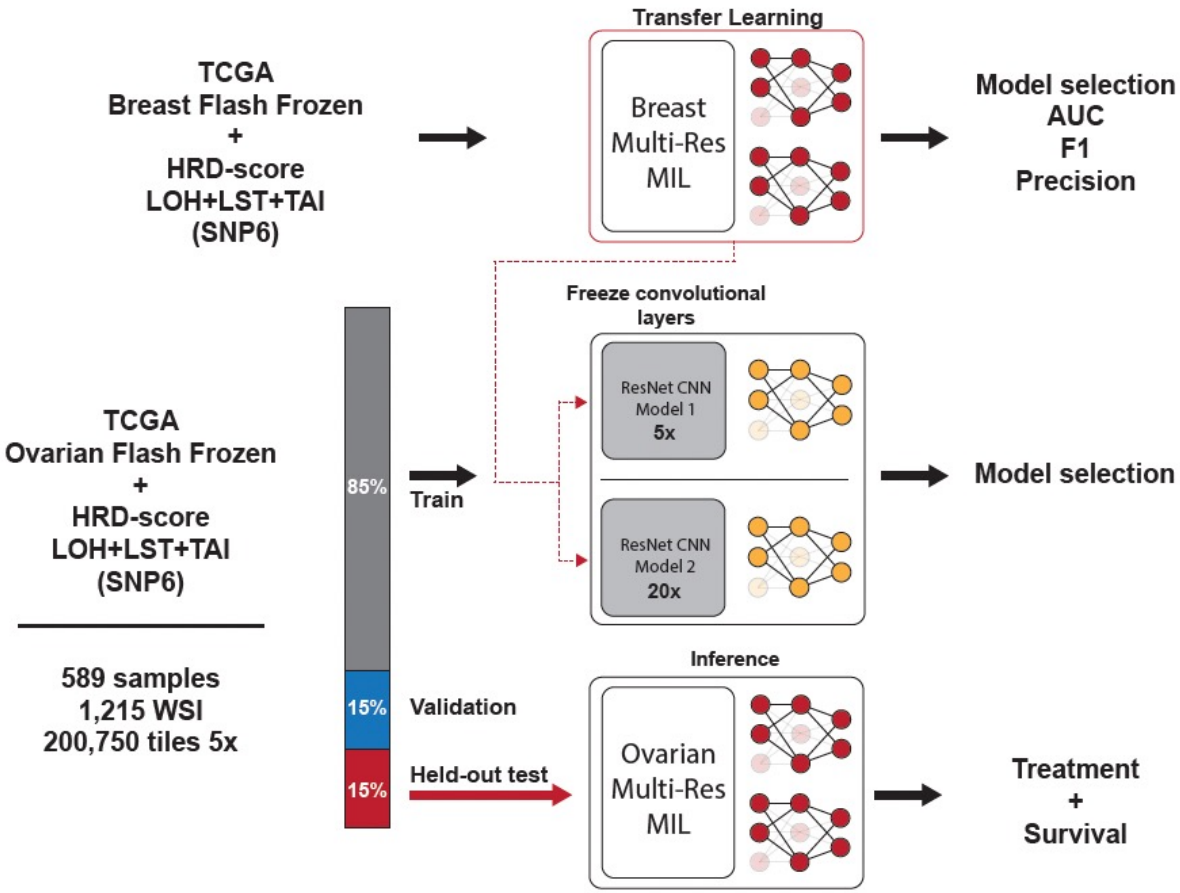
Platinum-treated Metastatic Breast Cancers



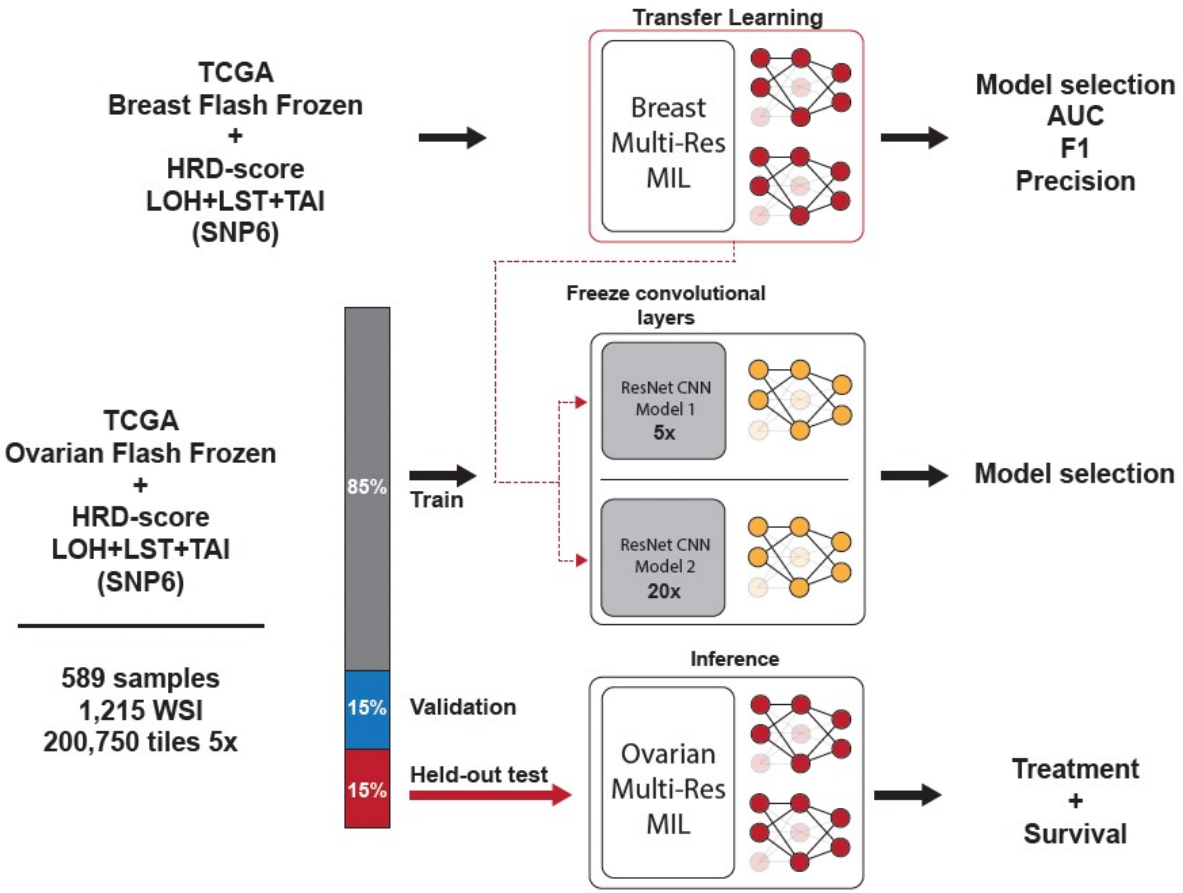


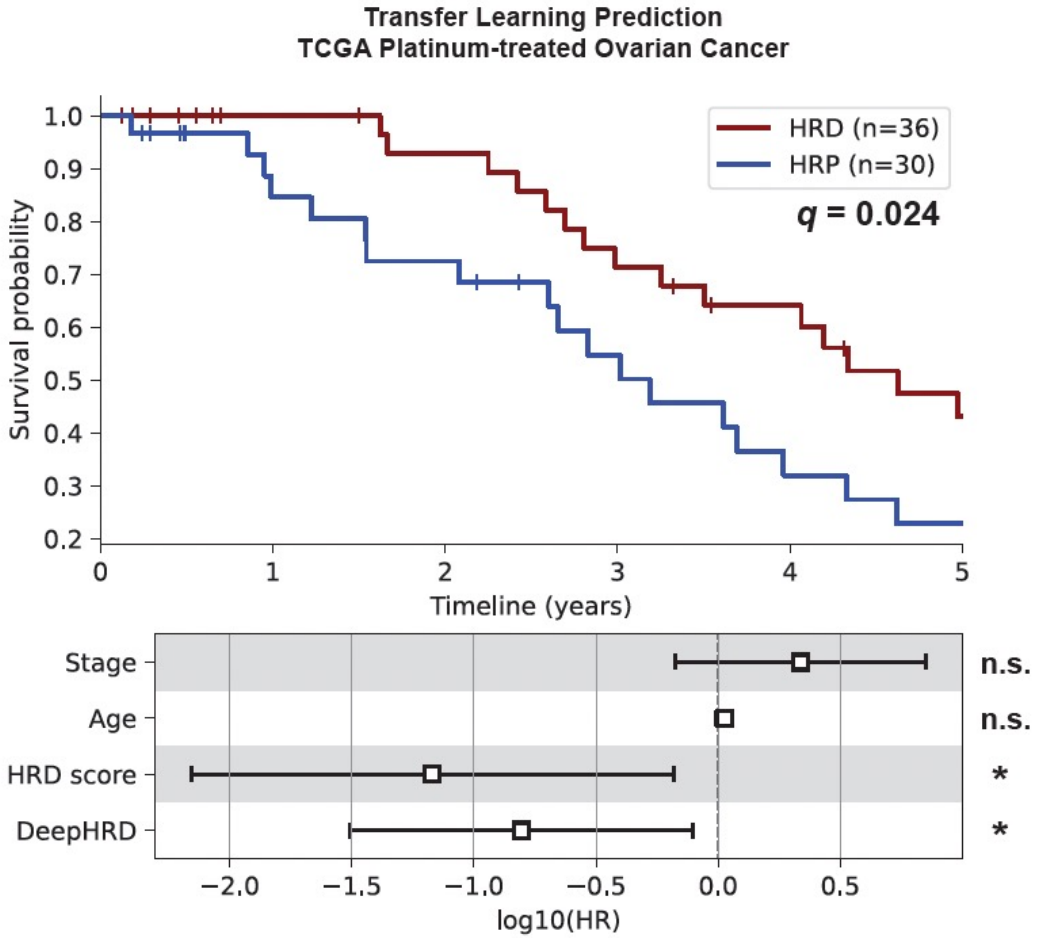


DeepHRD transfer learning predicts platinum response in ovarian cancer



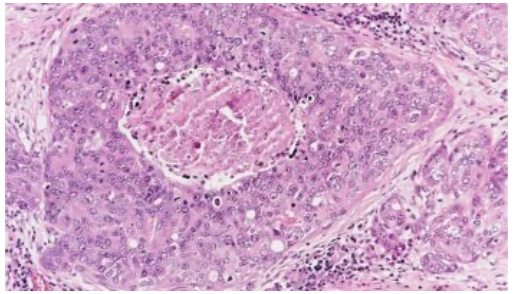
DeepHRD transfer learning predicts platinum response in ovarian cancer





Looking towards the future for detecting HRD score and other predictive biomarkers

Cancer Patient
(Breast/Ovarian/Pancreas)



Cancer Removed
Standard H&E Staining

Genomic Report

~14 days
$$$

DeepHRD Prediction
Detected Immediately

Summary

Summary

HRD

Stories of The Past

- Mutational signatures as a machine learning approach that allows detecting the *unusual patterns of somatic mutations*.
- Utilizing mutational signatures for developing cancer prevention strategies.
- Utilizing mutational signatures for understanding failed DNA repair and targeted cancer treatment.

Anecdotes of The Present

- Utilizing clustered mutations for understanding cancer development and evolution.
- The repertoire of copy-number signatures in human cancer.
- A novel machine learning approach for detecting homologous recombination deficiency.

Dreams of The Future

- Beyond genomics: Utilizing AI for addressing inequalities of cancer diagnosis

Acknowledgments: Lab Members & Funding Sources

UC San Diego
Moores Cancer Center

Alexandrov Lab Members

NIH
NATIONAL CANCER INSTITUTE
NIH NIEHS
CUREBOUND
ACCELERATING CANCER RESEARCH INTO CURES
the David & Lucile Packard FOUNDATION
UCSD
CANCER RESEARCH UK
GRAND CHALLENGE MUTOGRAPHS

Acknowledgments: Collaborators

Sanger Institute

Mike Stratton
Peter Campbell
Sam Behjati
Inigo Martincorena
Mia Petljak

University of California, San Diego

Scott Lippman
Jill Mesirov
Michael Karin
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Questions?