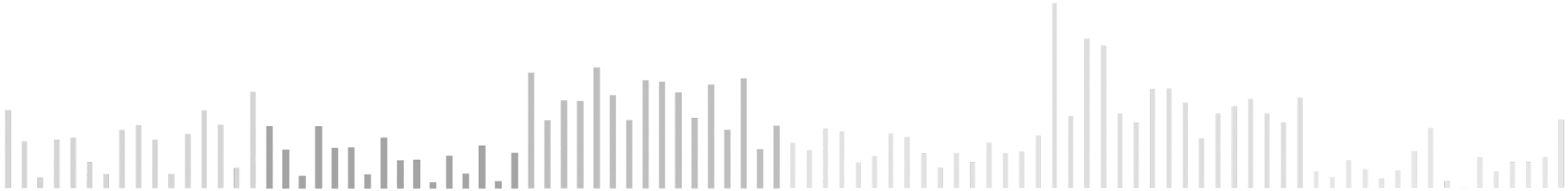
BIMM 143 – Class 18 Lab

Mutational Signatures in Cancer



Marcos Díaz-Gay

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marcos-diazg.github.io

@mdiazgay

Alexandrov Lab

Today's agenda

Basics of cancer genomics: genomic sequencing data and somatic mutations identification

- Exploring and obtaining tumor mutation data from **cBioPortal**

Characterization of the patterns of mutations in cancer

- Mutational matrix generation using **Maftools**

Exploration of the biological processes generating mutations in different cancer types

- Mutational signature analysis using **MutationalPatterns**

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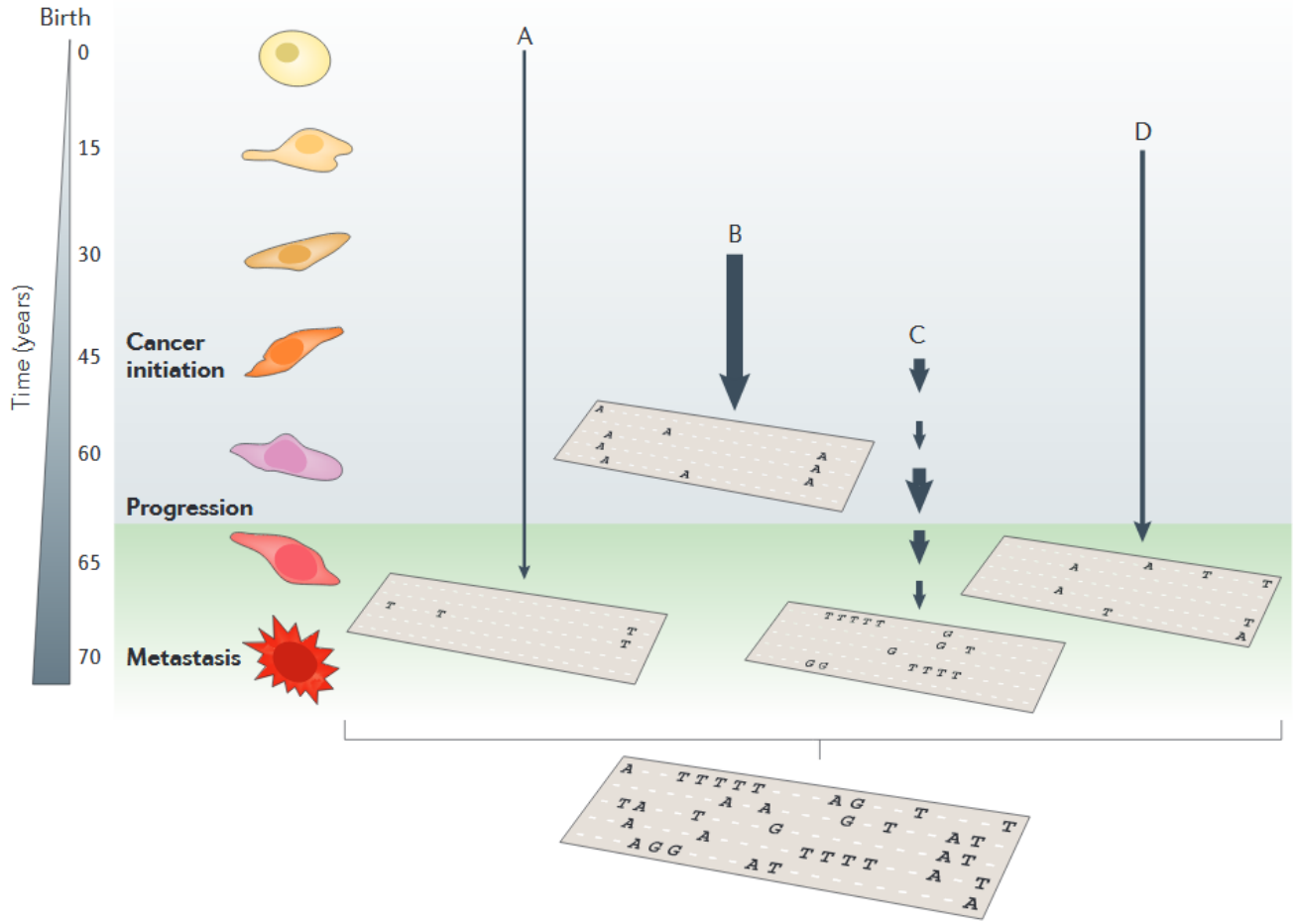
- Mutational signature analysis using **MutationalPatterns**

The mutational profile of a cancer patient is a mix of different processes characterized by specific mutational signatures



Helleday *et al.* 2014 Nature Reviews Genetics

The final cancer genome represents an archaeological record of the effect of the different mutagenic and DNA repair processes

Chemotherapy resistant recurrence

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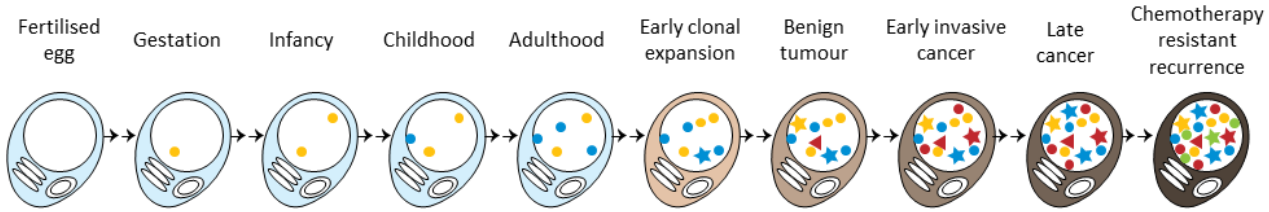

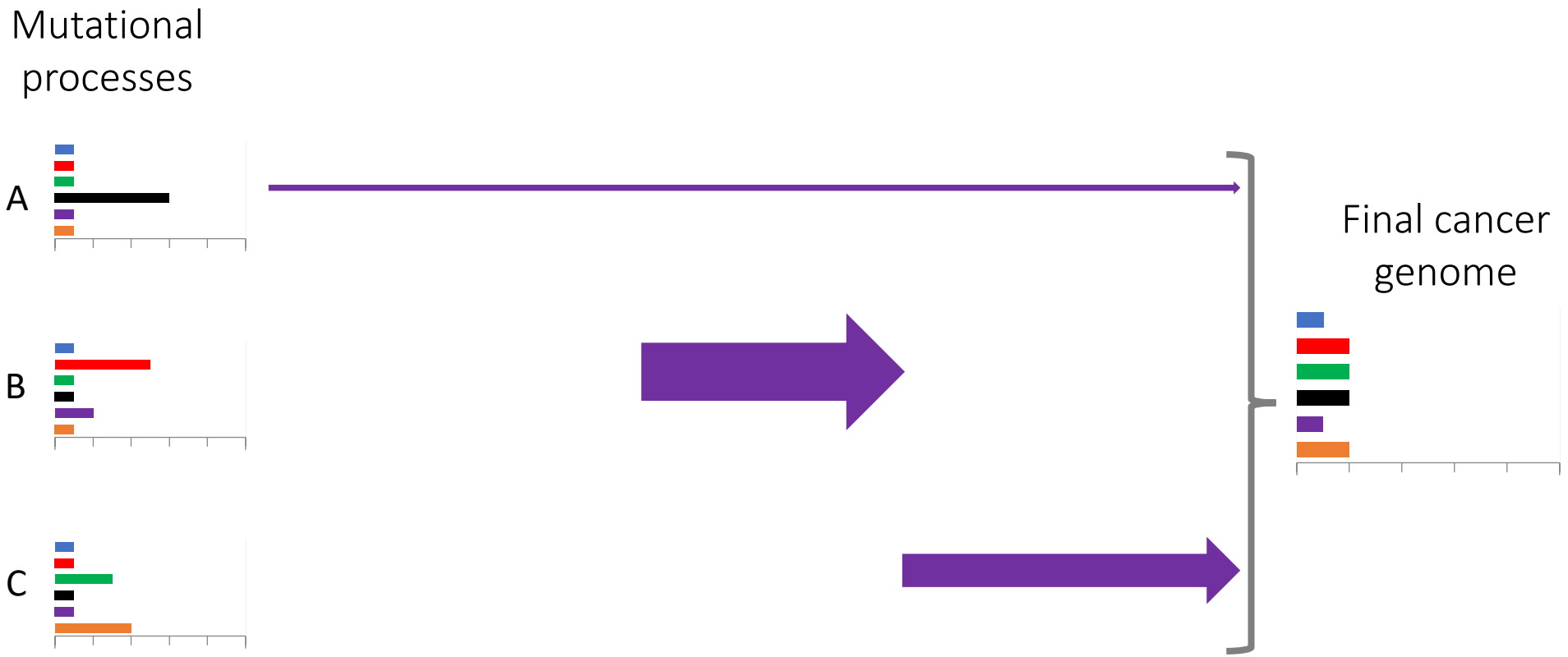

Mutational signatures can be determined based on mutational profiles across a set of individuals

Nik-Zainal *et al.* 2012 Cell

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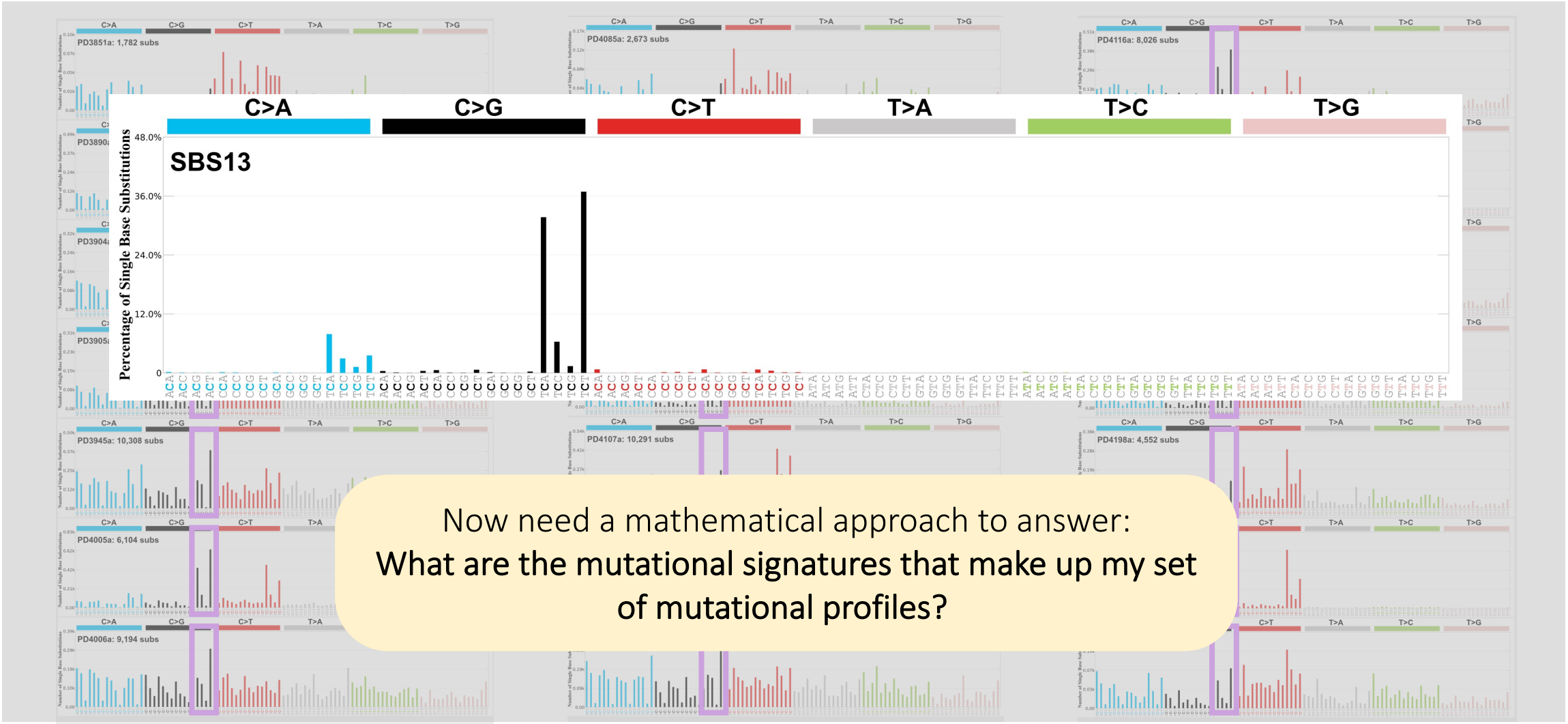
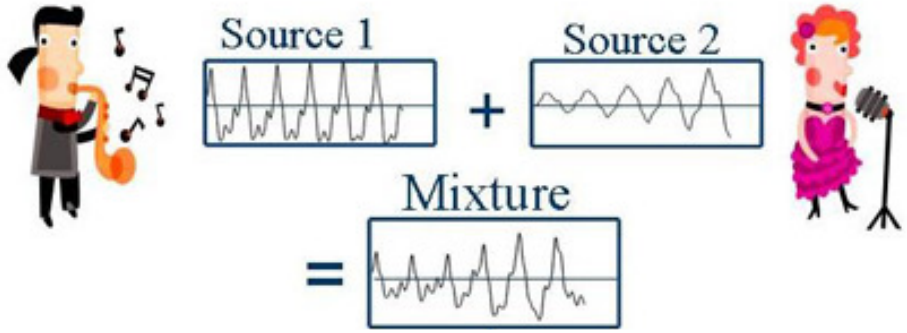


Now need a mathematical approach to answer:
What are the mutational signatures that make up my set of mutational profiles?

Mathematical models allows the *un-mixing* and the extraction of mutational signatures

Blind signal separation problem



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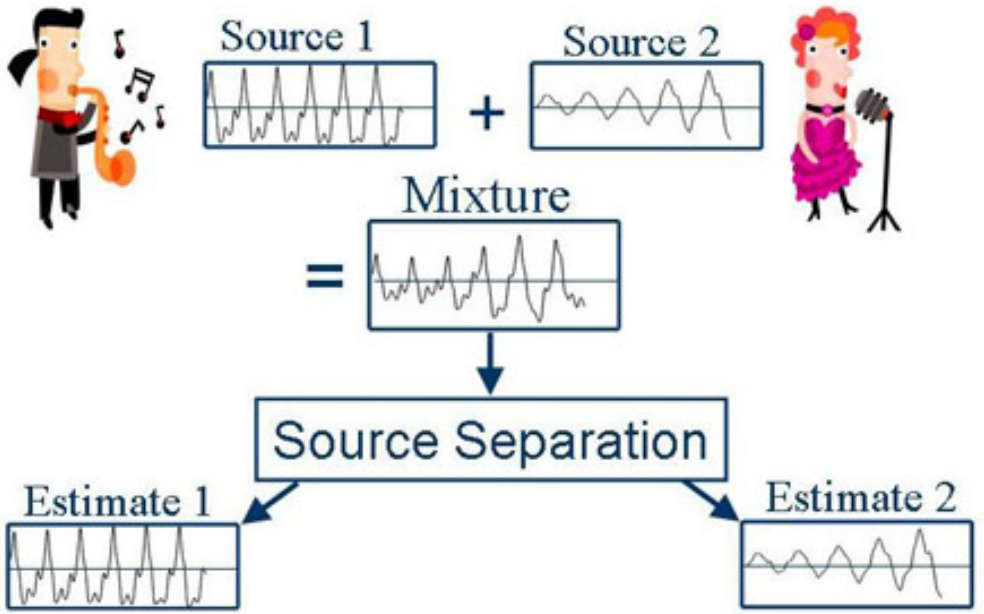

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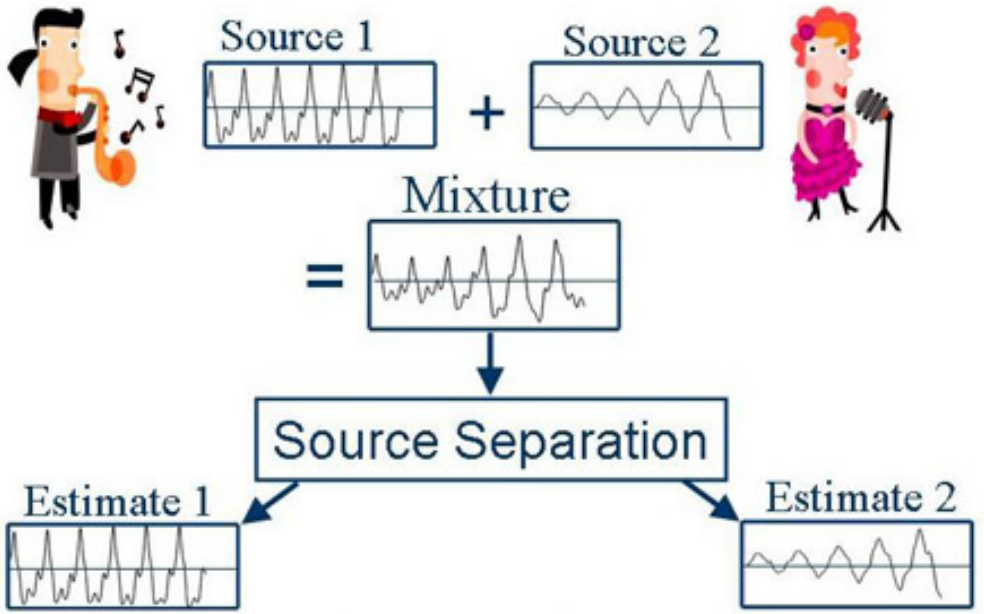


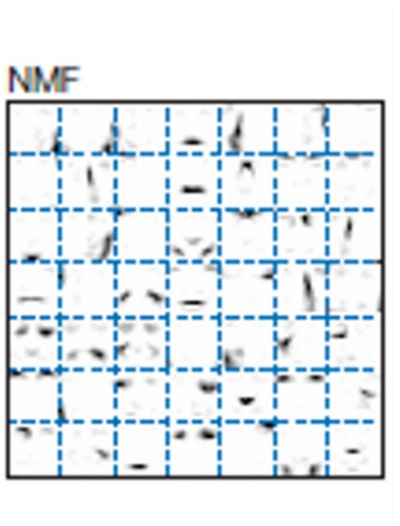
Non-negative matrix factorization

Mathematical models allows the *un-mixing* and the extraction of mutational signatures

Learning the parts of objects by non-negative matrix factorization

Daniel D. Lee* & H. Sebastian Seung*†

* *Bell Laboratories, Lucent Technologies, Murray Hill, New Jersey 07974, USA*
† *Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*

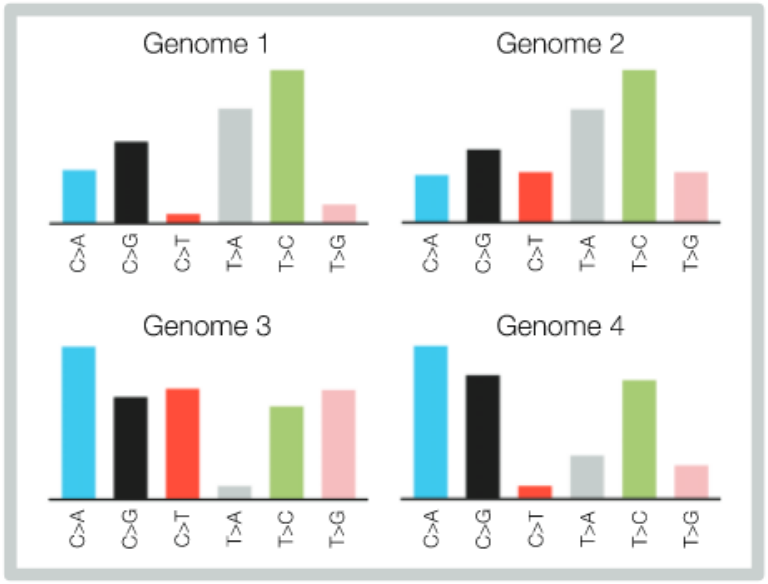


Mut. contexts × Samples ← $\mathbf{M} \approx \mathbf{S} \times \mathbf{A}$ → Signatures × Samples

Mut. contexts × Signatures

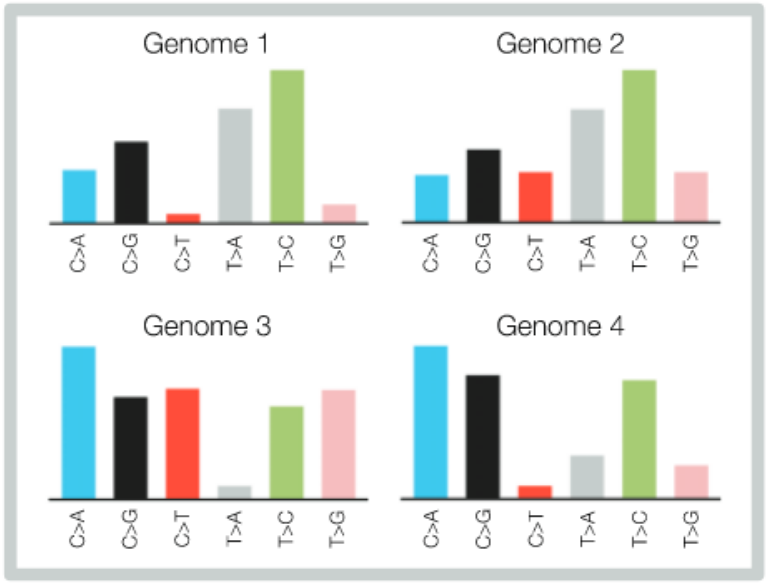
Lee & Seung 1999 Nature

Mathematical models allows the *un-mixing* and the extraction of mutational signatures

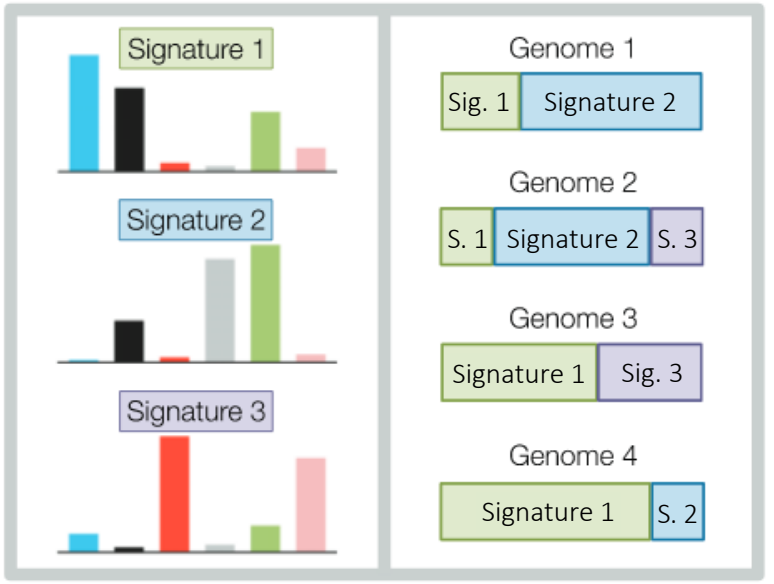


Large number of samples

Mathematical models allows the *un-mixing* and the extraction of mutational signatures

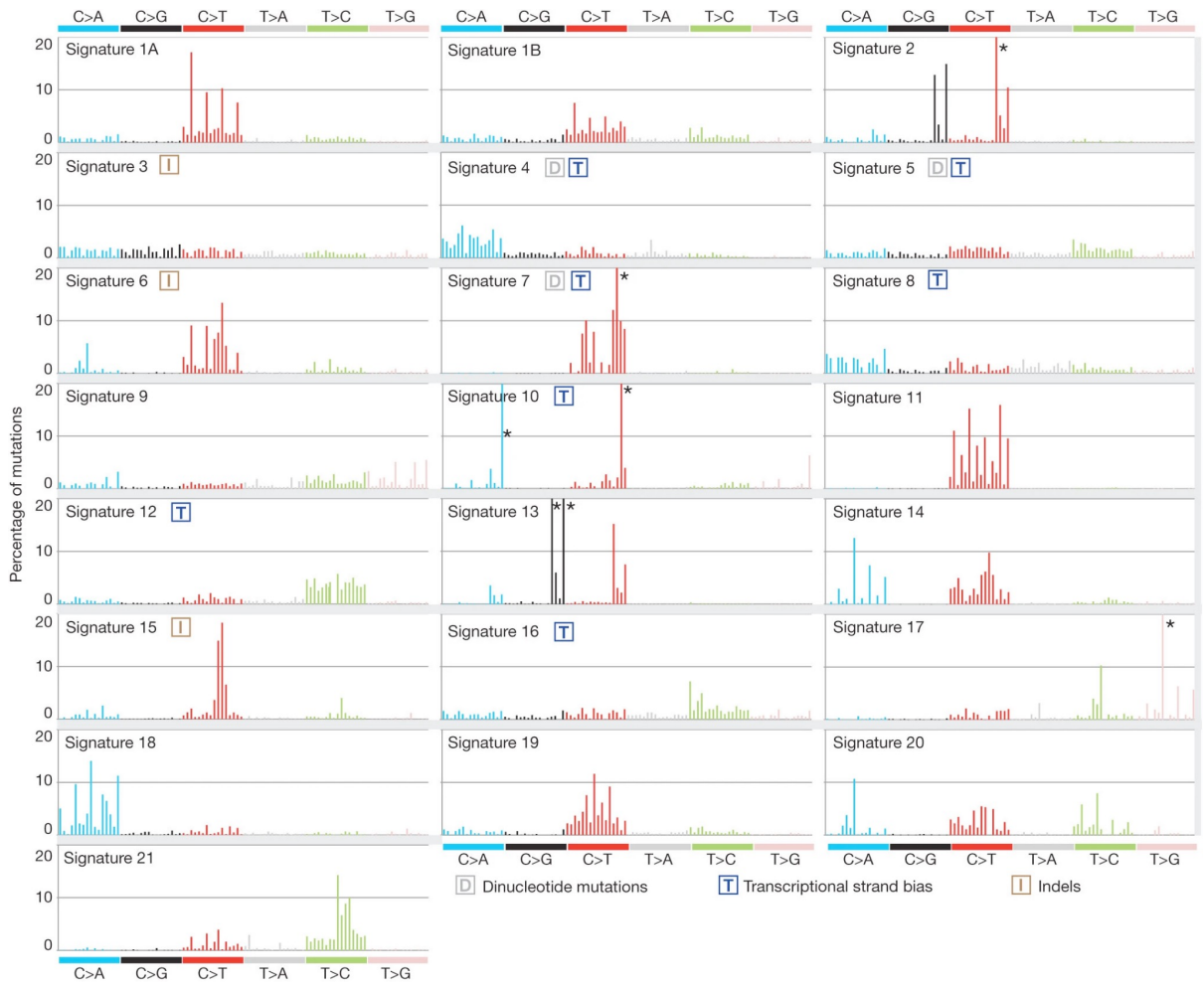


Large number of samples



Set of consensus signatures

Reference mutational signatures have been extracted from thousands of samples



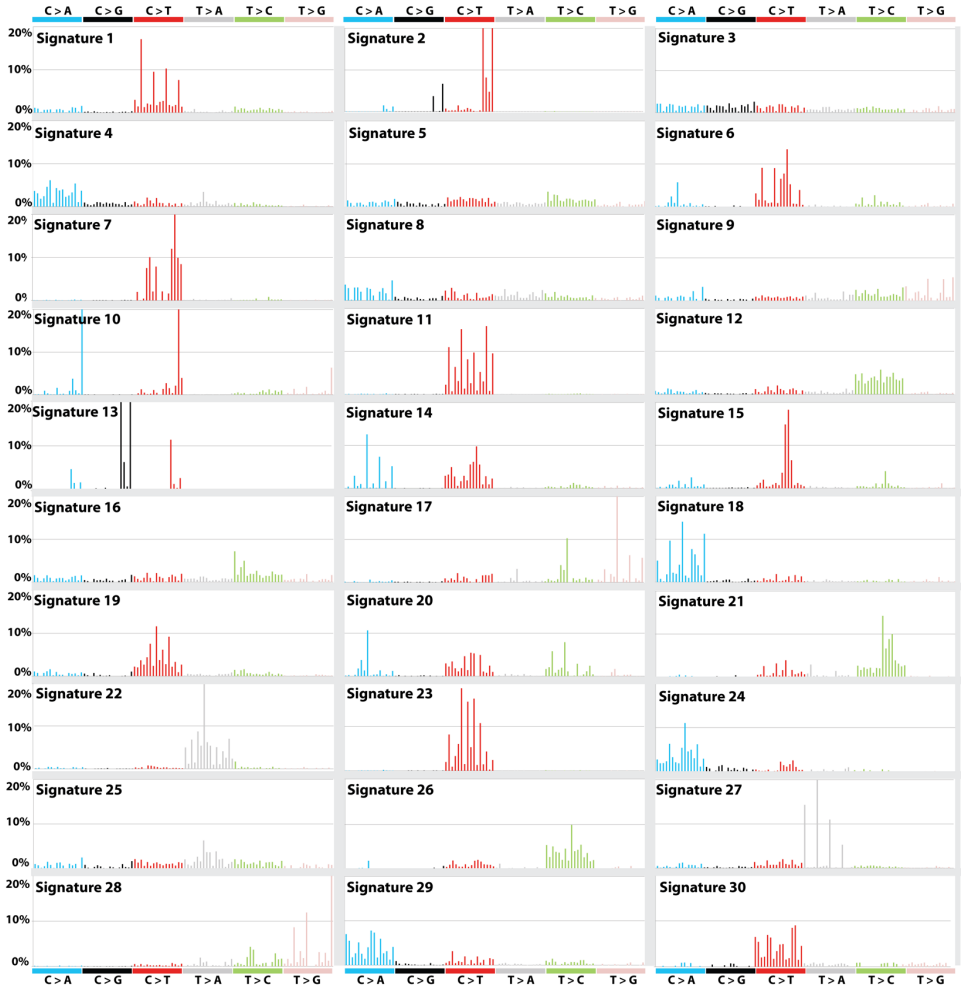
TCGA

v1 (August 2013)

- 21 SBS signatures

Alexandrov *et al.* 2013 Nature

Reference mutational signatures have been extracted from thousands of samples



TCGA

v1 (August 2013)

- 21 SBS signatures

v2 (March 2015)

- 30 SBS signatures

Reference mutational signatures have been extracted from thousands of samples

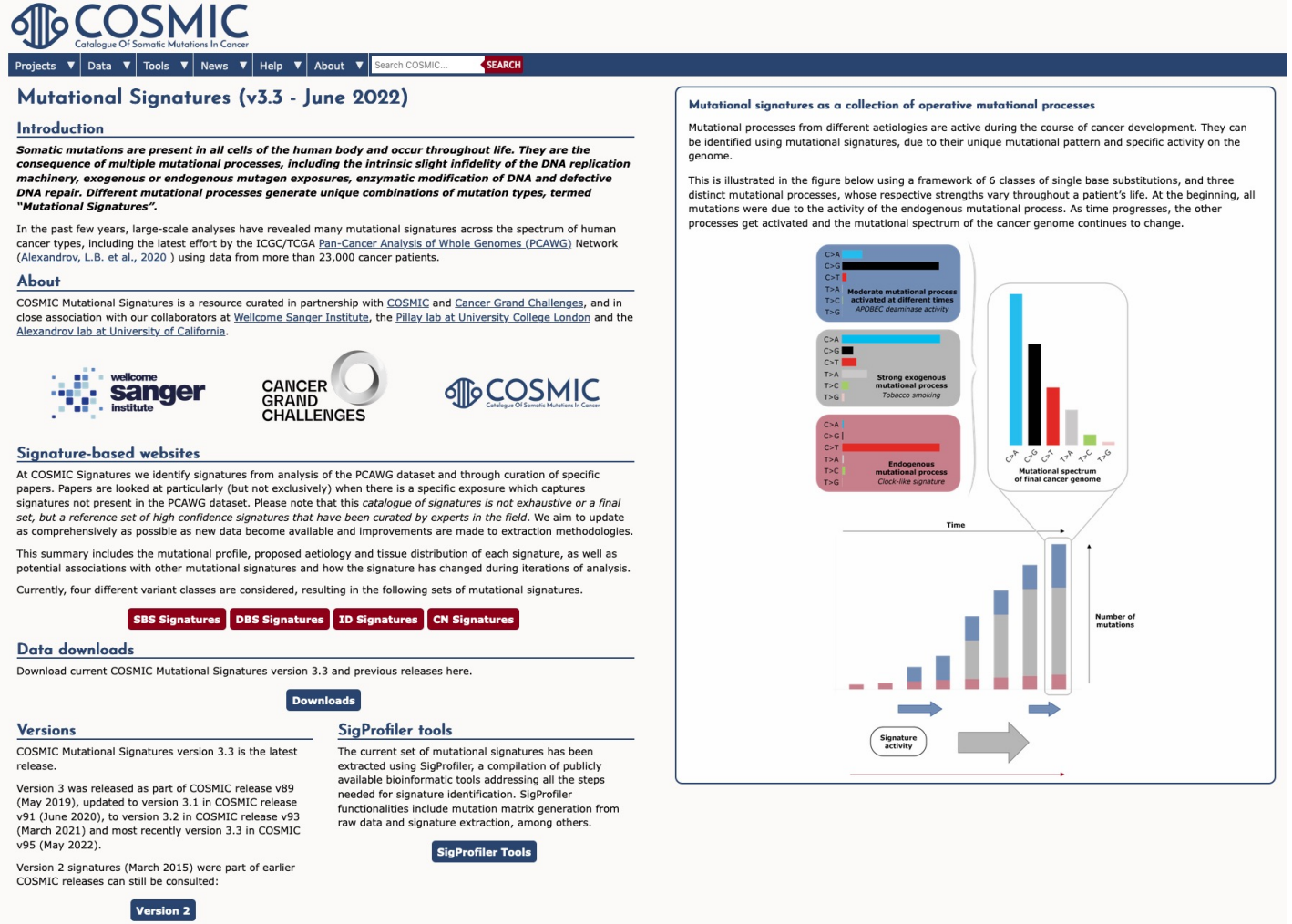
PCAWG
PanCancer Analysis of WHOLE GENOMES

v3 (May 2019)

- 67 SBS signatures
- 11 DBS signatures
- 17 ID signatures

Alexandrov *et al.* 2020 Nature

Reference mutational signatures have been extracted from thousands of samples



COSMIC
Catalogue Of Somatic Mutations In Cancer

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Mutational Signatures (v3.3 - June 2022)

Introduction

Somatic mutations are present in all cells of the human body and occur throughout life. They are the consequence of multiple mutational processes, including the intrinsic slight infidelity of the DNA replication machinery, exogenous or endogenous mutagen exposures, enzymatic modification of DNA and defective DNA repair. Different mutational processes generate unique combinations of mutation types, termed "Mutational Signatures".

In the past few years, large-scale analyses have revealed many mutational signatures across the spectrum of human cancer types, including the latest effort by the ICGC/TCGA Pan-Cancer Analysis of Whole Genomes (PCAWG) Network (Alexandrov, L.B. et al., 2020) using data from more than 23,000 cancer patients.

About

COSMIC Mutational Signatures is a resource curated in partnership with COSMIC and Cancer Grand Challenges, and in close association with our collaborators at Wellcome Sanger Institute, the Pillay lab at University College London and the Alexandrov lab at University of California.

wellcome sanger institute | CANCER GRAND CHALLENGES | COSMIC

Signature-based websites

At COSMIC Signatures we identify signatures from analysis of the PCAWG dataset and through curation of specific papers. Papers are looked at particularly (but not exclusively) when there is a specific exposure which captures signatures not present in the PCAWG dataset. Please note that this *catalogue of signatures is not exhaustive or a final set, but a reference set of high confidence signatures that have been curated by experts in the field*. We aim to update as comprehensively as possible as new data become available and improvements are made to extraction methodologies.

This summary includes the mutational profile, proposed aetiology and tissue distribution of each signature, as well as potential associations with other mutational signatures and how the signature has changed during iterations of analysis.

Currently, four different variant classes are considered, resulting in the following sets of mutational signatures.

SBS Signatures | DBS Signatures | ID Signatures | CN Signatures

Data downloads

Download current COSMIC Mutational Signatures version 3.3 and previous releases here.

Downloads

Versions

COSMIC Mutational Signatures version 3.3 is the latest release.

Version 3 was released as part of COSMIC release v89 (May 2019), updated to version 3.1 in COSMIC release v91 (June 2020), to version 3.2 in COSMIC release v93 (March 2021) and most recently version 3.3 in COSMIC v95 (May 2022).

Version 2 signatures (March 2015) were part of earlier COSMIC releases can still be consulted:

Version 2

SigProfiler tools

The current set of mutational signatures has been extracted using SigProfiler, a compilation of publicly available bioinformatic tools addressing all the steps needed for signature identification. SigProfiler functionalities include mutation matrix generation from raw data and signature extraction, among others.

SigProfiler Tools

Mutational signatures as a collection of operative mutational processes

Mutational processes from different aetiologies are active during the course of cancer development. They can be identified using mutational signatures, due to their unique mutational pattern and specific activity on the genome.

This is illustrated in the figure below using a framework of 6 classes of single base substitutions, and three distinct mutational processes, whose respective strengths vary throughout a patient's life. At the beginning, all mutations were due to the activity of the endogenous mutational process. As time progresses, the other processes get activated and the mutational spectrum of the cancer genome continues to change.

COSMIC
Catalogue Of Somatic Mutations In Cancer

Current set (v3.3)

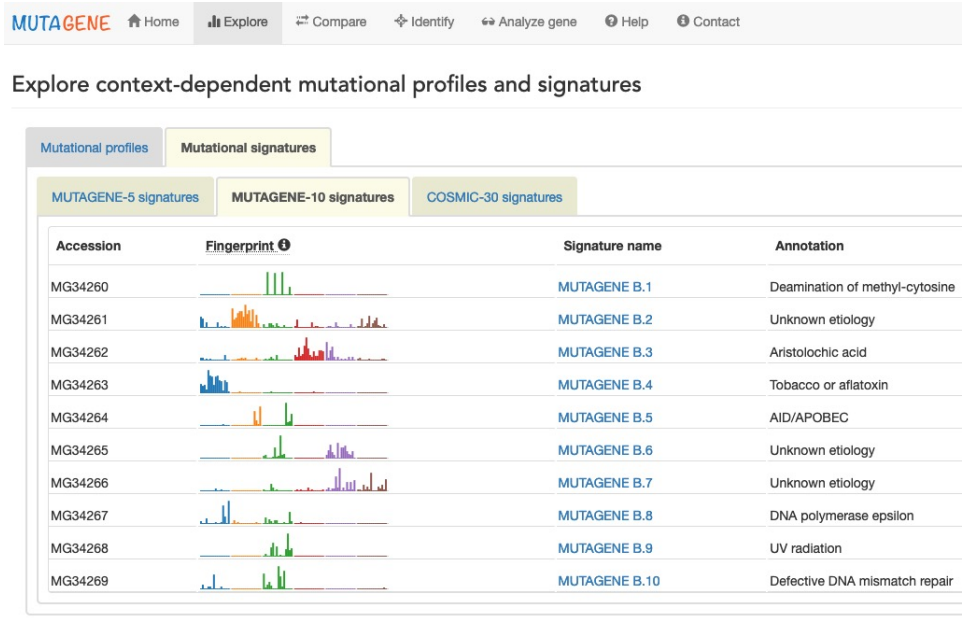
- 78 SBS signatures
- 11 DBS signatures
- 18 ID signatures
- 21 CN signatures

https://cancer.sanger.ac.uk/signatures/

Reference mutational signatures have been extracted from thousands of samples

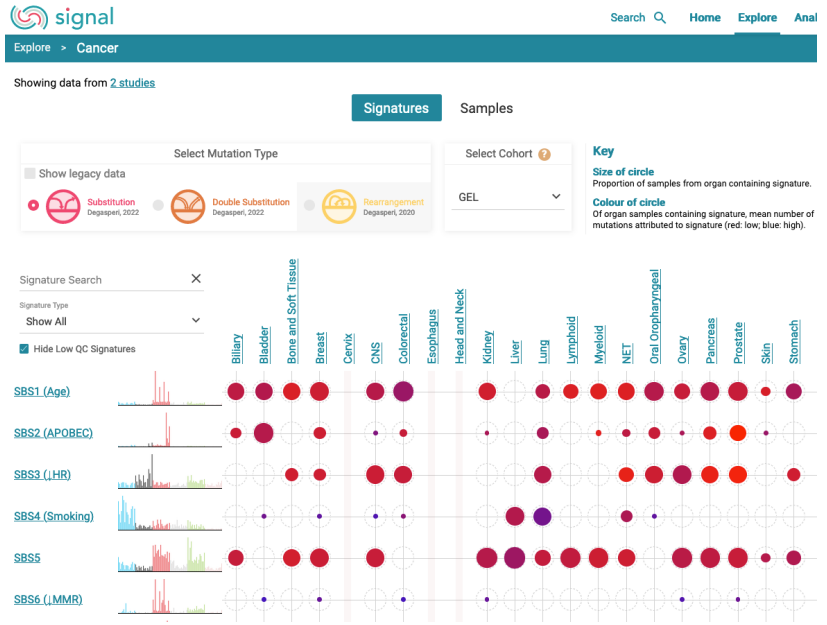
Other reference databases exist that include different variant classes

MUTAGENE



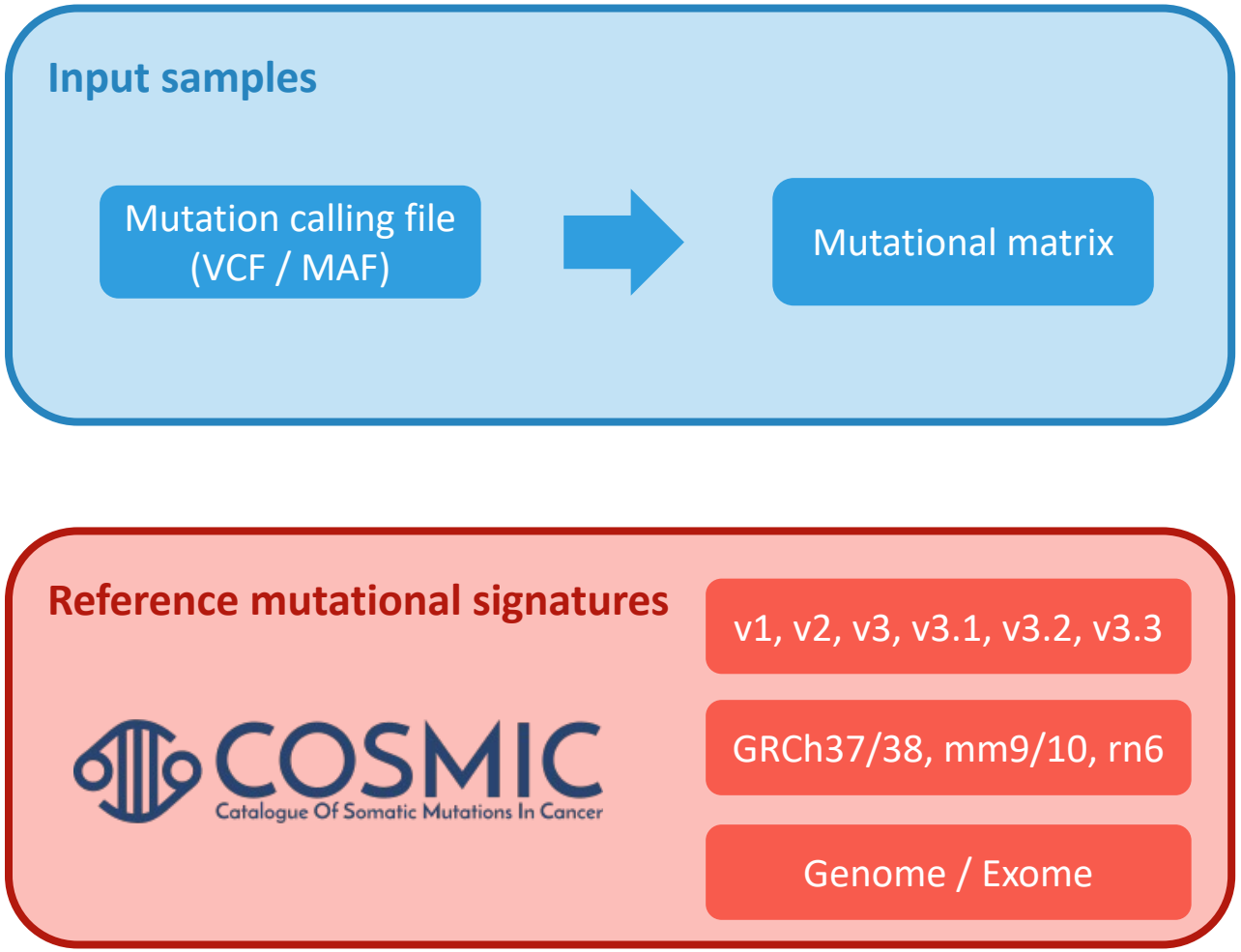
https://www.ncbi.nlm.nih.gov/research/mutagene/

signal



https://signal.mutationalsignatures.com/

Overview of mutational signature assignment analysis



Overview of mutational signature assignment analysis

Input samples

Mutation calling file (VCF / MAF) → Mutational matrix

$$\underset{t\,x\,n}{\mathbf{M}} = \underset{t\,x\,k}{\mathbf{S}} \times \underset{k\,x\,n}{\mathbf{A}}$$

Reference mutational signatures

COSMIC
Catalogue Of Somatic Mutations In Cancer

- v1, v2, v3, v3.1, v3.2, v3.3
- GRCh37/38, mm9/10, rn6
- Genome / Exome

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$$\underset{t\,x\,n}{\mathbf{M}} = \underset{t\,x\,k}{\mathbf{S}} \times \underset{k\,x\,n}{\mathbf{A}}$$

t mutational contexts
n samples
k signatures

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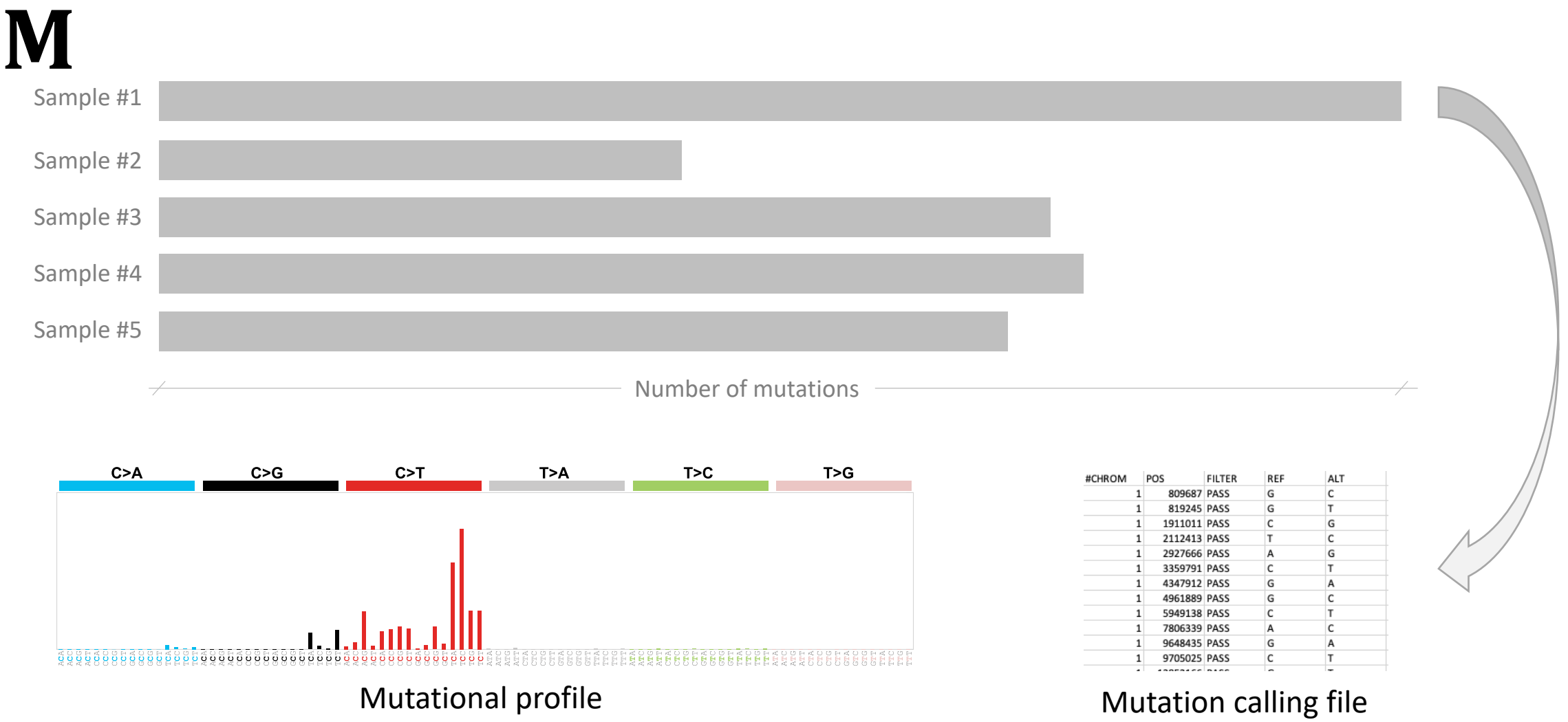
Assigning reference signatures to individual samples



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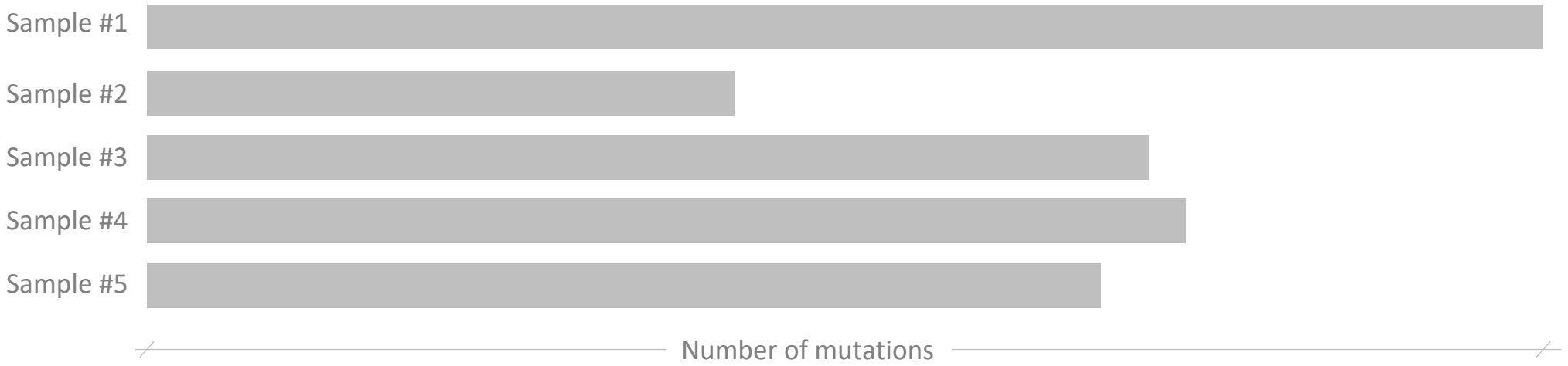
1	819245	PASS	G	T
1	1911011	PASS	C	G
1	2112413	PASS	T	C
1	2927666	PASS	A	G
1	3359791	PASS	C	T
1	4347912	PASS	G	A
1	4961889	PASS	G	C
1	5949138	PASS	C	T
1	7806339	PASS	A	C
1	9648435	PASS	G	A
1	9705025	PASS	C	T

Mutational profile

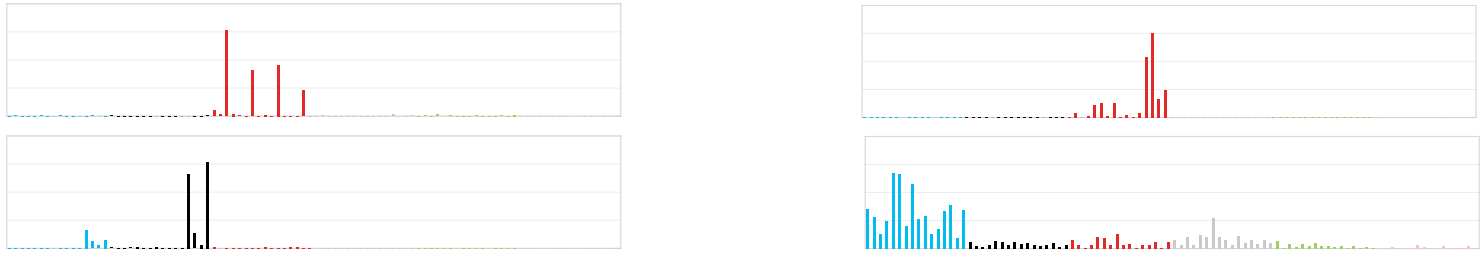
Mutation calling file

Assigning reference signatures to individual samples

M

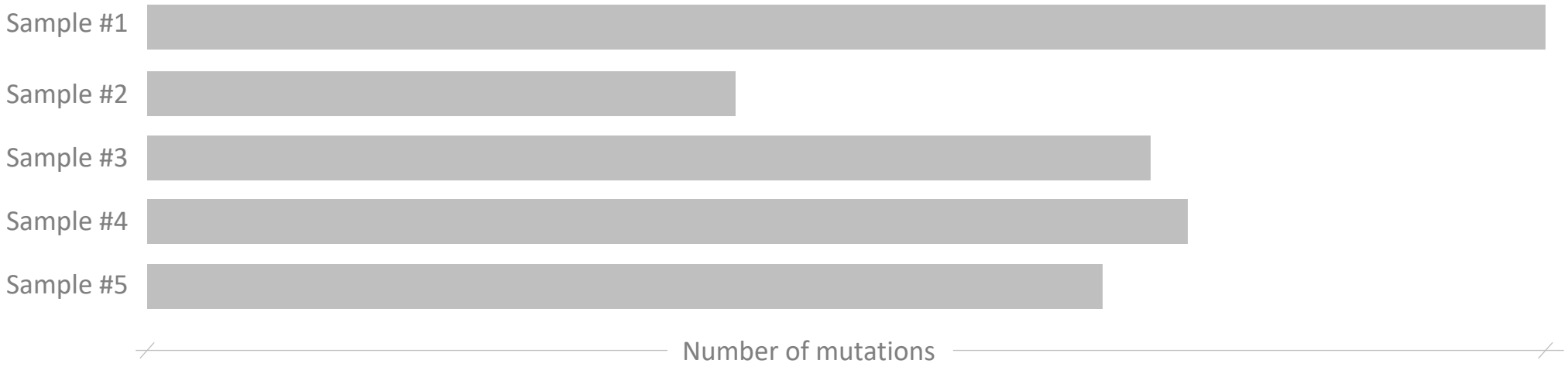


S

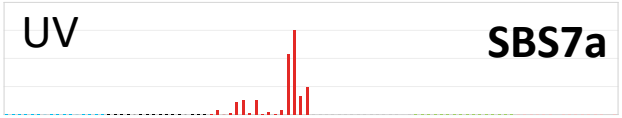


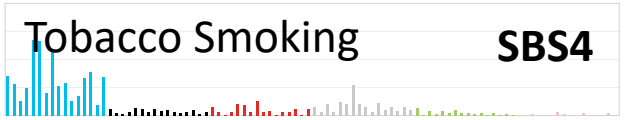
Assigning reference signatures to individual samples

M



S

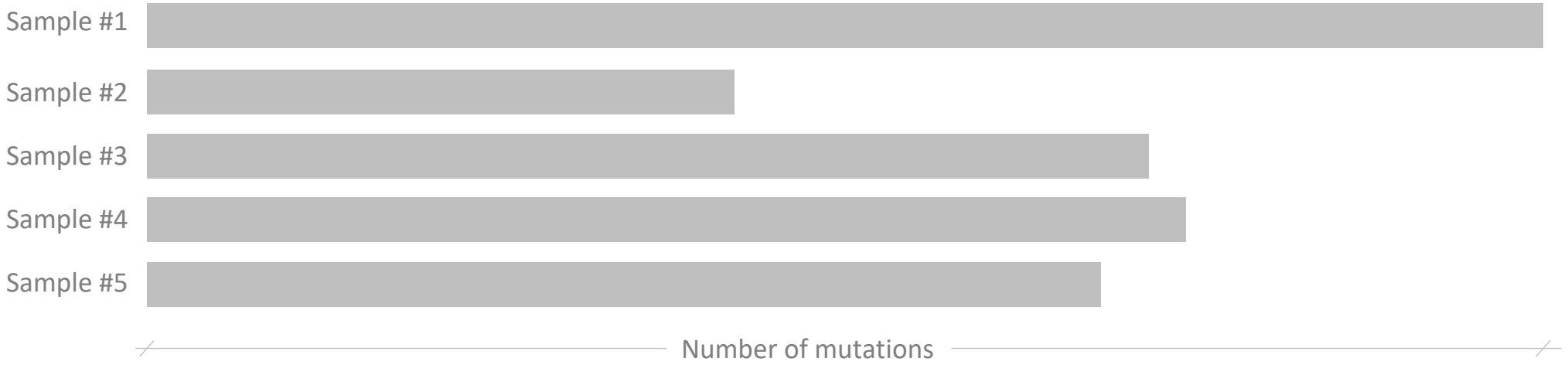




COSMIC
Catalogue Of Somatic Mutations In Cancer

Assigning reference signatures to individual samples

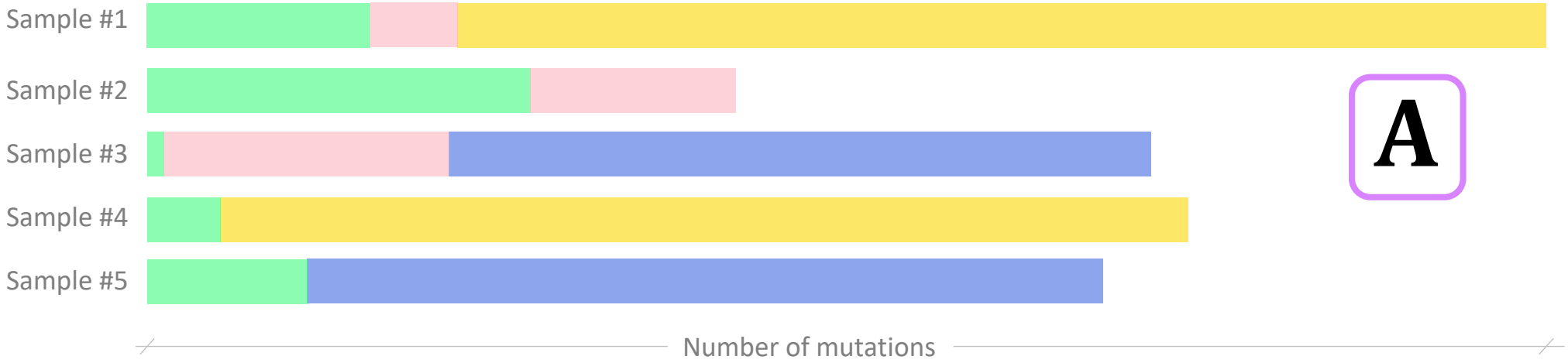
M



S

Assigning reference signatures to individual samples

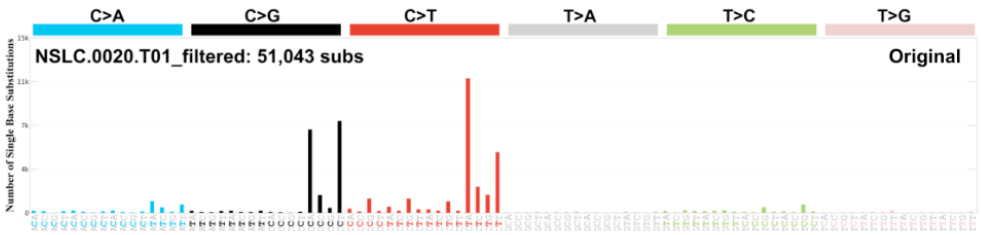
M



A

S

Assigning reference signatures to individual samples



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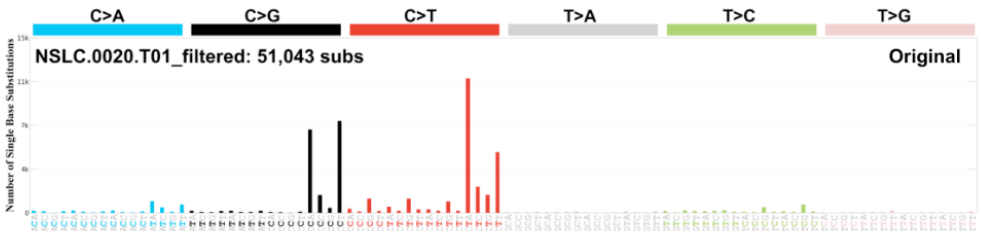

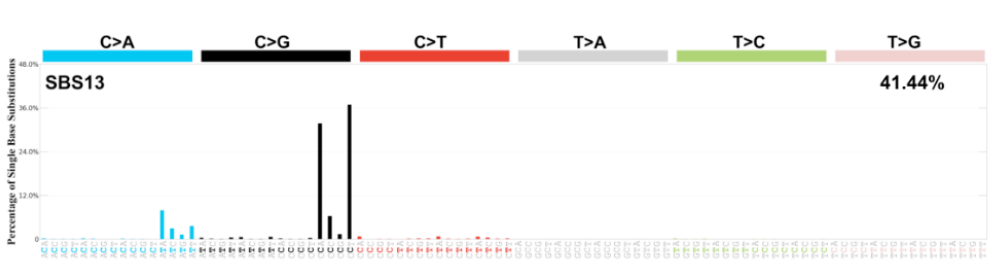

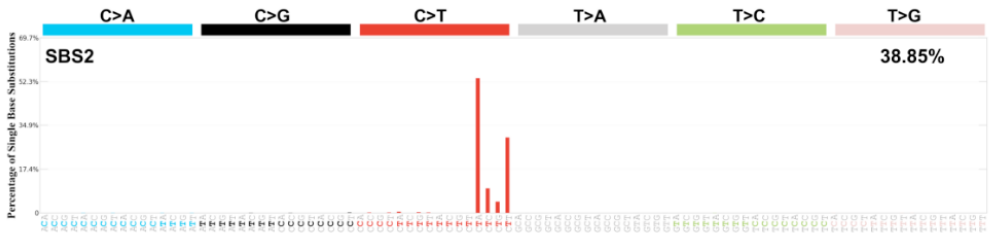

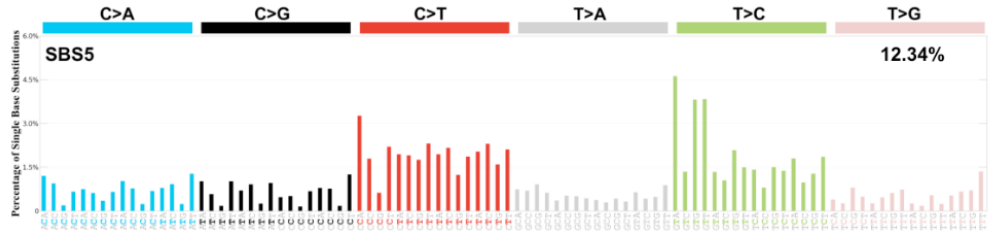

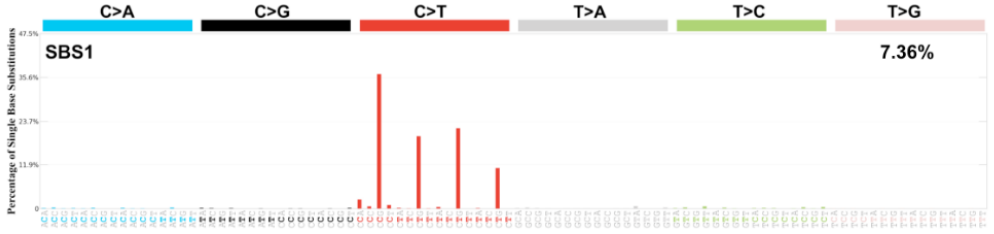

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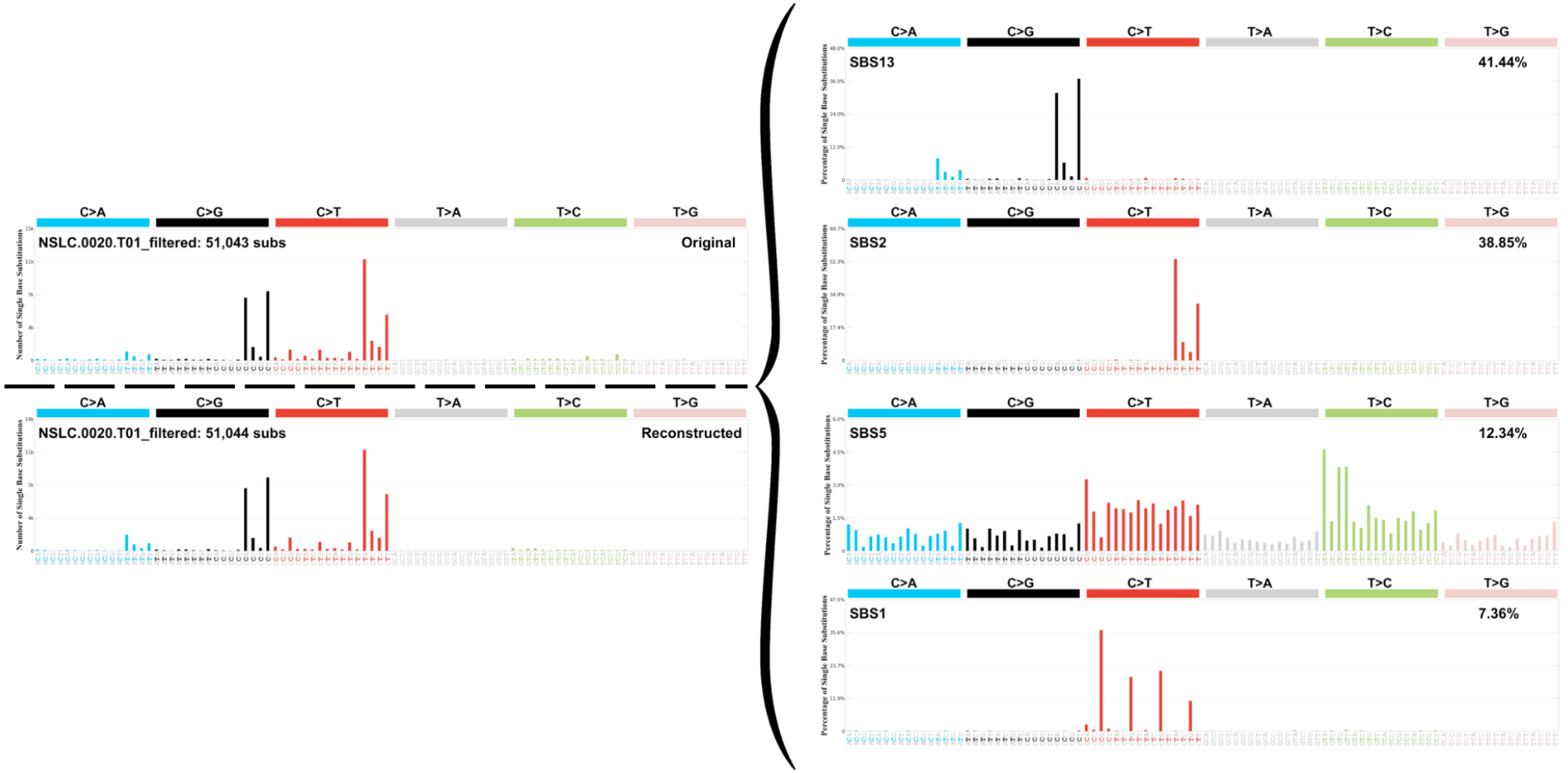

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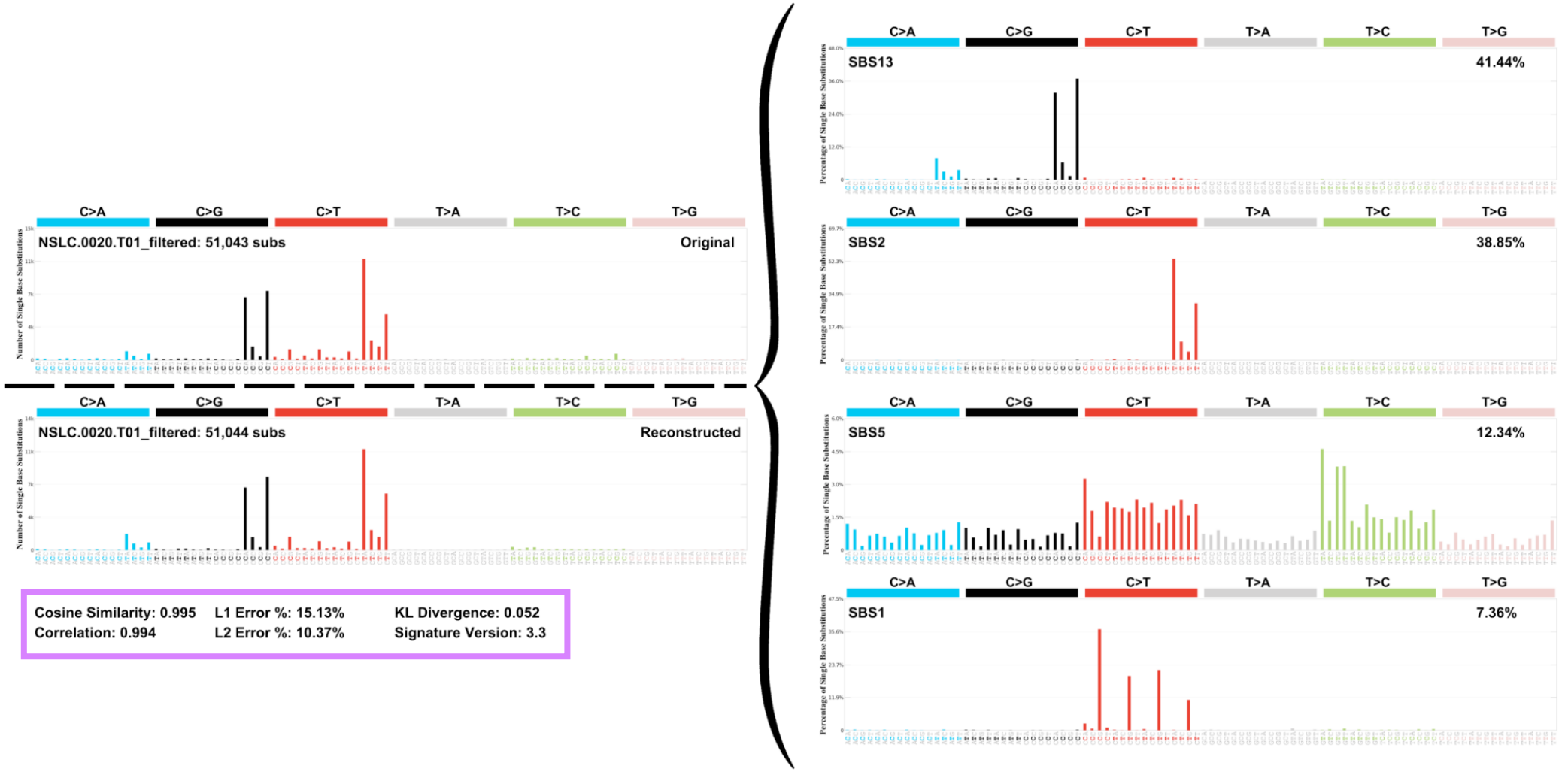


Mutational signature analysis marked a turning point in cancer diagnosis, prognosis and treatment

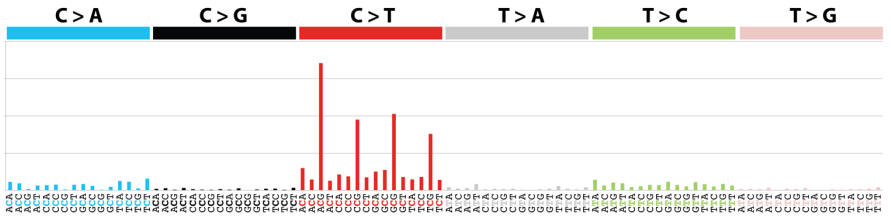
CellPress

Cancer Cell
Article

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

Judith E. Grolleman,[1,36] Richarda M. de Voer,[1,36,38,*] Fadwa A. Elsayed,[2,36] Maartje Nielsen,[3,36] Robbert D.A. Weren,[1,36] Claire Palles,[4] Marjolijn J.L. Ligtenberg,[1,5] Janet R. Vos,[6] Sanne W. ten Broeke,[3] Noel F.C.C. de Miranda,[2] Renske A. Kuiper,[1] Eveline J. Kamping,[1] Erik A.M. Jansen,[1] M. Elisa Vink-Börger,[5] Isabell Popp,[7] Alois Lang,[8] Isabel Spier,[9,10] Robert Hüneburg,[10,11] Paul A. James,[12] Na Li,[13,14] Marija Staninova,[15] Helen Lindsay,[16]

nature medicine



HRDetect is a predictor of *BRCA1* and *BRCA2* deficiency based on mutational signatures

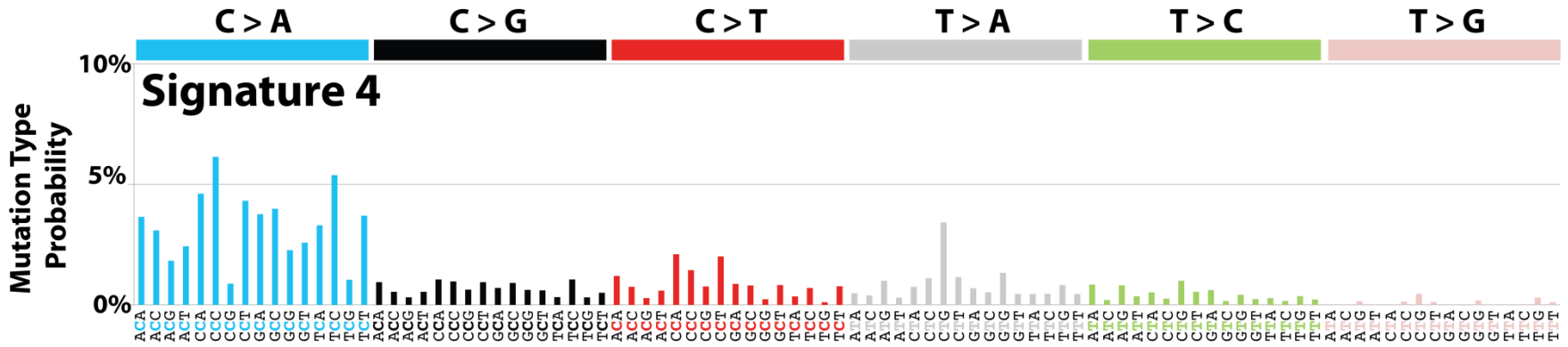
Helen Davies[1,32], Dominik Glodzik[1,32], Sandro Morganella[1], Lucy R Yates[1,2], Johan Staaf[3], Xueqing Zou[1], Manasa Ramakrishna[1,4], Sancha Martin[1], Sandrine Boyault[5], Anieta M Sieuwerts[6], Peter T Simpson[7], Tari A King[8], Keiran Raine[1], Jorunn E Eyfjord[9], Gu Kong[10], Åke Borg[3], Ewan Birney[11], Hendrik G Stunnenberg[12], Marc J van de Vijver[13], Anne-Lise Børresen-Dale[14,15], John W M Martens[6], Paul N Span[16,17], Sunil R Lakhani[7,18], Anne Vincent-Salomon[19,20], Christos Sotiriou[21], Andrew Tutt[22,23], Alastair M Thompson[24], Steven Van Laere[25,26], Andrea L Richardson[27,28], Alain Viari[29,30], Peter J Campbell[1], Michael R Stratton[1] & Serena Nik-Zainal[1,31]

Summary

- Different mutational processes generate somatic mutations, including endogenous and exogenous sources
- The pattern of mutations imprinted by a particular mutational process is known as mutational signature
- Reference mutational signatures have been identified and deposited in COSMIC after the analysis of thousands of cancer samples
- Leveraging these reference signatures, the contributions of the different mutational processes to a given tumor can be quantified
- Mutational signatures can be used clinically as biomarkers for cancer prevention, prognosis and treatment

How do you know mutational signature etiologies?

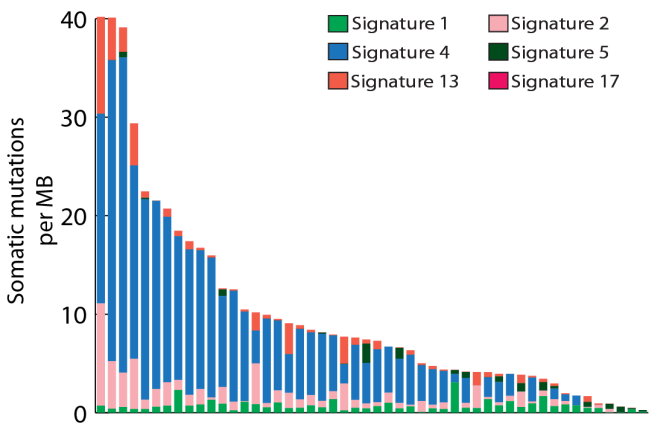
Signature SBS4 is likely due to tobacco smoking



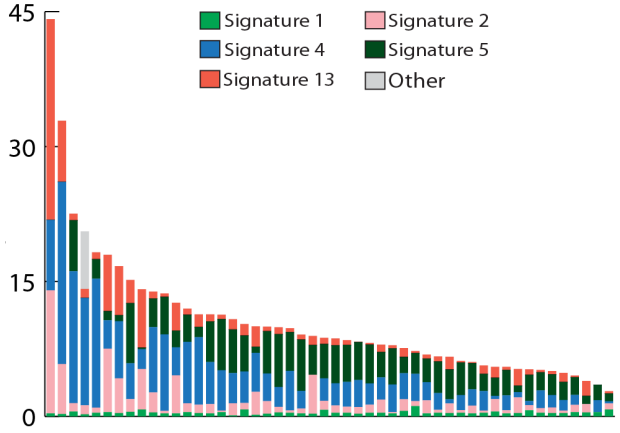
Contributions of mutational signatures to smoking induced and non-smoking induced cancer types

Smoking induced cancer types

Lung adenocarcinoma

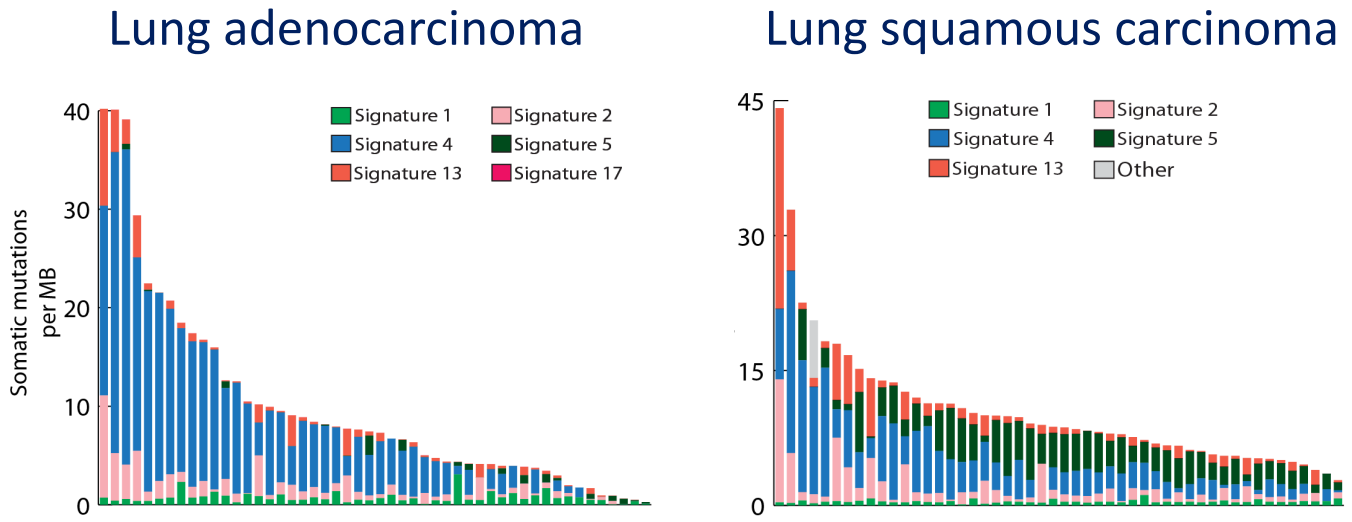


Lung squamous carcinoma

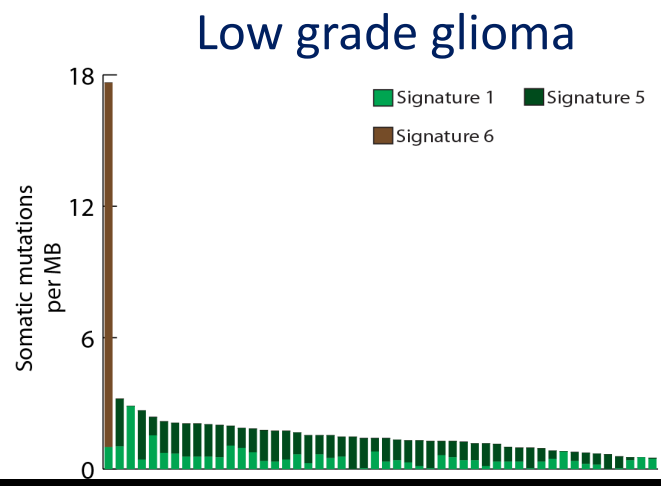


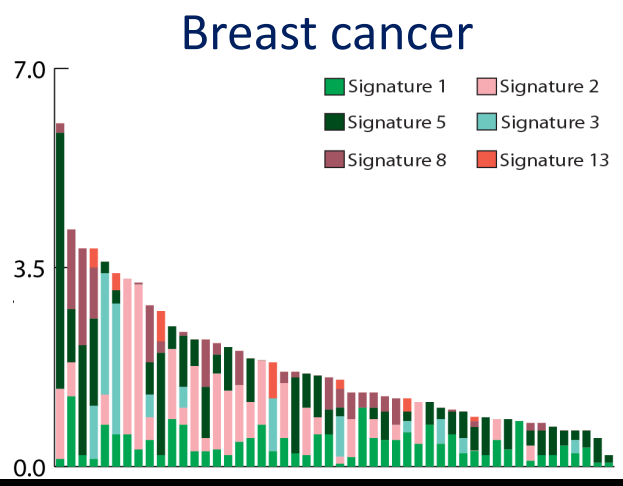
Contributions of mutational signatures to smoking induced and non-smoking induced cancer types

Smoking induced cancer types



Non-smoking induced cancer types

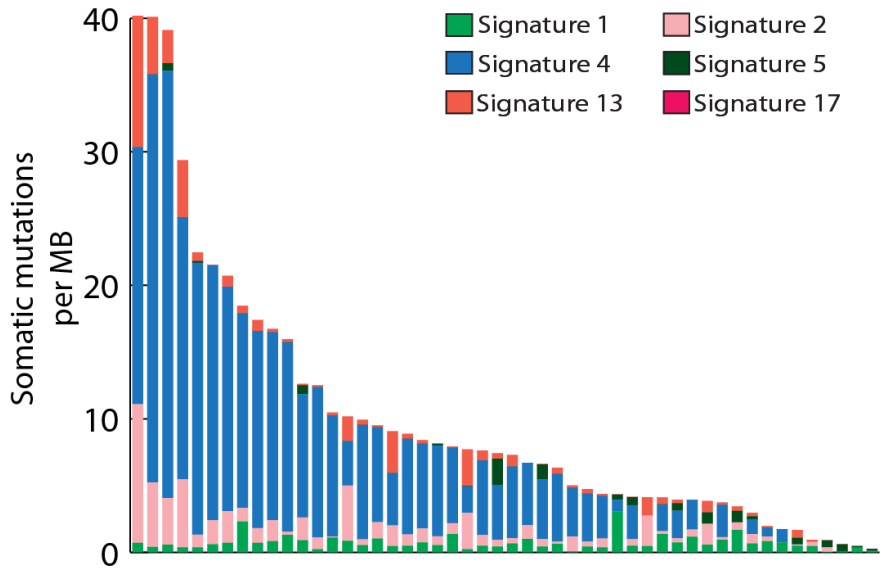




Contributions of mutational signatures to lung adenocarcinomas

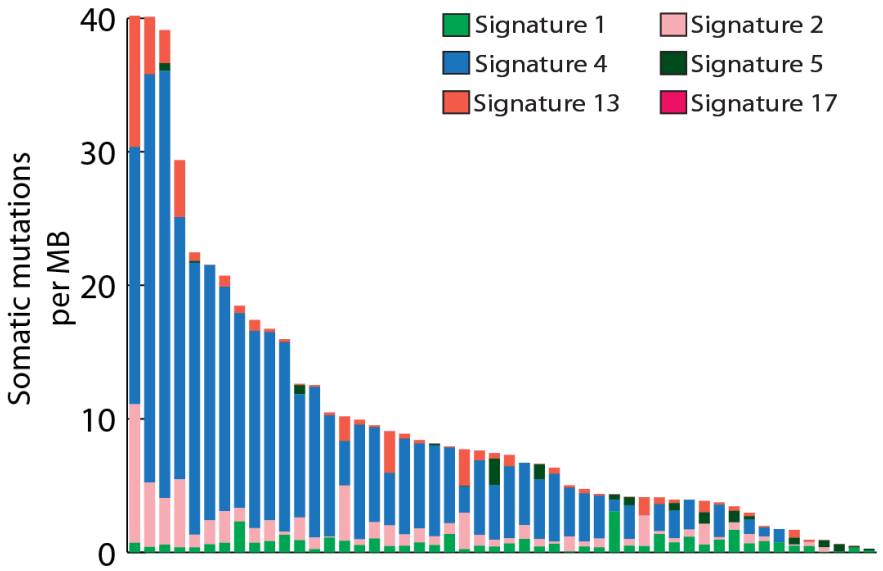
Contributions of mutational signatures to lung adenocarcinomas

Tobacco smokers

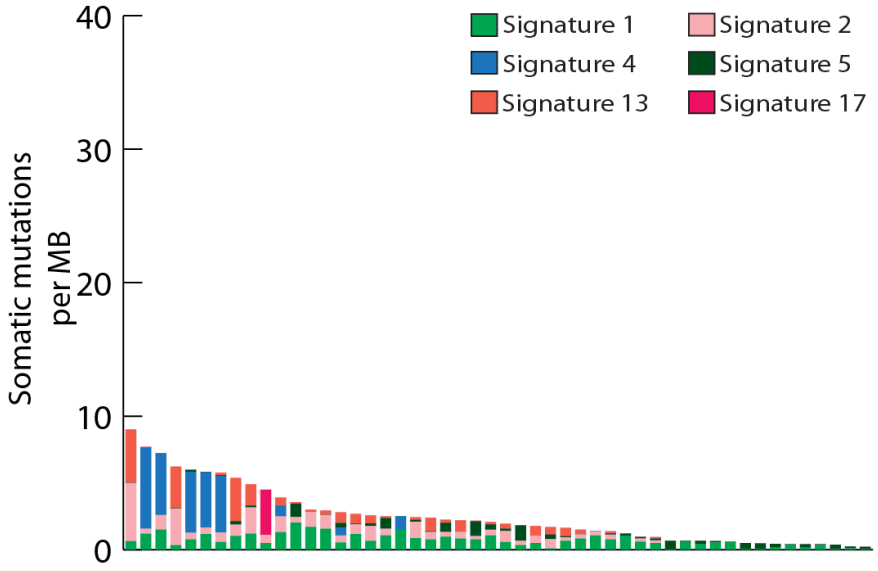


Contributions of mutational signatures to lung adenocarcinomas

Tobacco smokers

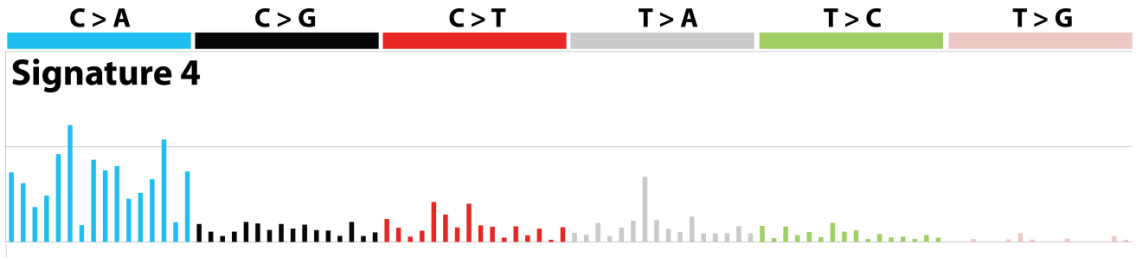


Life-long non-smokers



The mutational signature of in vitro benzo[a]pyrene exposure is similar to signature 4

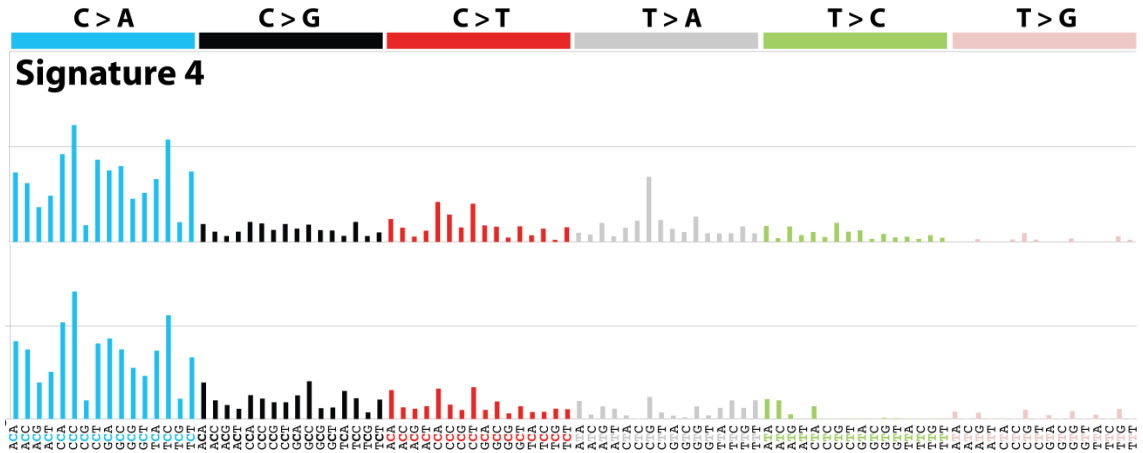
Signature 4 extracted from human cancers



The mutational signature of in vitro benzo[a]pyrene exposure is similar to signature 4

Signature 4 extracted from human cancers

Signature of benzo[*a*]pyrene exposure *in vitro*



Evidence for the aetiology of signature 4

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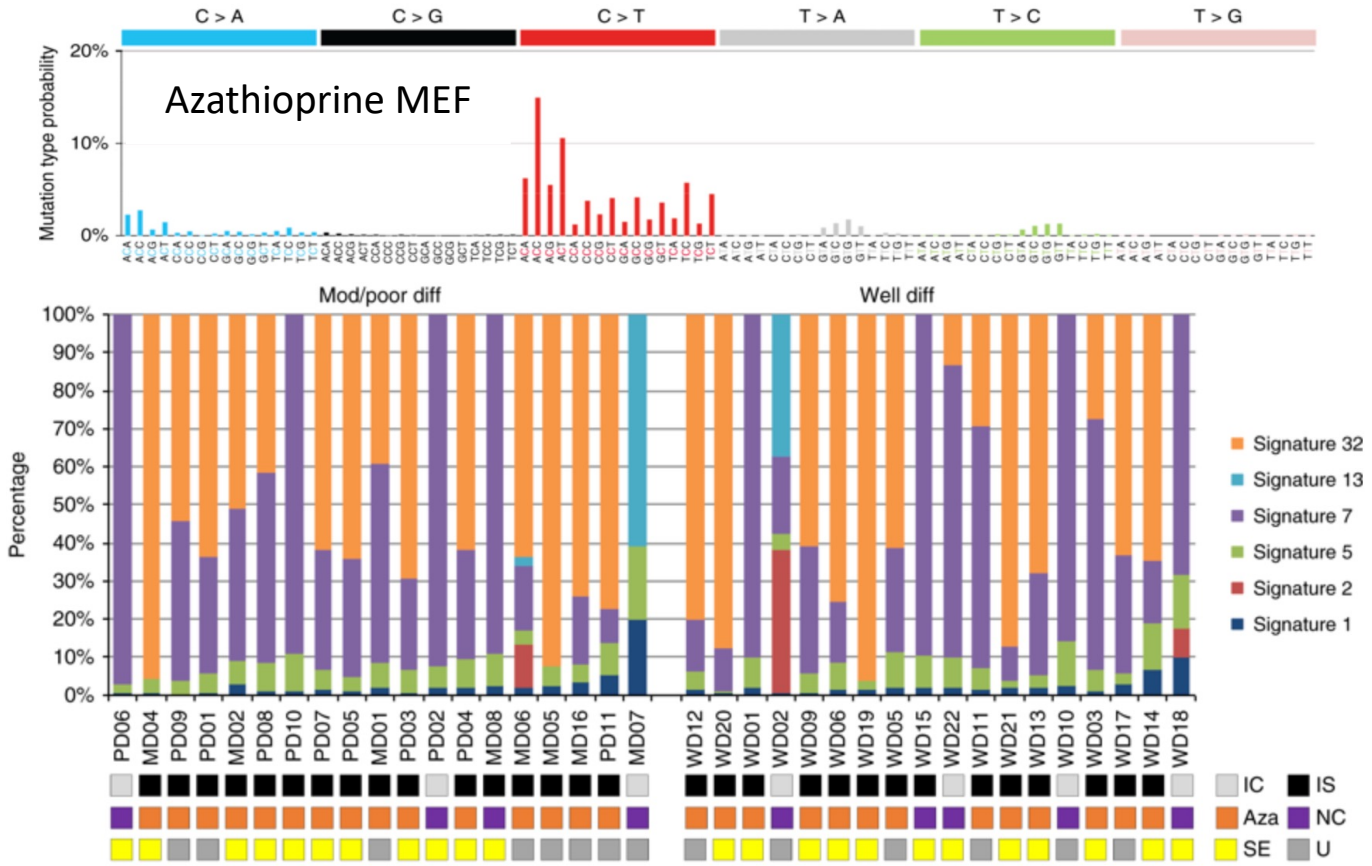
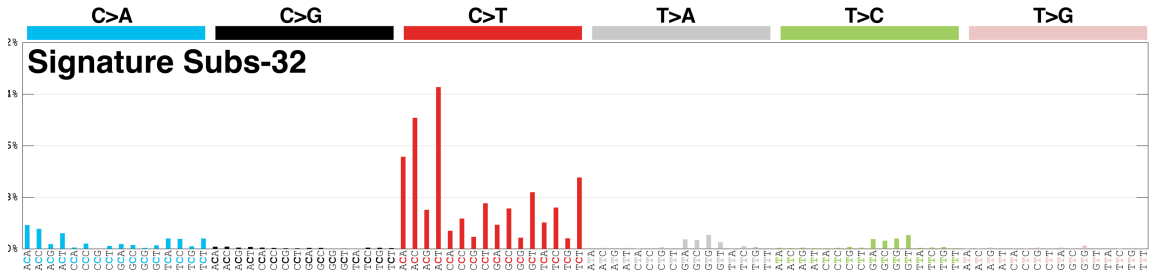
The pattern of signature 4 matches *in vitro* experimental results in which cells were exposed to known tobacco carcinogens

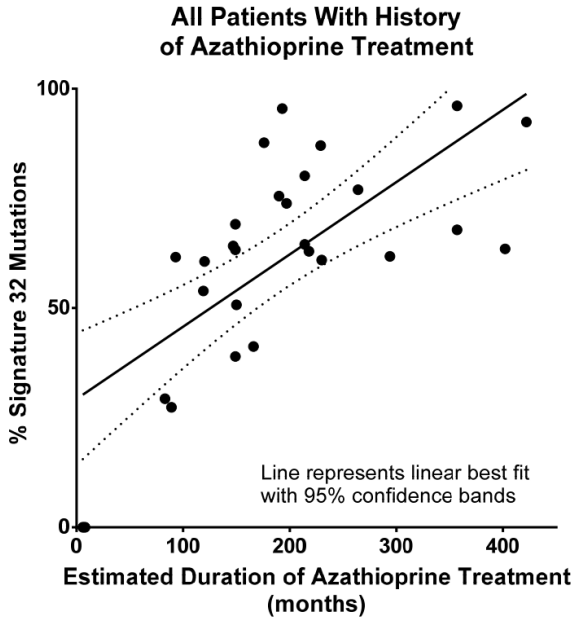
Clinical examples

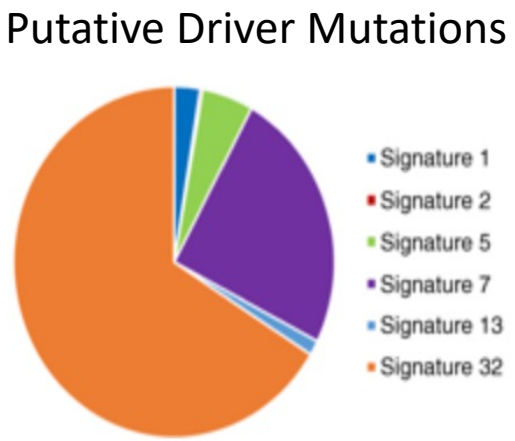
(Somewhat) unexpected carcinogens: Azathioprine

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.



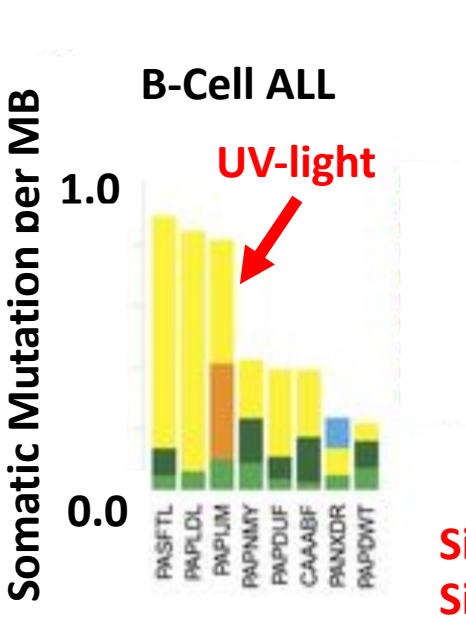


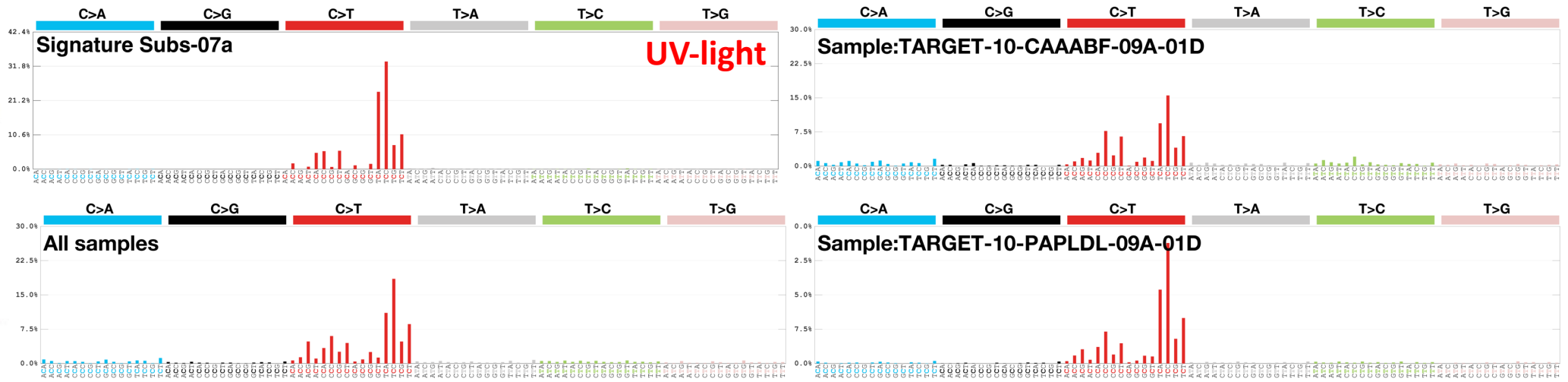




Inman *et al.* 2018 Nature Communications

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

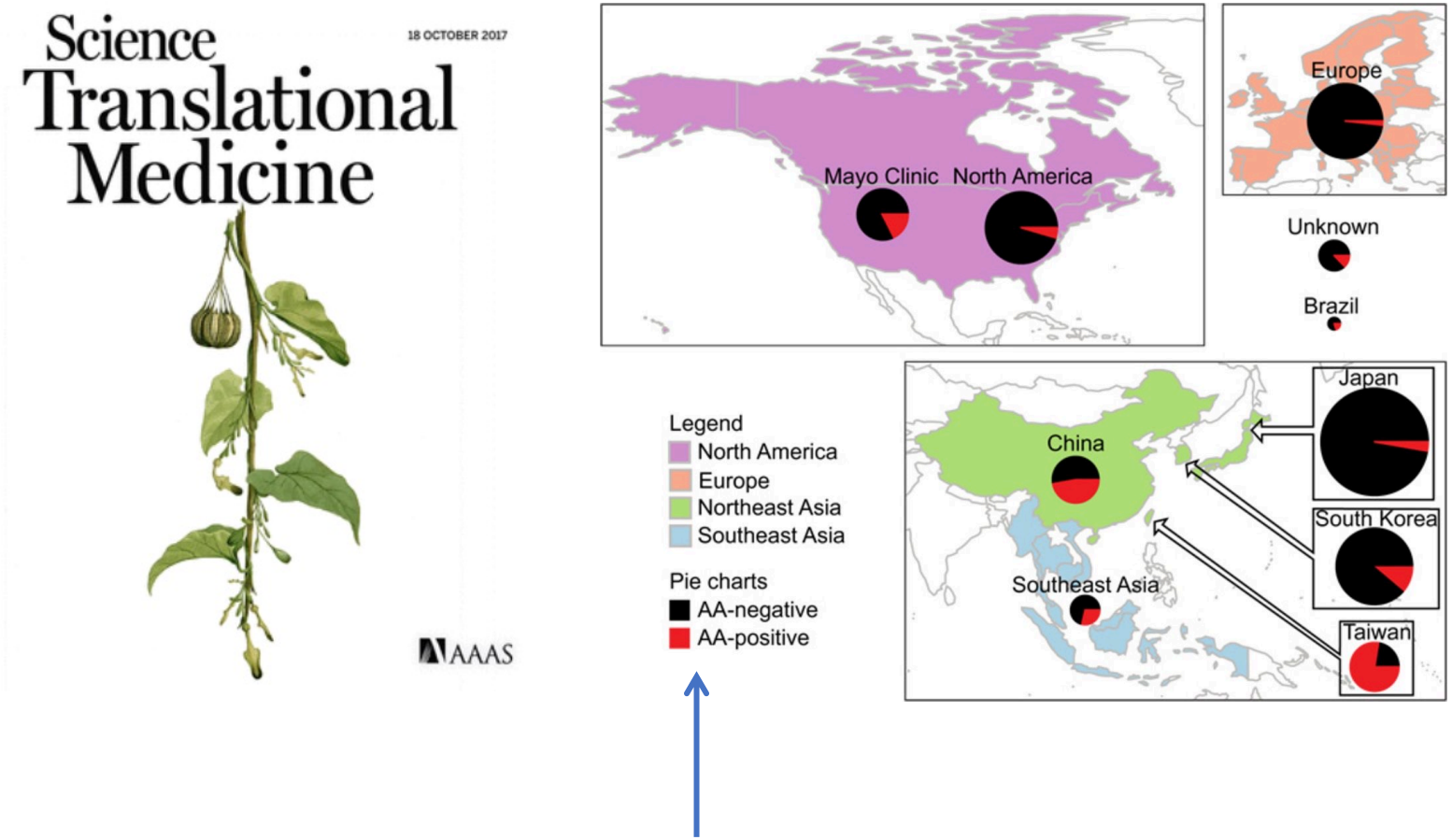
Astrid Coste, Denis Hémon, Laurent Orsi, Mathieu Boniol, Jean-François Doré, Laure Faure, Jacqueline Clavel, Stéphanie Goujon

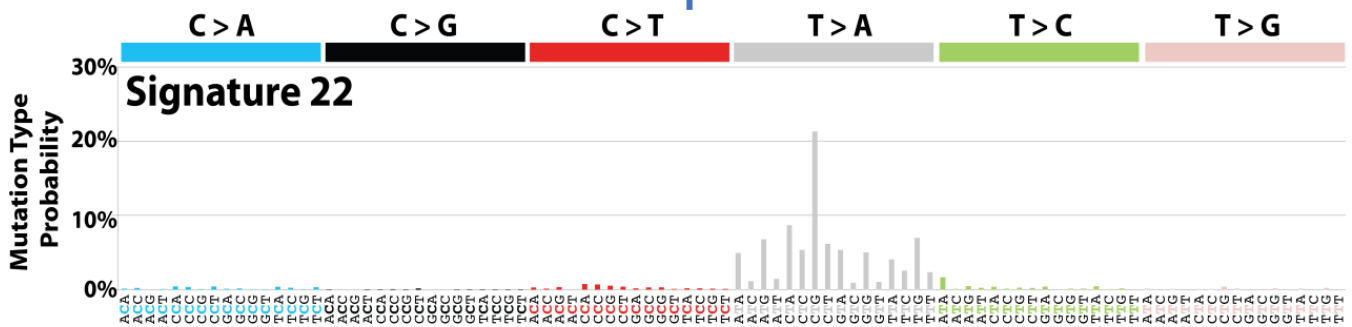
UV-light high confidence cancer types:

- **Basal Cell Carcinoma**
- **Squamous cell carcinoma**
- **Cutaneous melanoma (NOT in uveal melanoma)**
- **Lip cancer (H&N)**
- **B-cell ALL (childhood)**
- **Sarcomas (adulthood)**
- **Squamous cell lung carcinoma (all melanoma metastasis)**

Ma *et al.* 2018 Nature

Quantification of known carcinogens in suspected cancer types





Ng *et al.* 2017 Science Translational Medicine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School of Medicine