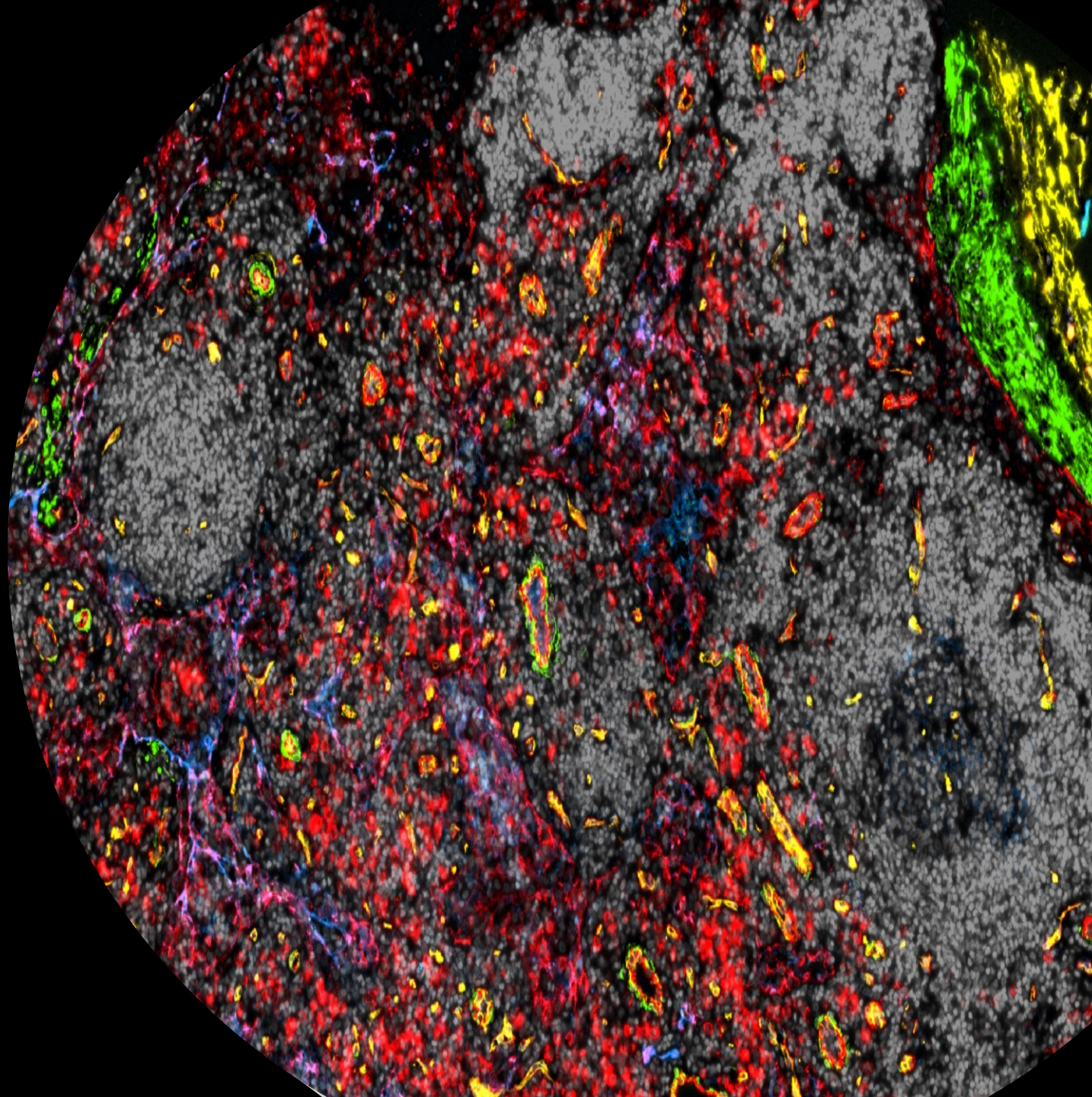
Cancer Biology I

Part-II

Week 9



AGENDA

Nov 5th: Cancer genomics- mutations

Nov 11th: Cancer genomics-copy number alteration, heterogeneity, evolution *(recording)*

Nov 18th: Cancer Epigenetics- chromatin 3D structure, cell plasticity

Nov 25th: – Major signaling pathways leading to cancer

Dec 2th: Cancer Therapies – chemo and targeted therapies

Dec 9th: Introduction to immunotherapies –

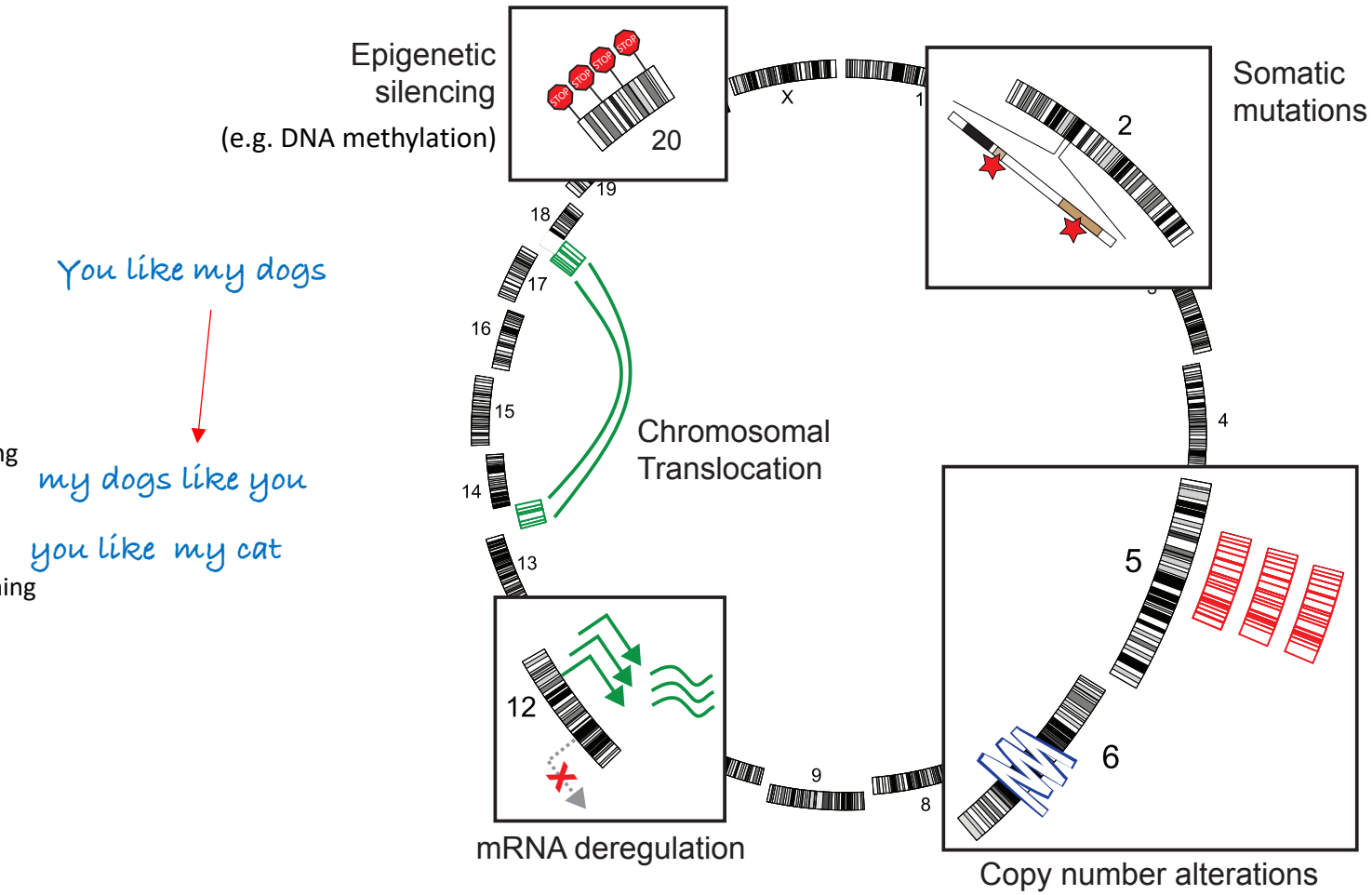
Dec 16th: Exam
(if it conflicts with another exam it is possible to do the exam on Dec 18th)

Dec 18th: discussion of exam questions and career development discussion towards a PhD or not…

Is it cancer only driven by somatic mutations?

What are they?

Cancer Genomic Alterations



You like my dogs

Invert the meaning

my dogs like you

you like my cat

change the meaning

You like my dogs

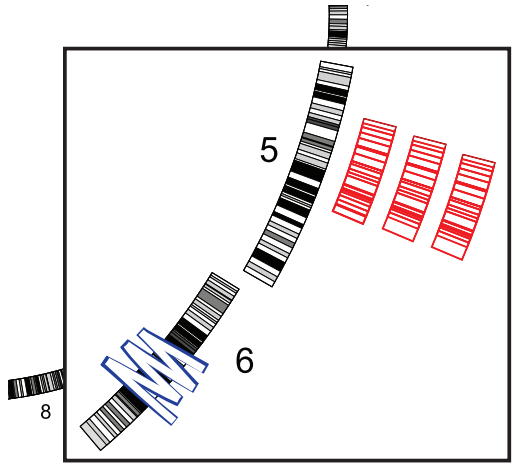
You like _ dogs

You like like my dogs

Copy Number Alterations

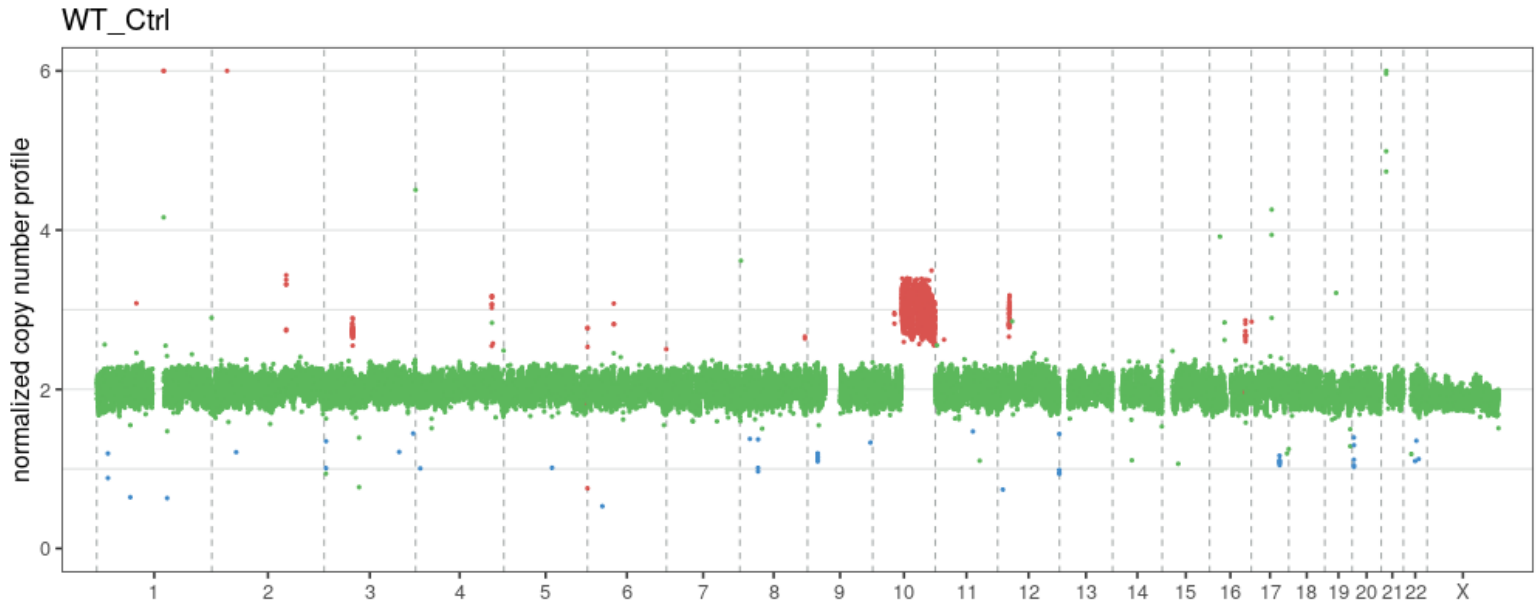
- *Deletion*: Loss of chromosomal regions
  (Heterozygous or Homozygous)

- *Amplifications*: Acquire one or more copy of chromosomal regions
  (Duplication or Amplification)



Copy number alterations

Copy Number Alterations: whole genome sequencing or SNP array



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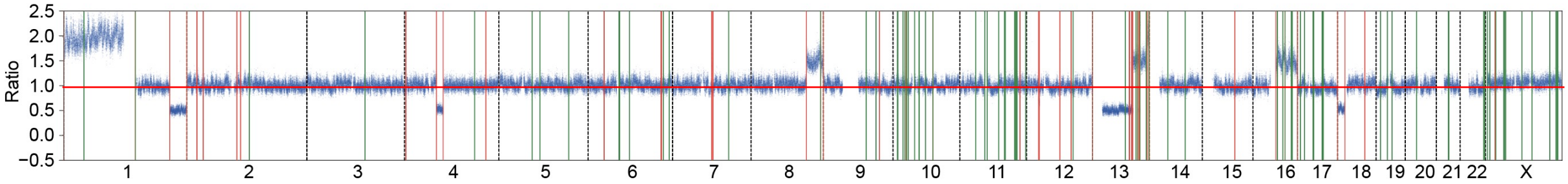
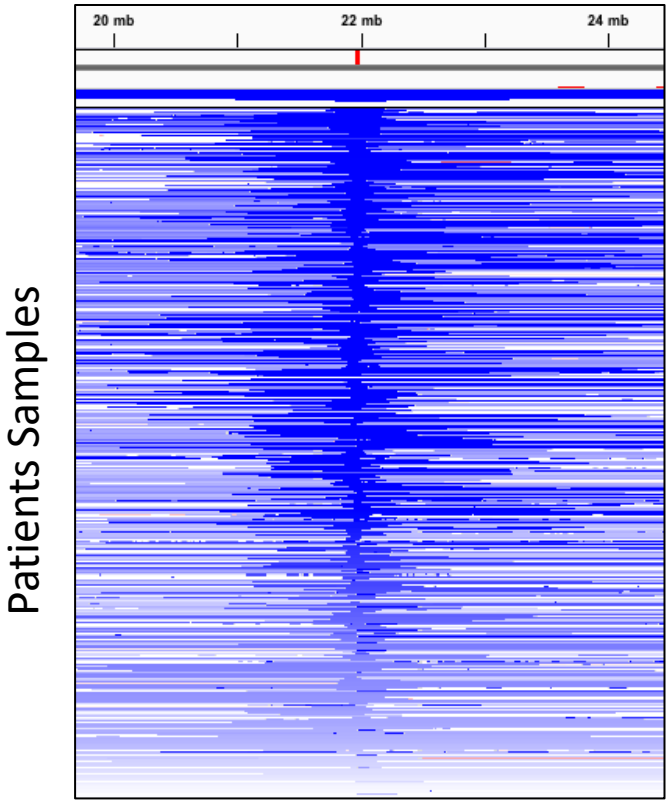
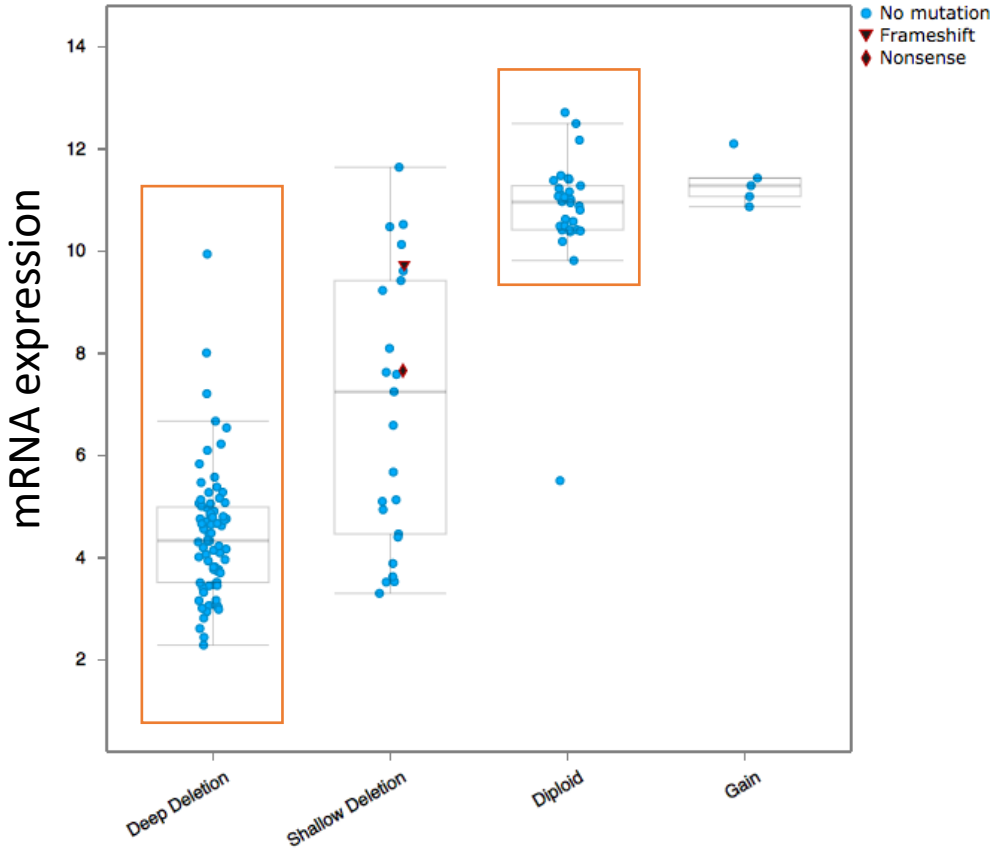


Focal Deletions derived from multiple cancer patients

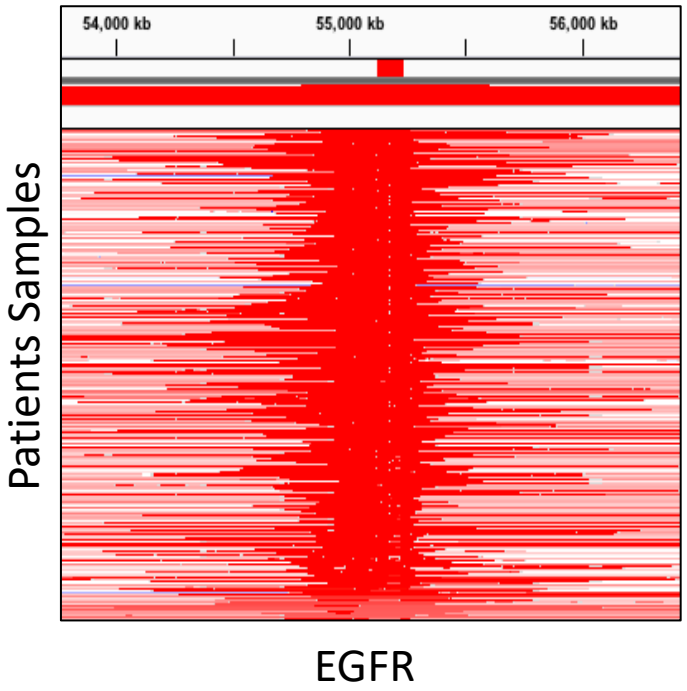
(inactivating a **tumor suppressor**)

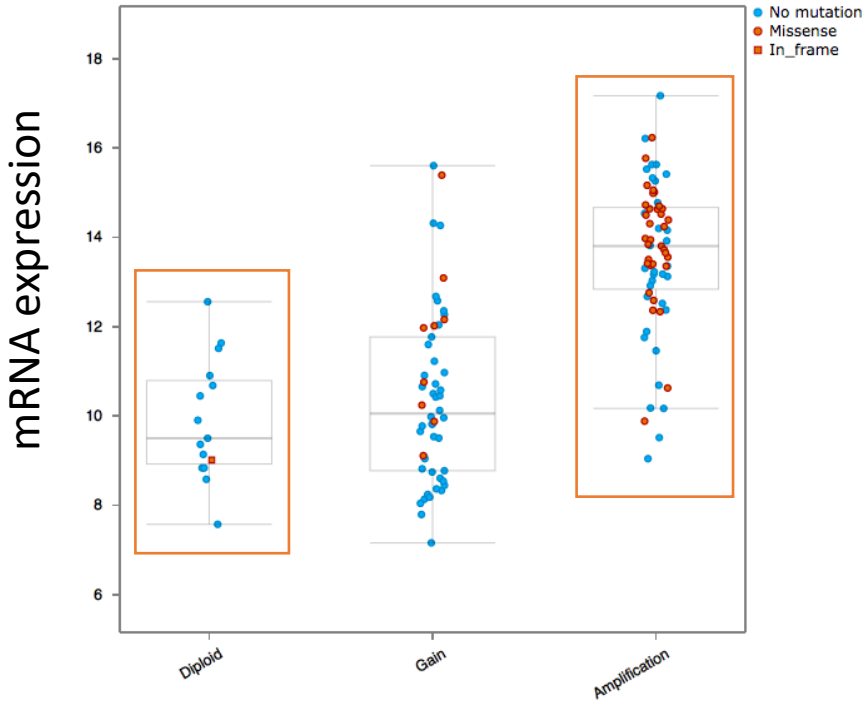




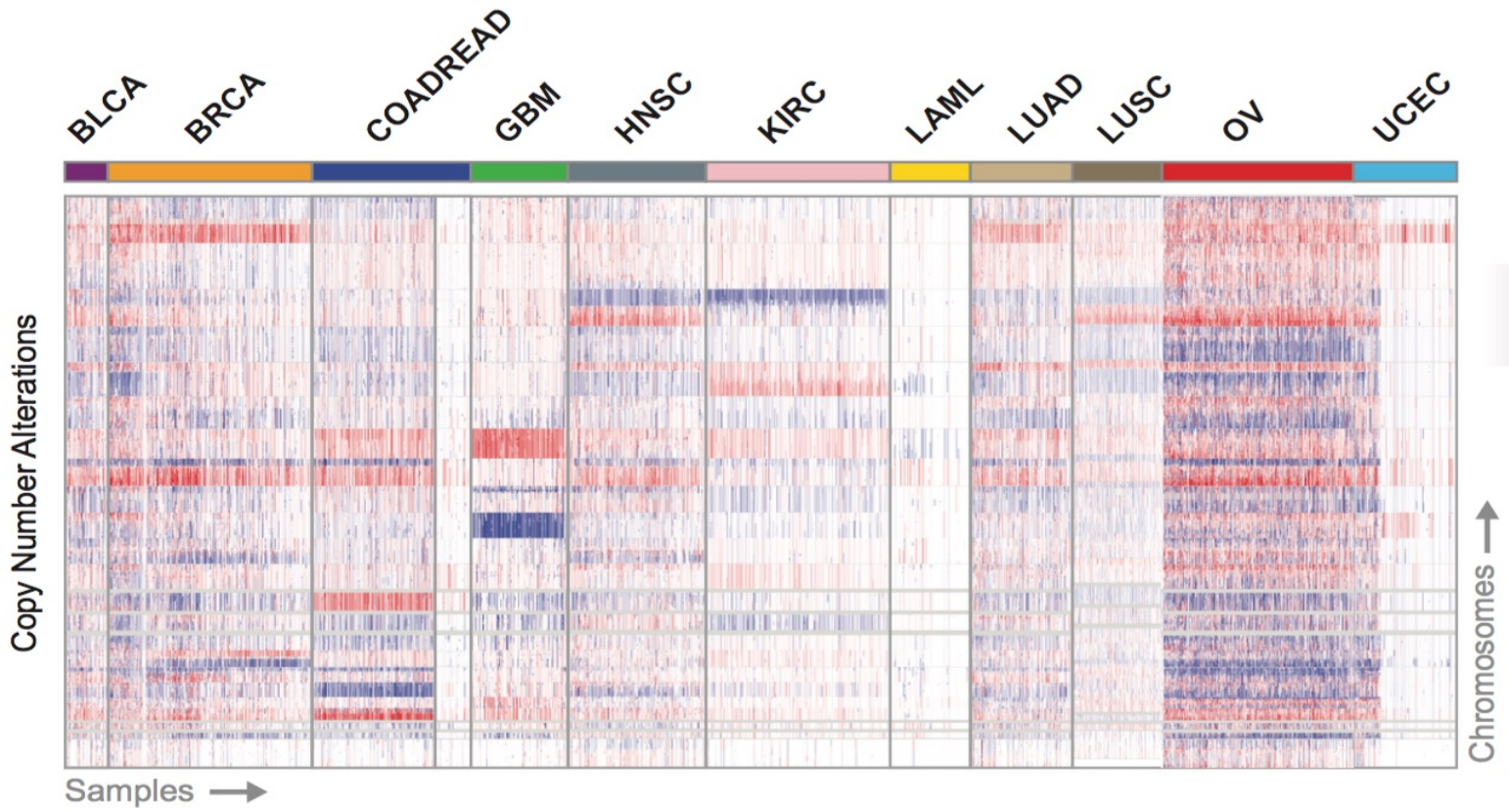
Focal Amplifications

(activating an **oncogene**)





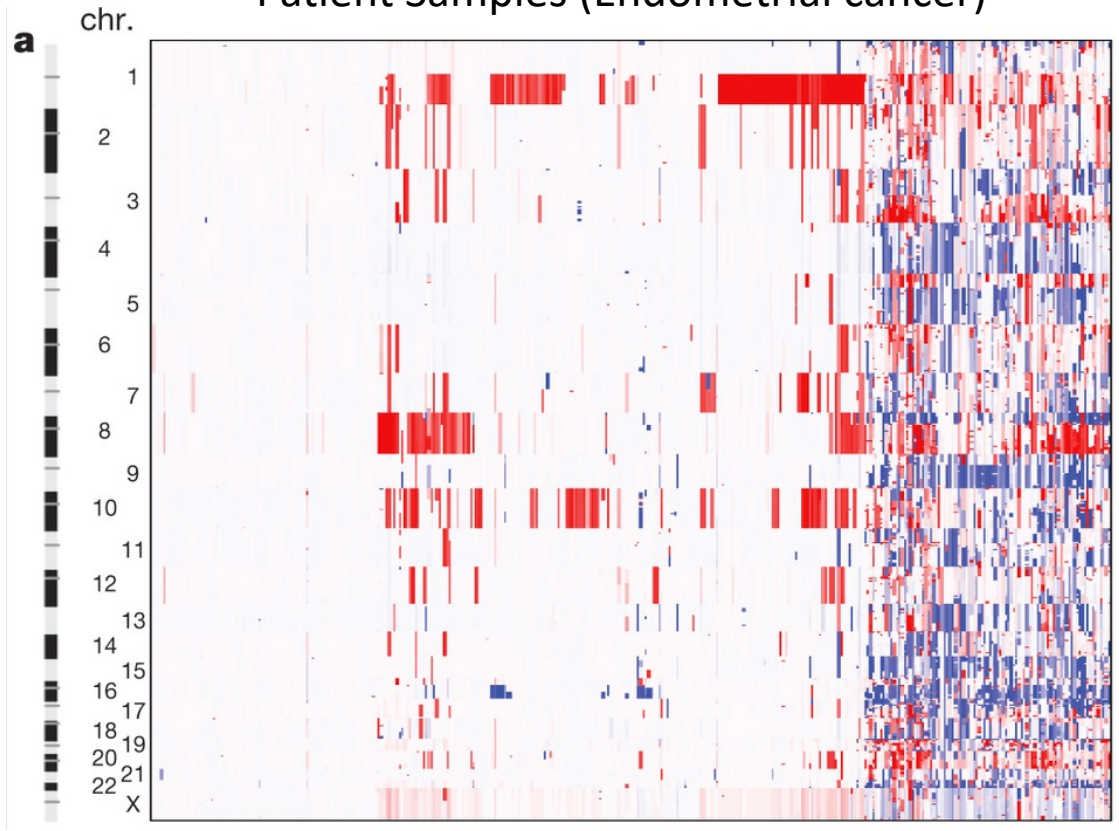
Copy Number Alterations inter-tumor heterogeneity

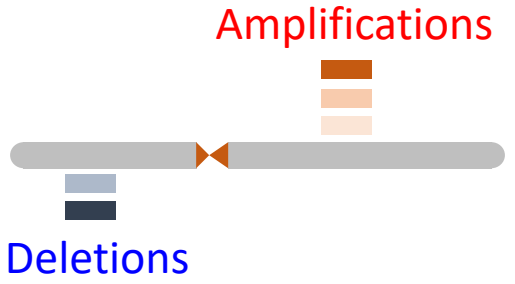


Copy Number Alterations inter patient heterogeneity

Patient Samples (Endometrial cancer)

Chromosomes





(TCGA, Nature 2013)

- **Tumor subtypes defined by copy number alterations**

What are they?

Cancer Genomic Alterations

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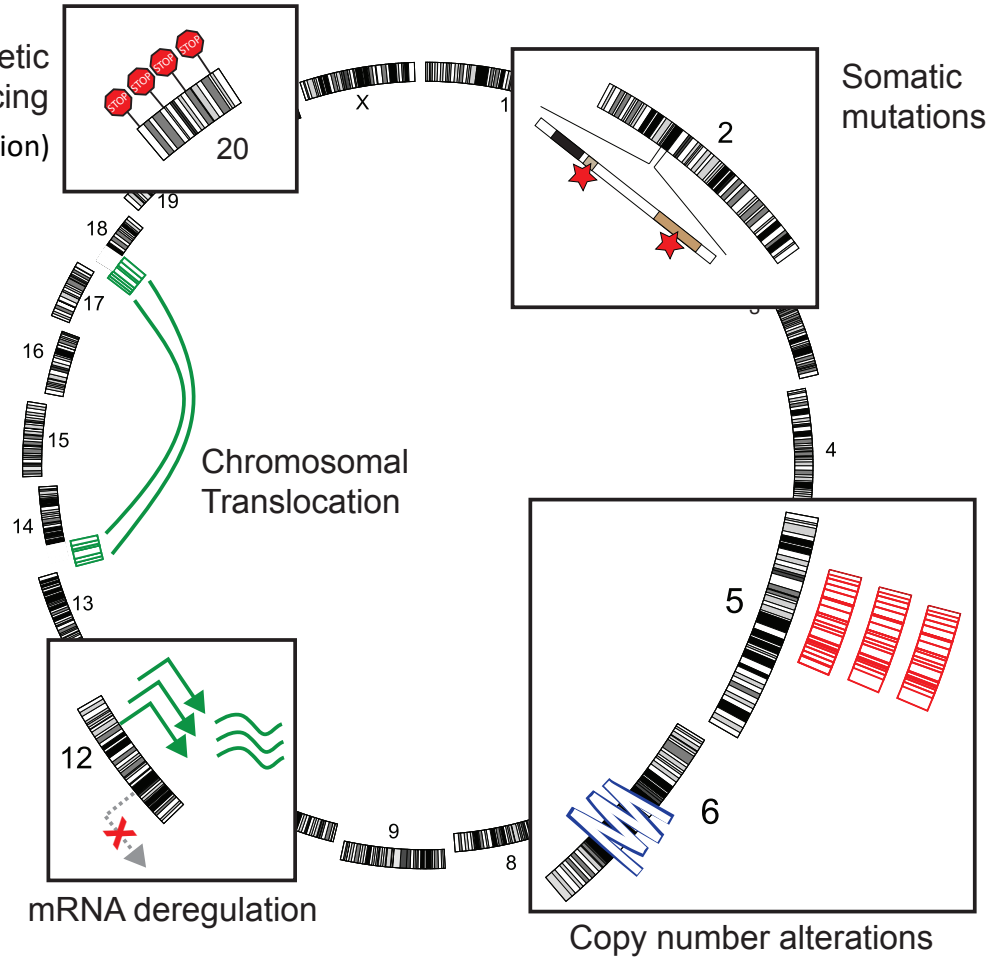
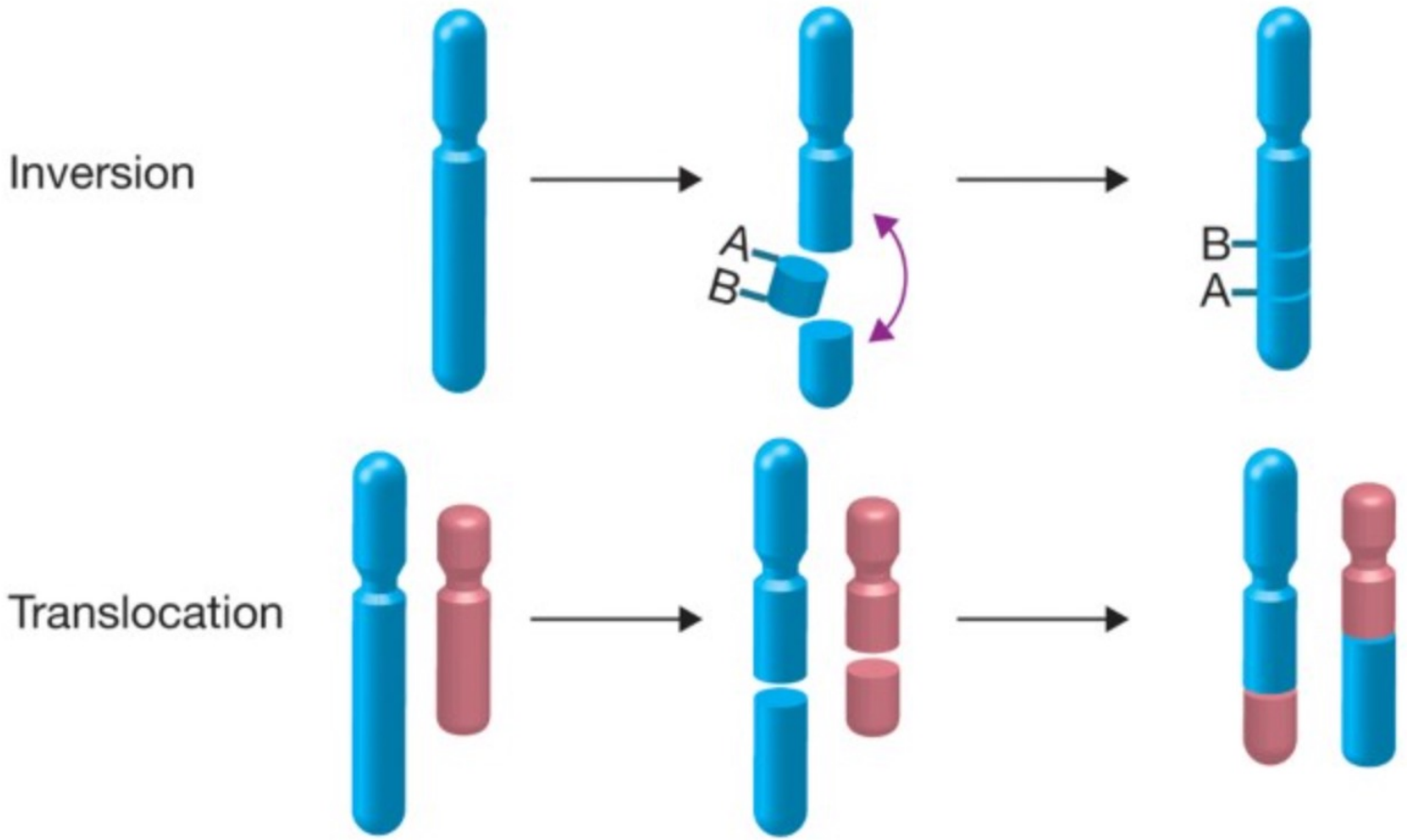
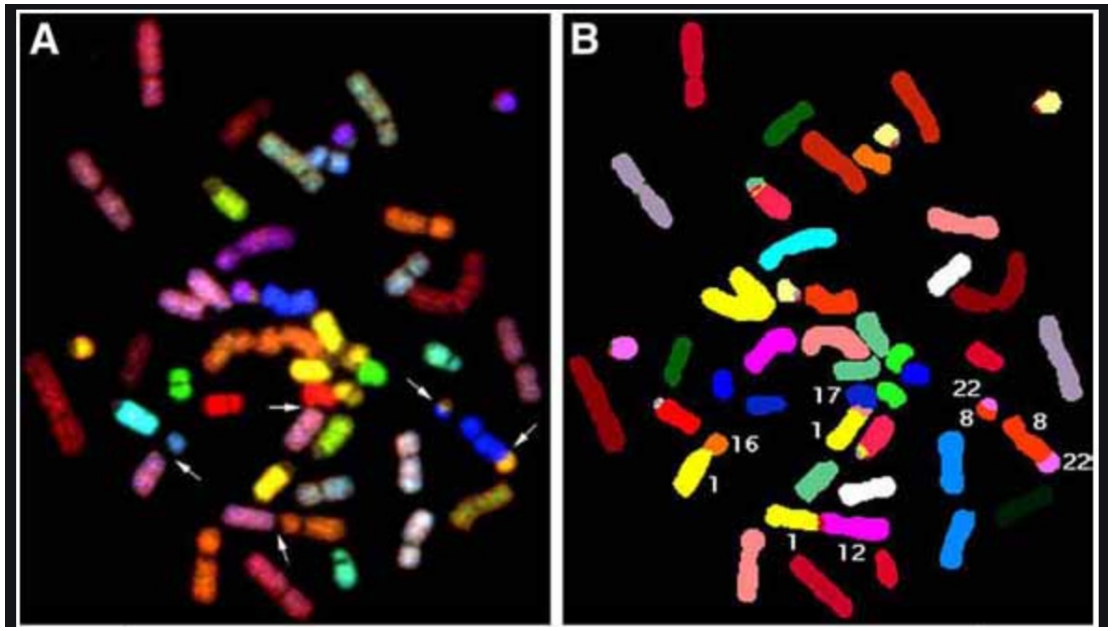


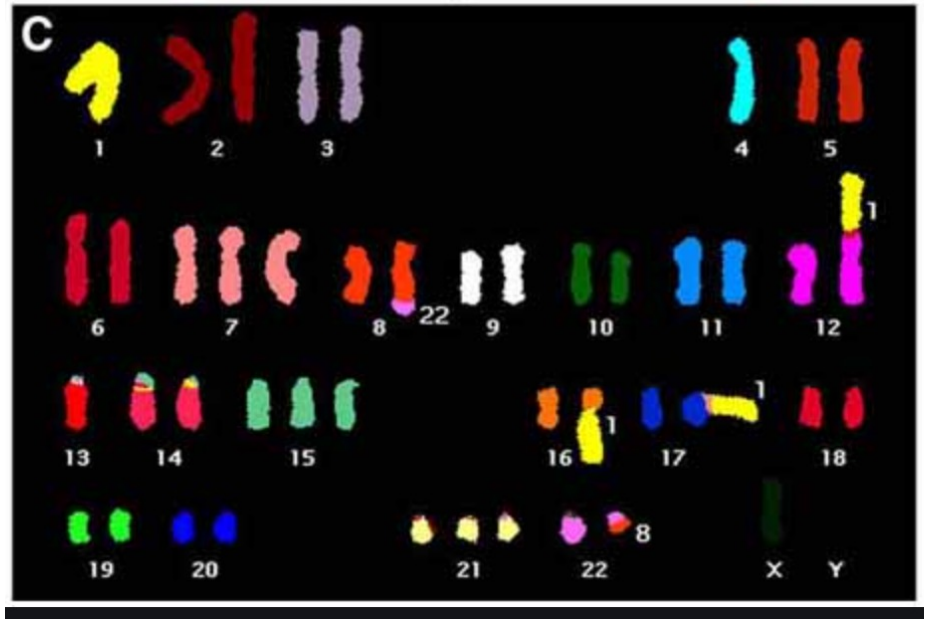
Chromosomal Structural Variants



Chromosomal Structural Variants

Translocations became apparent from “chromosome painting” (long before NGS techniques)





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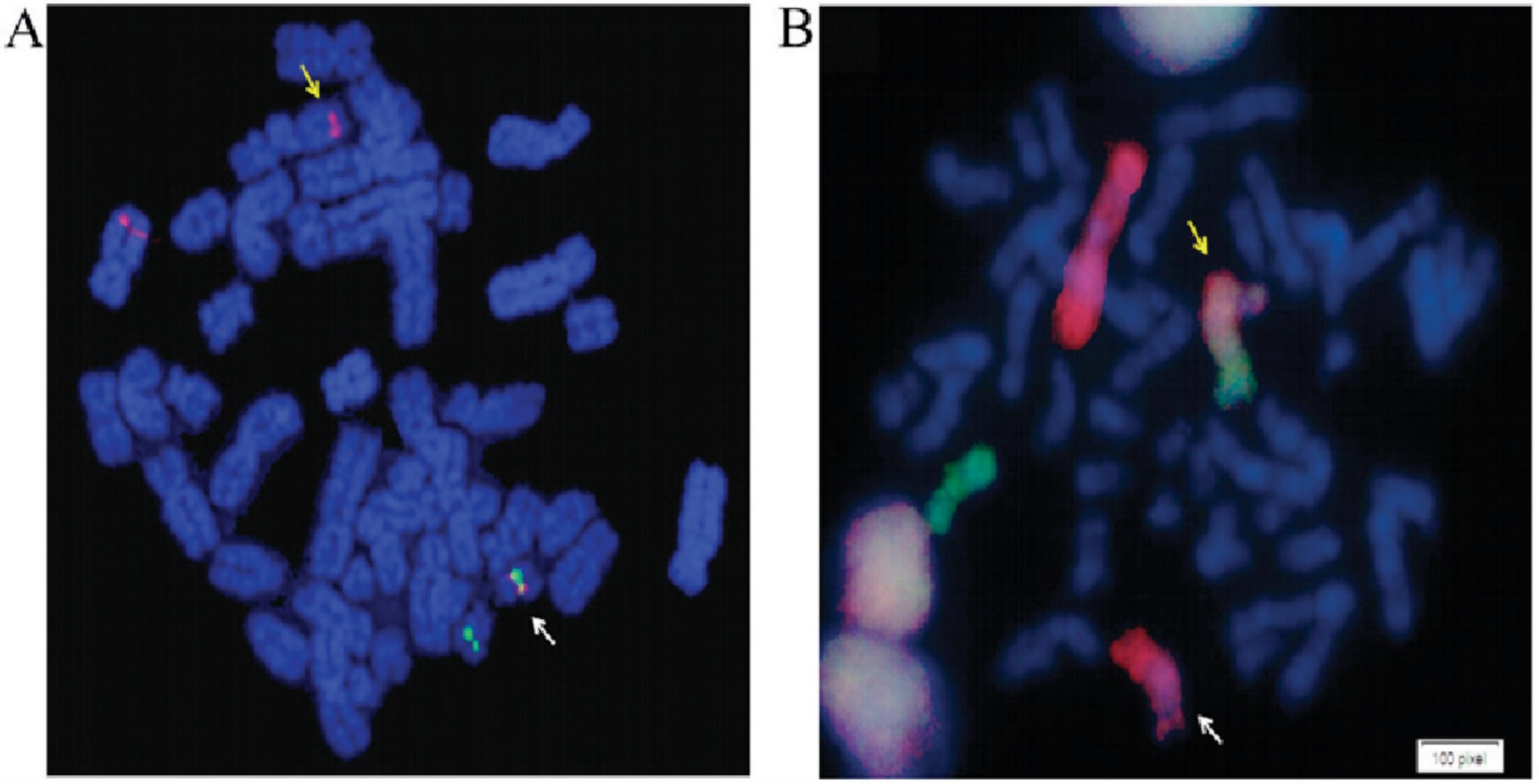

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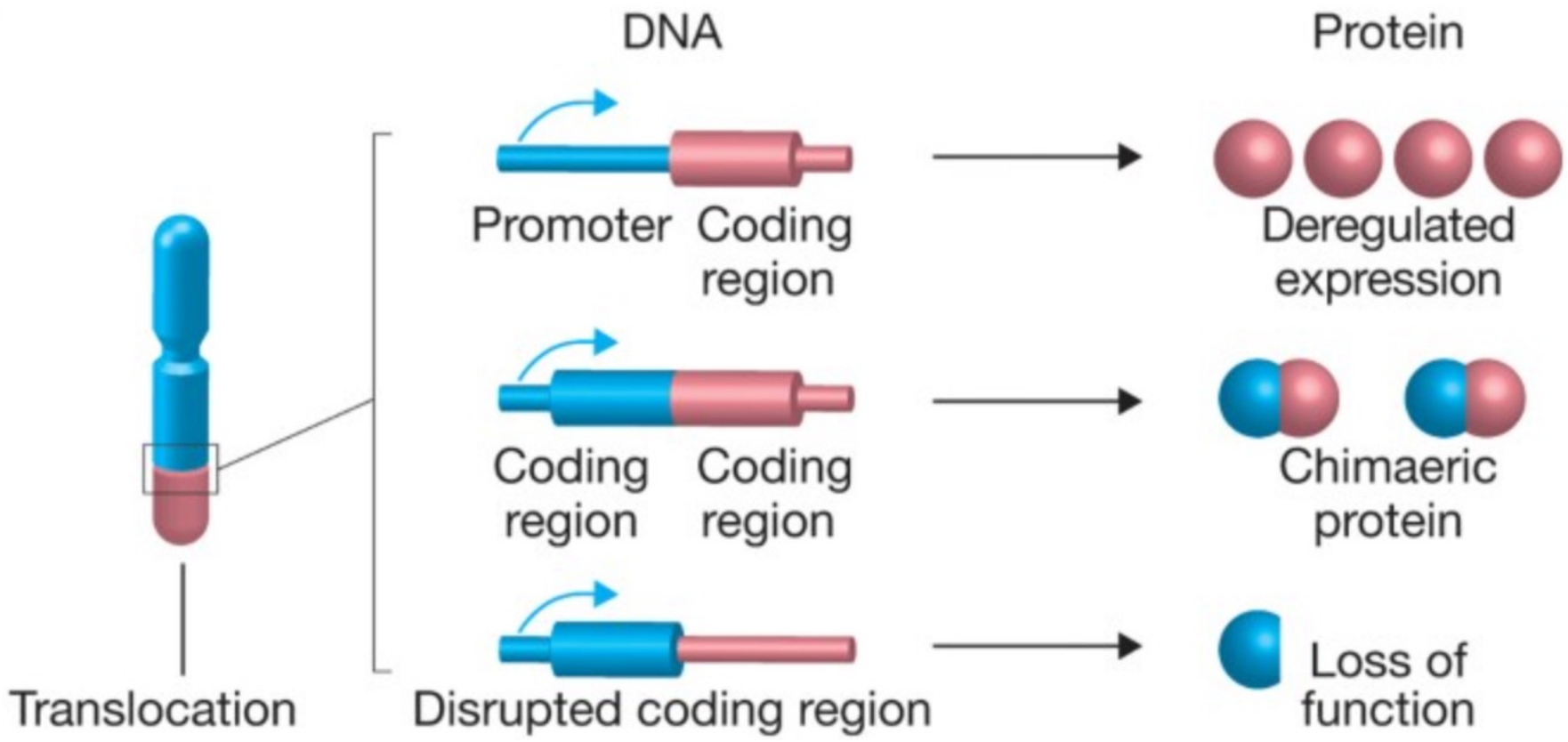
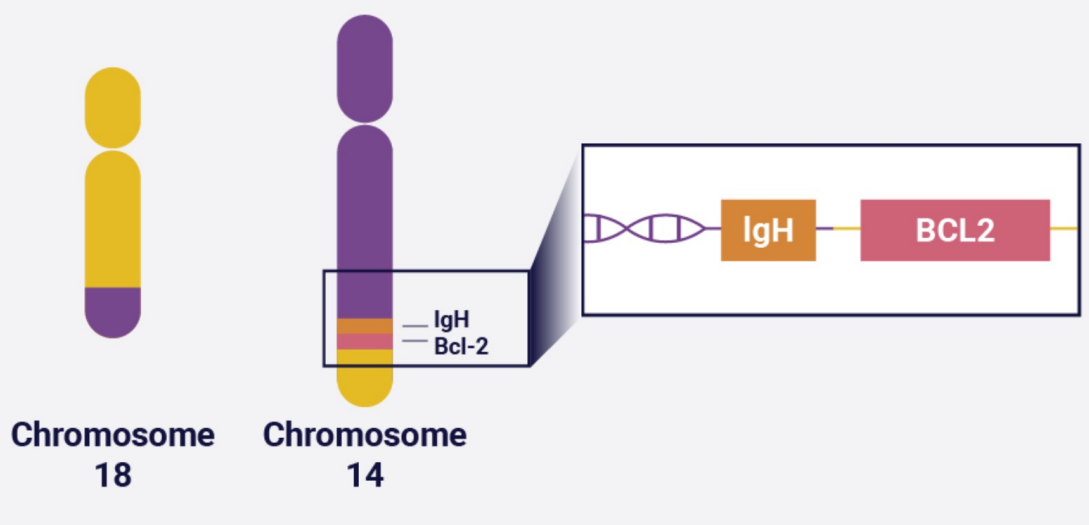
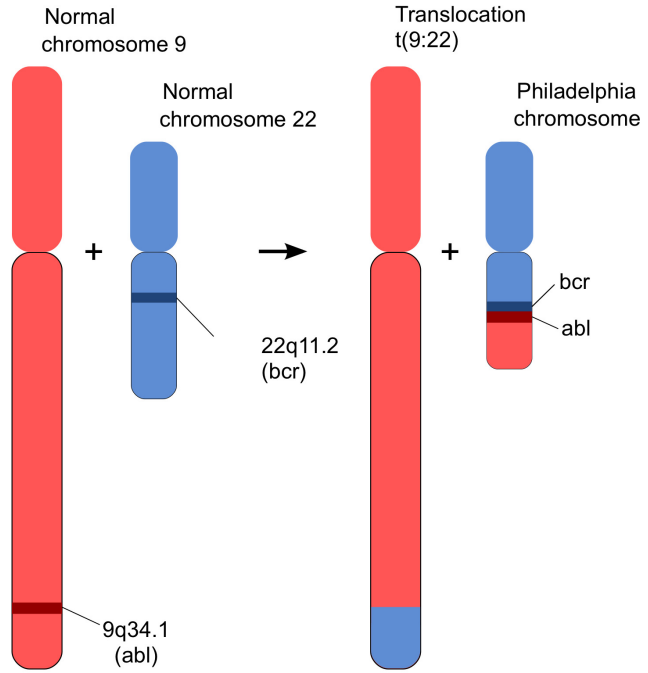


Chromosomal Structural Variants

t(14,18) translocation puts BCL2 under the IgH promoter: BCL2 gets upregulated in lymphoma



BCR-ABL fusion protein: fusion generate a new protein with hyper-active kinase activity



Patterns of genomic alterations

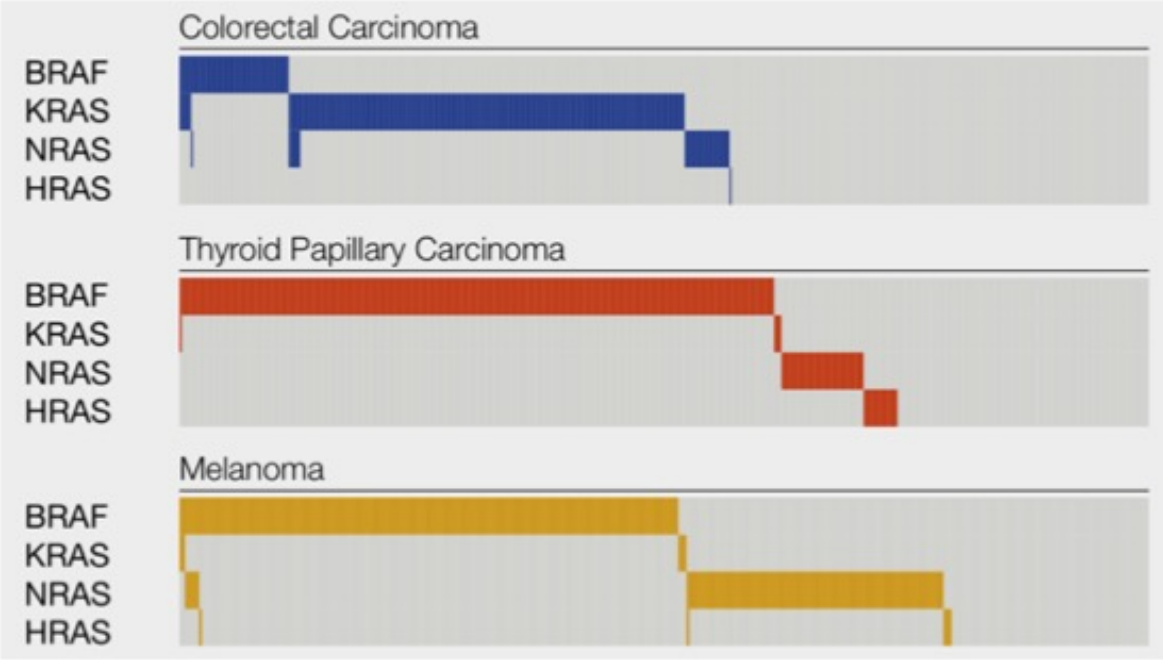
Considering both mutations and copy number changes:

MUTUALLY EXCLUSIVE: rarely occur together

CONCURRENT ALTERATIONS: frequently occur together

Mutual Exclusivity

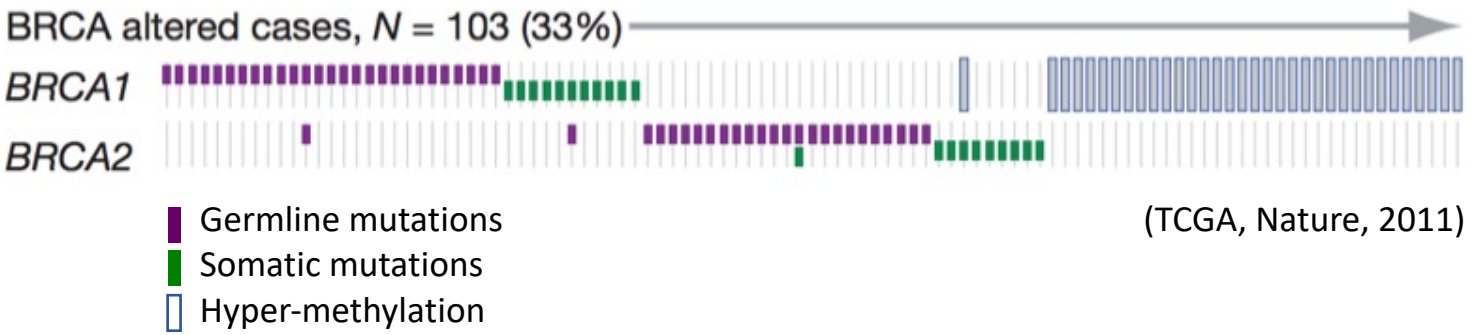
- Observations of mutually exclusive alterations



Patient Samples

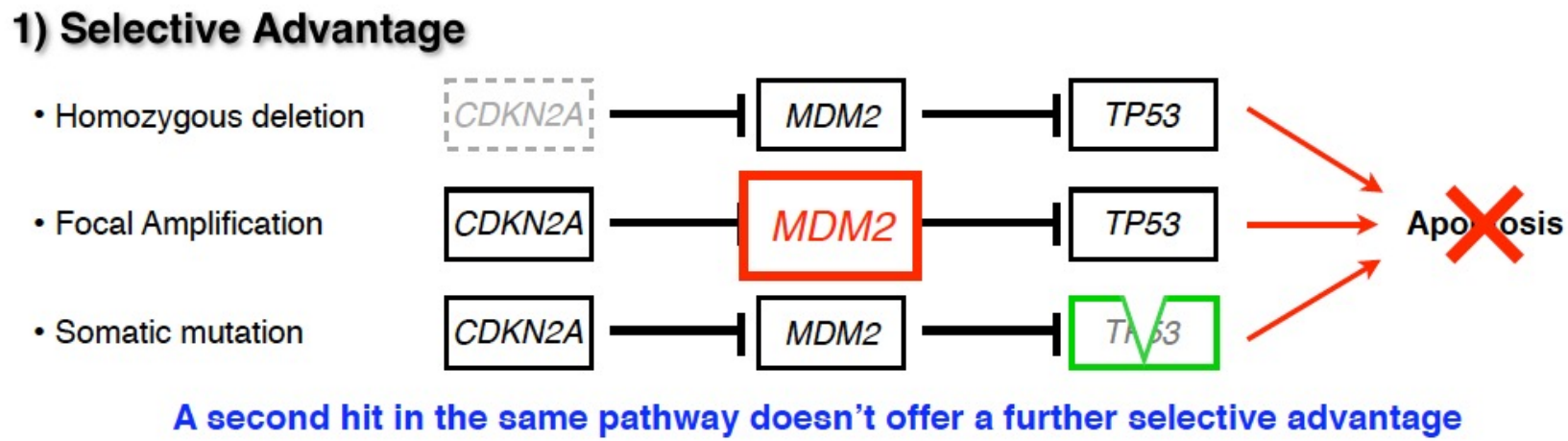
Mutual Exclusivity

- Observations of mutually exclusive alterations

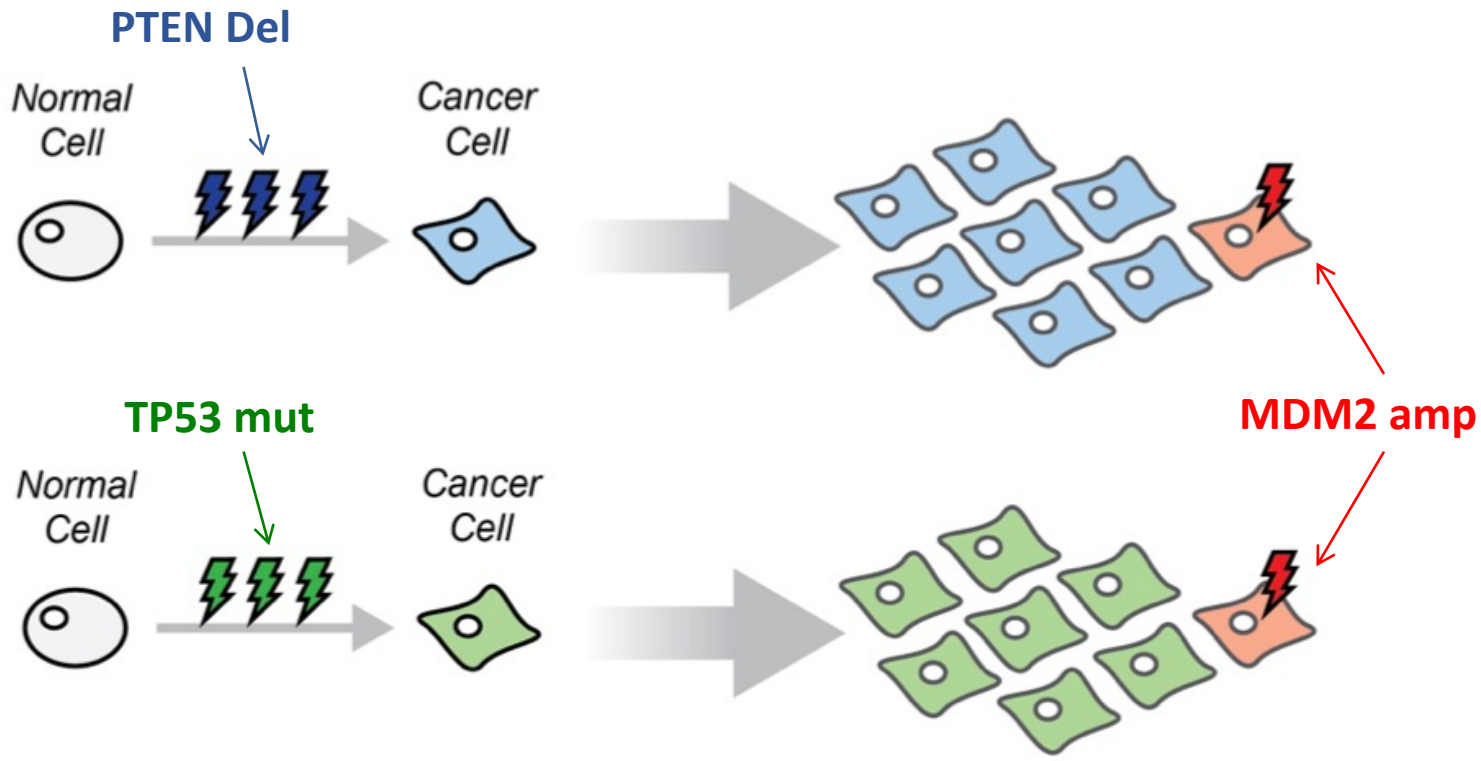


(TCGA, Nature, 2011)

Why Mutual Exclusivity?



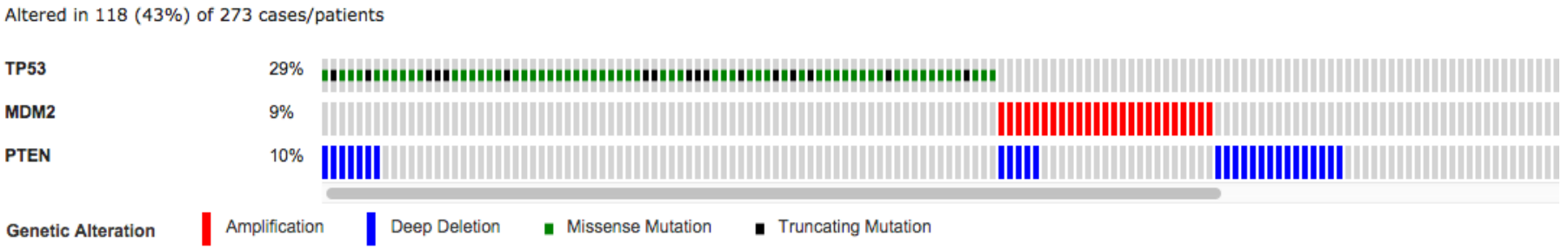
Mutual Exclusivity reflects Selection



Is MDM2 amplification giving the same advantage in the 2 cases?

Mutual Exclusivity reflects Selection

TCGA Glioblastoma Dataset



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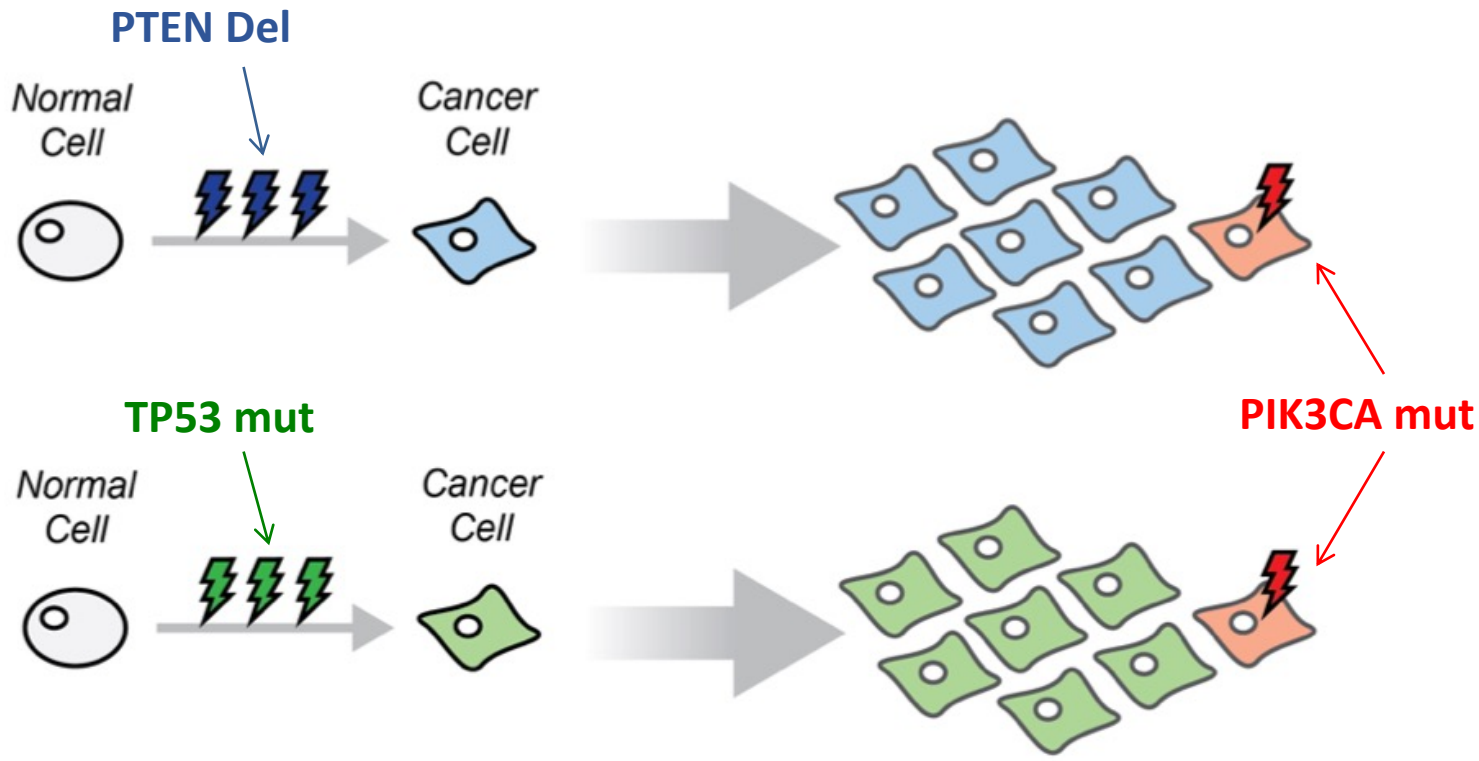
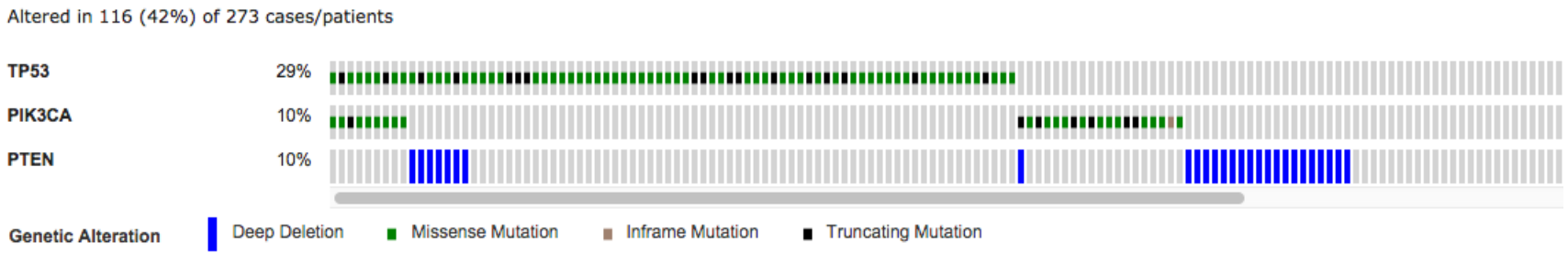


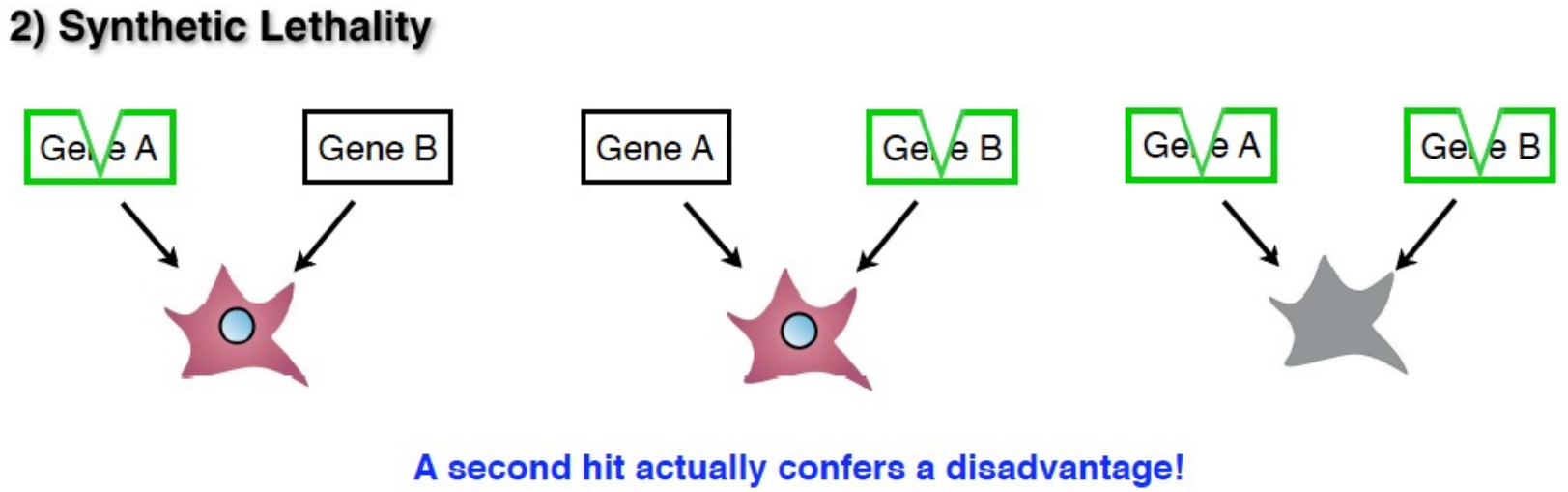
Is PIK3CA mutation giving the same advantage in the 2 cases?

Mutual Exclusivity reflects Selection

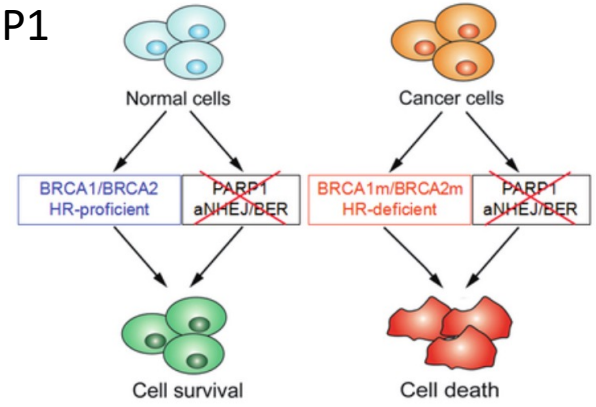
TCGA Glioblastoma Dataset (source cBioPortal)



Why mutual exclusivity?



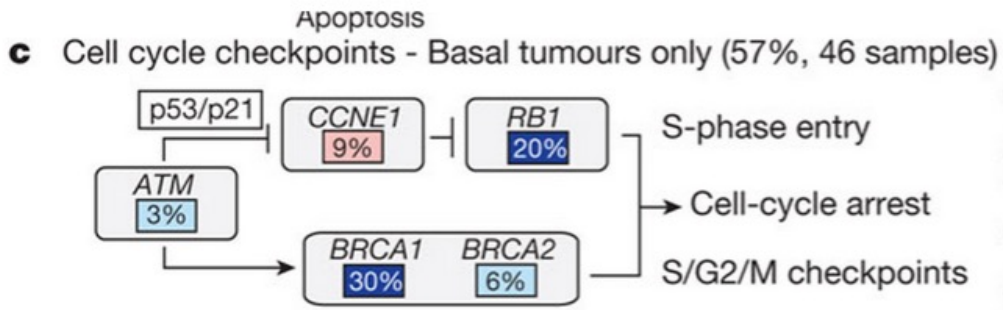
e.g. BRCA1/2 and PARP1



Synthetic Lethal interactions

Mutual exclusivity between alterations in DNA repair genes BRCA1/2 and cell cycle regulators CCNE1 and RB1 in **ovarian cancer** and **Basal breast cancer**

(Ciriello et al. Genome Res. 2012)



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Synthetic lethality between *CCNE1* amplification and loss of *BRCA1*

Dariush Etemadmoghadam[a,b,c], Barbara A. Weir[d,e], George Au-Yeung[a,f], Kathryn Alsop[a,f], Gillian Mitchell[a,b], Joshy George[a,f], Australian Ovarian Cancer Study Group[a,g,h,i,1], Sally Davis[a,c], Alan D. D'Andrea[d], Kaylene Simpson[b,c,j], William C. Hahn[d,e], and David D. L. Bowtell[a,b,c,f,2]

(PNAS, 2013)

(TCGA, Nature 2012)

What are the challenges?

- **Prioritize the multitude of genetic aberrations**

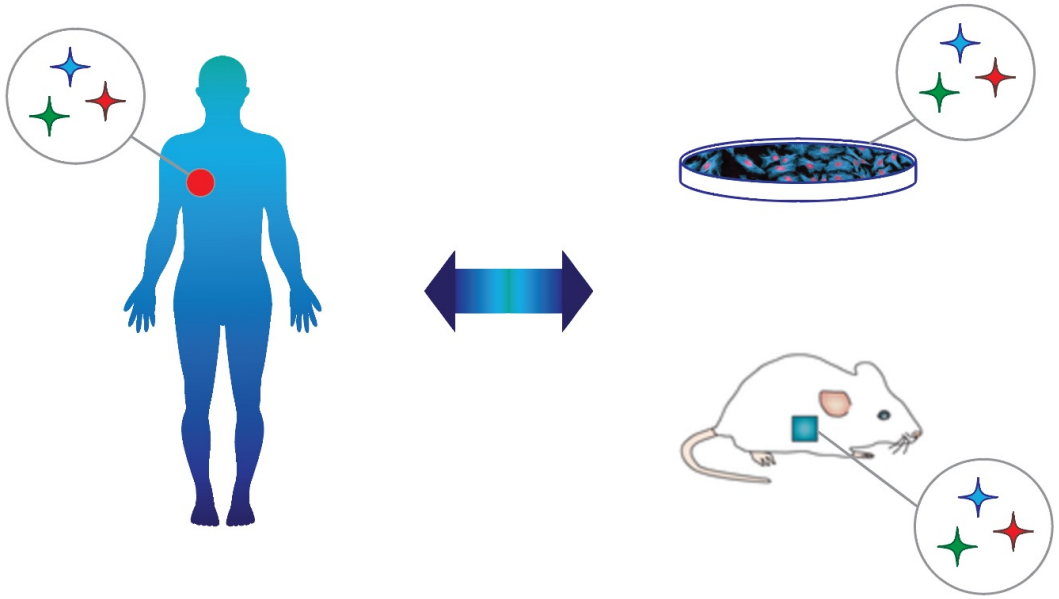
  Several studies classified genomic alteration based on **statistical analyses**

- **Functional Annotations of Genomic Alterations**

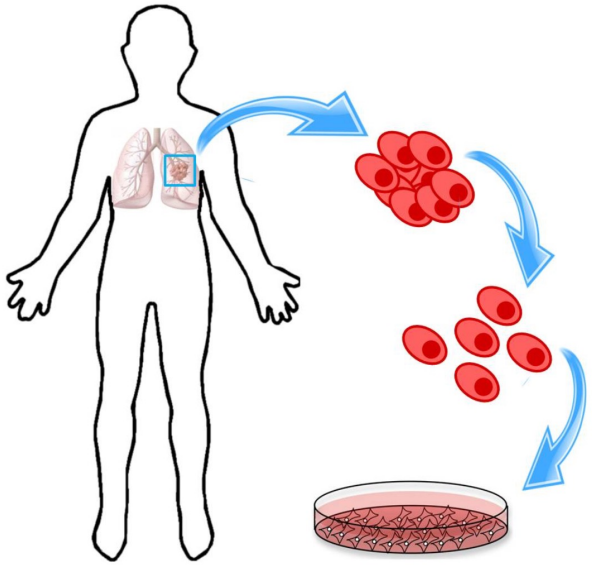
  Define the biological impact of genetic alteration in the tumor development

How to study this complexity?

Disease-model matching



Multiple cell lines isolated from different tumors

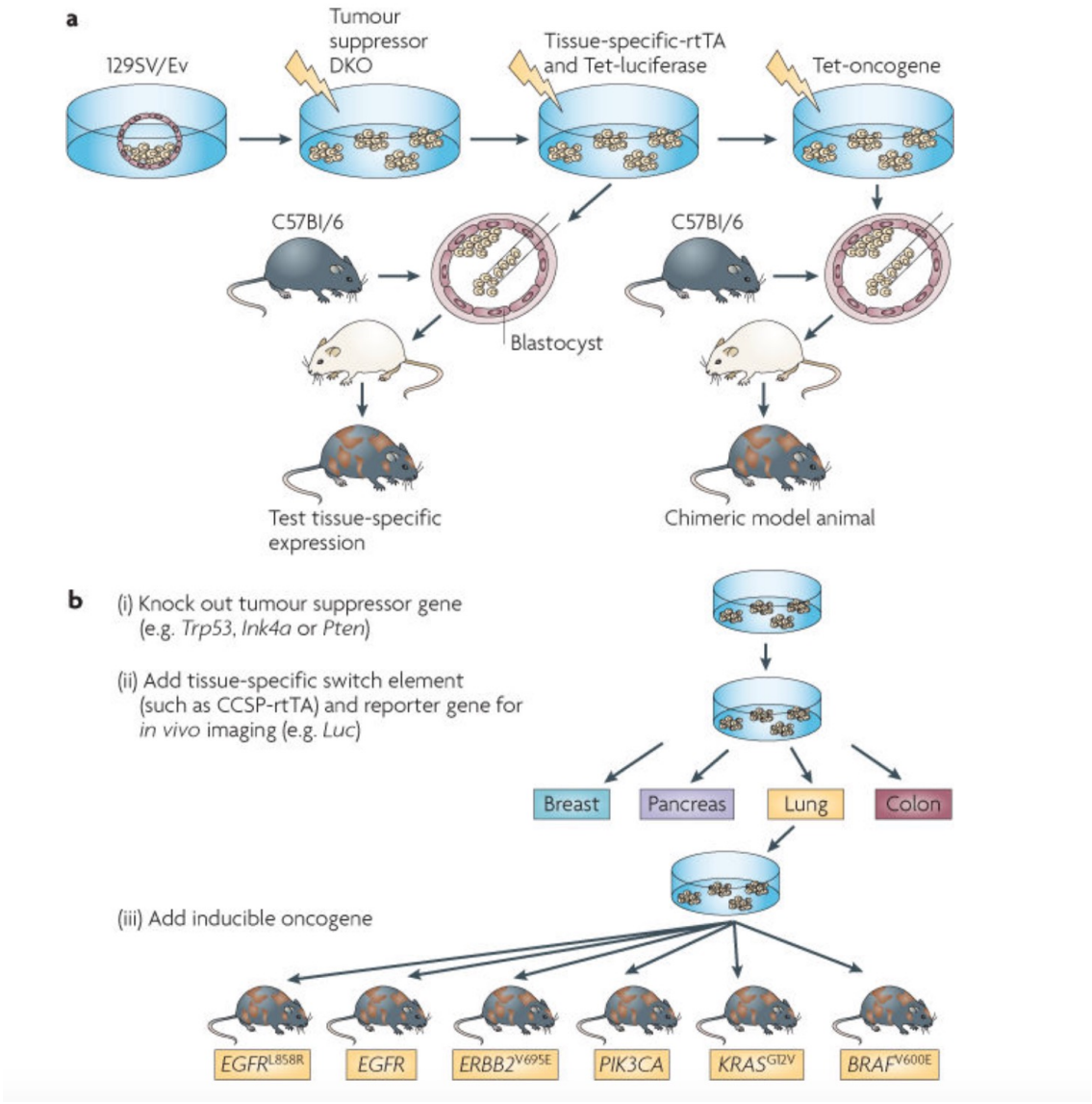


Cancer cells grow for forever

Cancer cell line encyclopedia

https://portals.broadinstitute.org/ccle

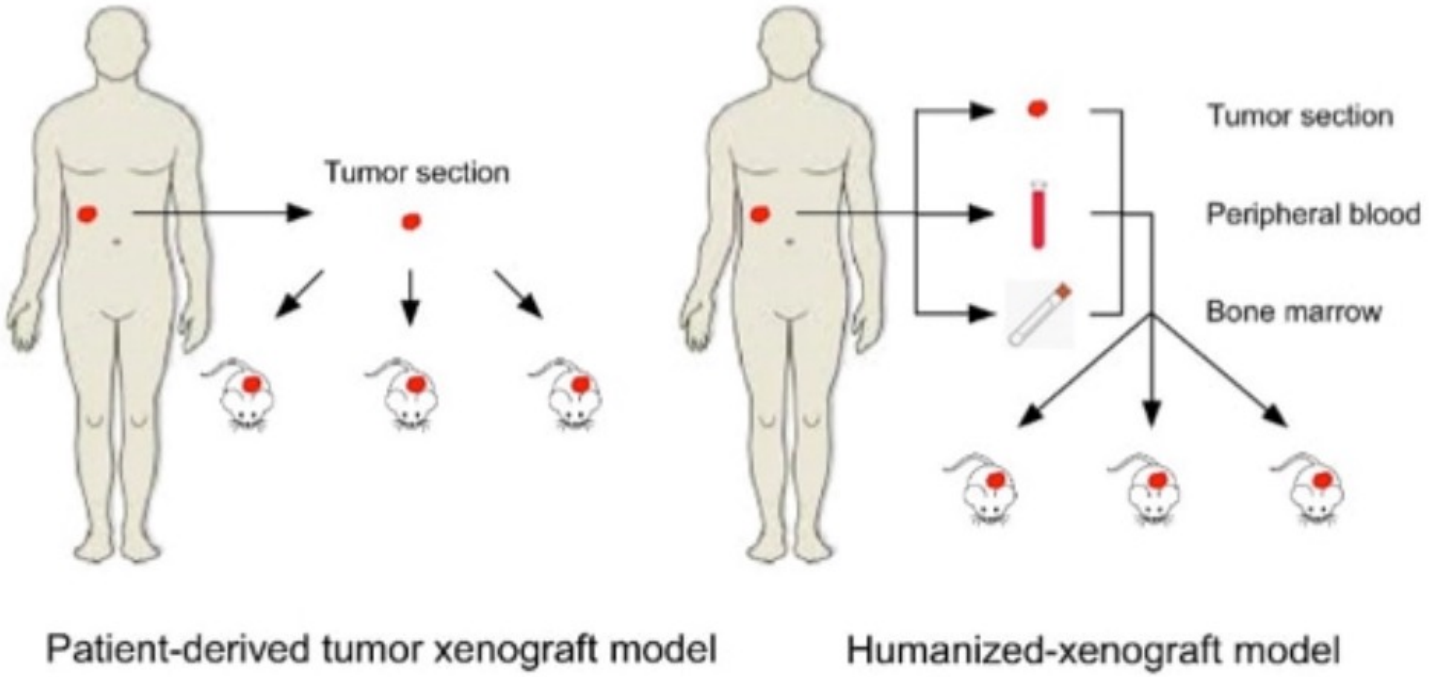
Transgenic animal models



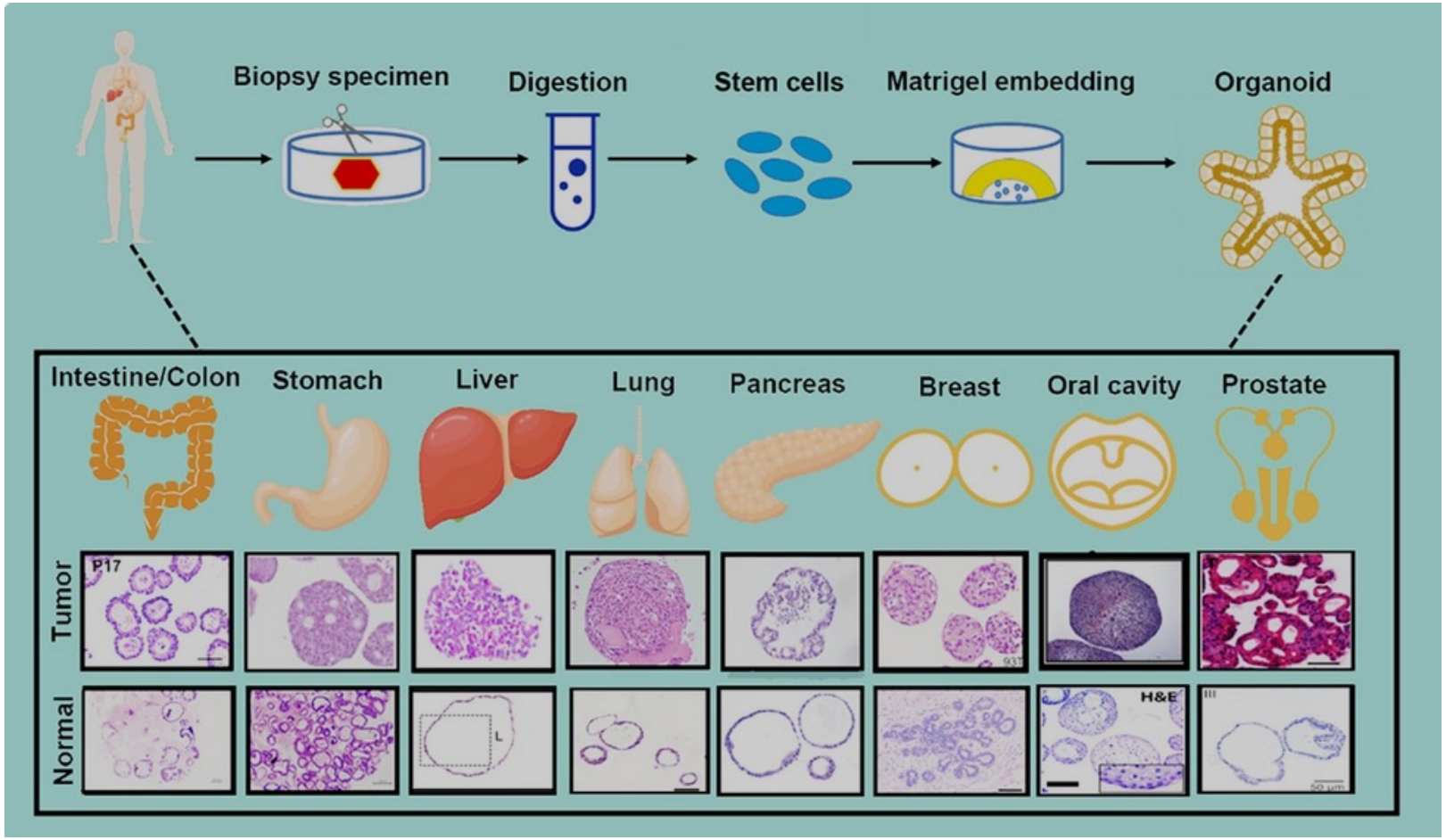
Heyer et al. Nature Rev. Cancer, 2013

The Human Relevance

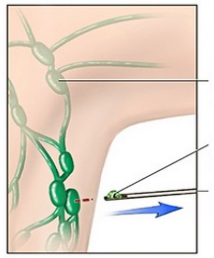
Patient derived xenograft
and
Humanized-xenogaft model



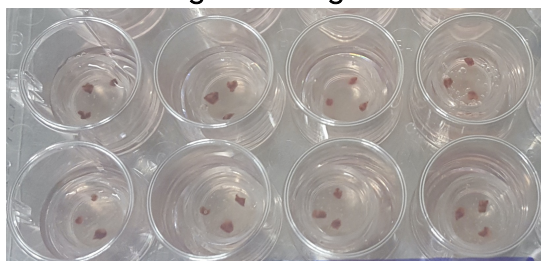
Organoids


Biopsy specimen
Digestion
Stem cells
Matrigel embedding
Organoid
Intestine/Colon
Stomach
Liver
Lung
Pancreas
Breast
Oral cavity
Prostate
Tumor
Normal
P17
H&E

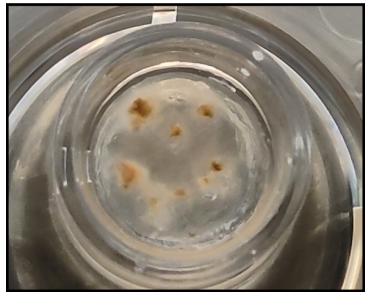
Fragments of tumors



Tumor biopsies
from the surgery room

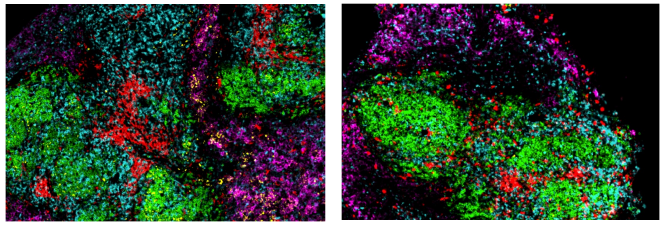


Treatment for
1-2 weeks



Determine the most effective therapeutic option
for each cancer patient

Compare response with clinical outcome



Analyses of tumor structures with
advanced imaging and molecular technologies

Patient avatars

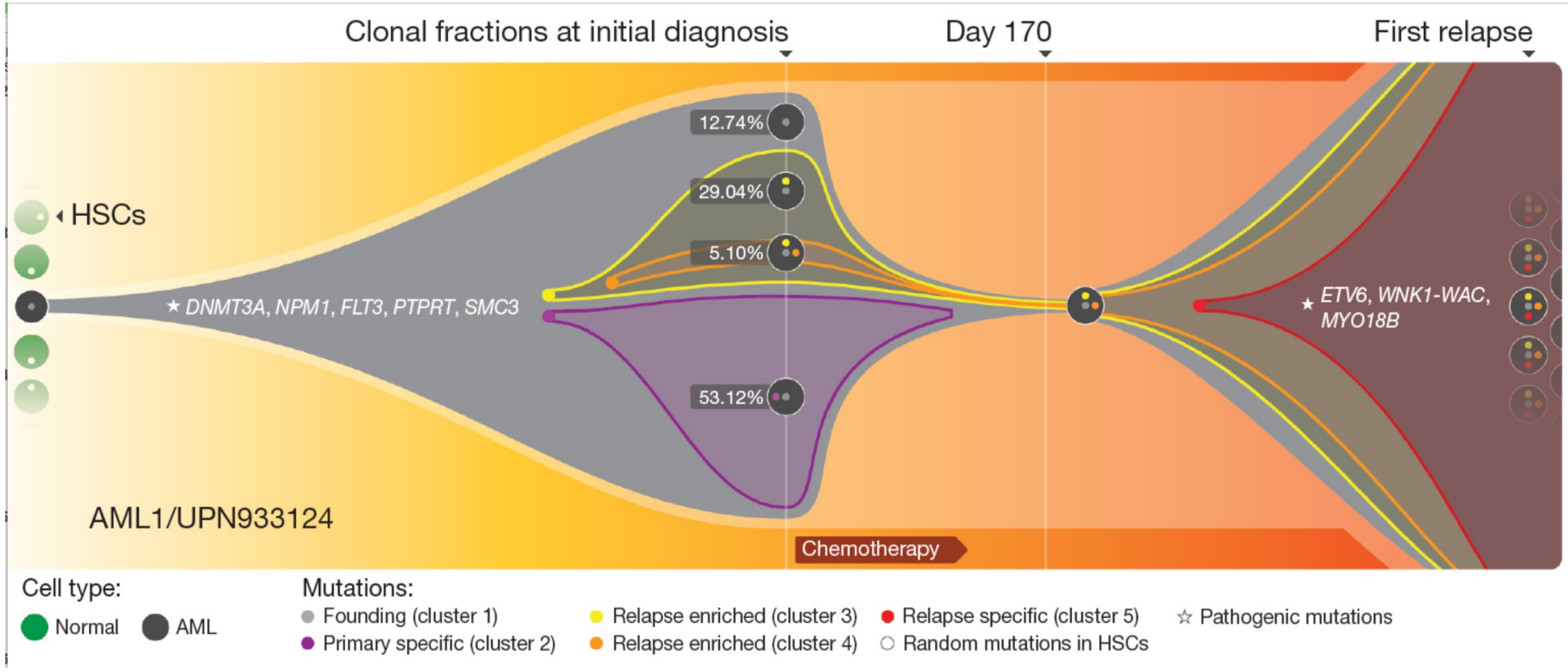
A

	Genomic Sequencing	Metabolomics/ Proteomics	Patient-Derived Cell Lines	Patient-Derived Xenografts	Patient-Derived Tissue Explants	Patient-Derived Organoids	Patient-Derived 3D Micro-Models
Predictive Power	+++	++	+	+++	++	+++	+++
Predictable Therapies	T	T	C/R	T/C/IO*/R	T/C/IO/R	T/C/R	T/C/IO/R
Speed	+++	+++	+	-	+++	++	+++
Establishment Success from Biopsy	+++	++	-	+	-	+	++
Throughput	+++	+++	+	-	-	+	+++
TME	-	-	-	++*	+++	-	++
Reproducibility	+++	+++	++	+++	-	++	+++
Cost	+	+	+	+++	++	++	+

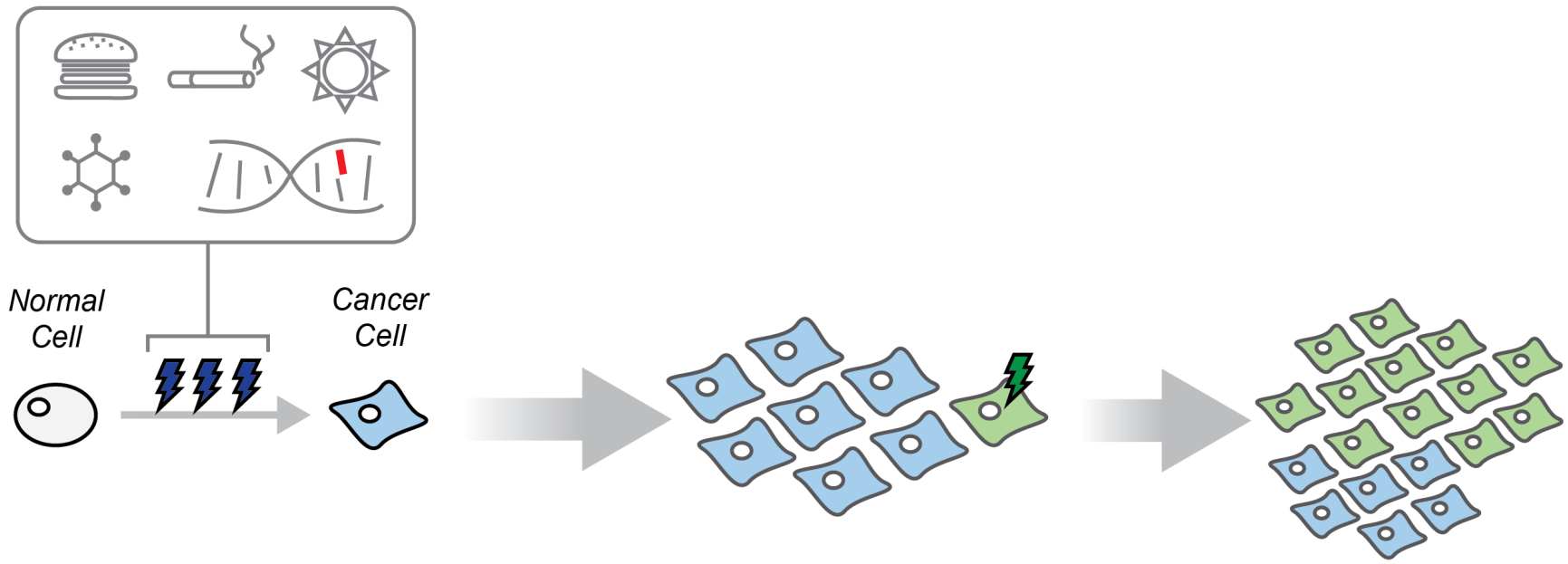
T = Targeted Therapies, C = Chemotherapies, R = Radiation, IO = Immuno-oncology Therapies, TME = Tumor Microenvironment
*PDX models include mouse stromal cells in the TME and require immune reconstitution with humanized mouse models to adequately recapitulate IO therapies.

Cancer intra-tumor heterogeneity and its evolution

Cancer is a disease that evolves



A simplified model of cancer evolution



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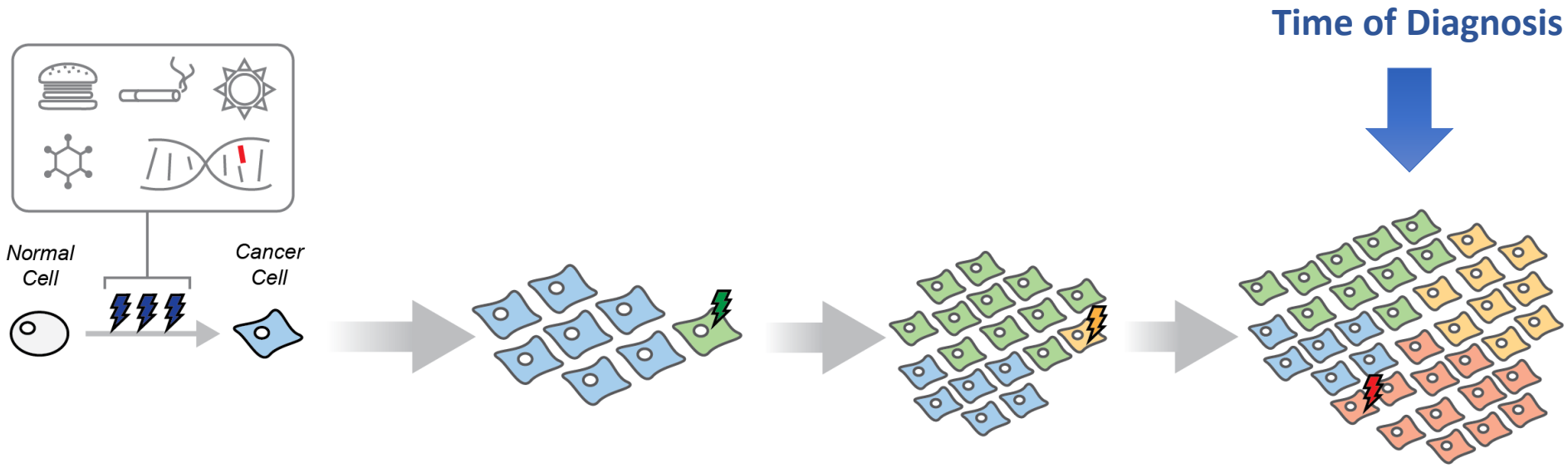

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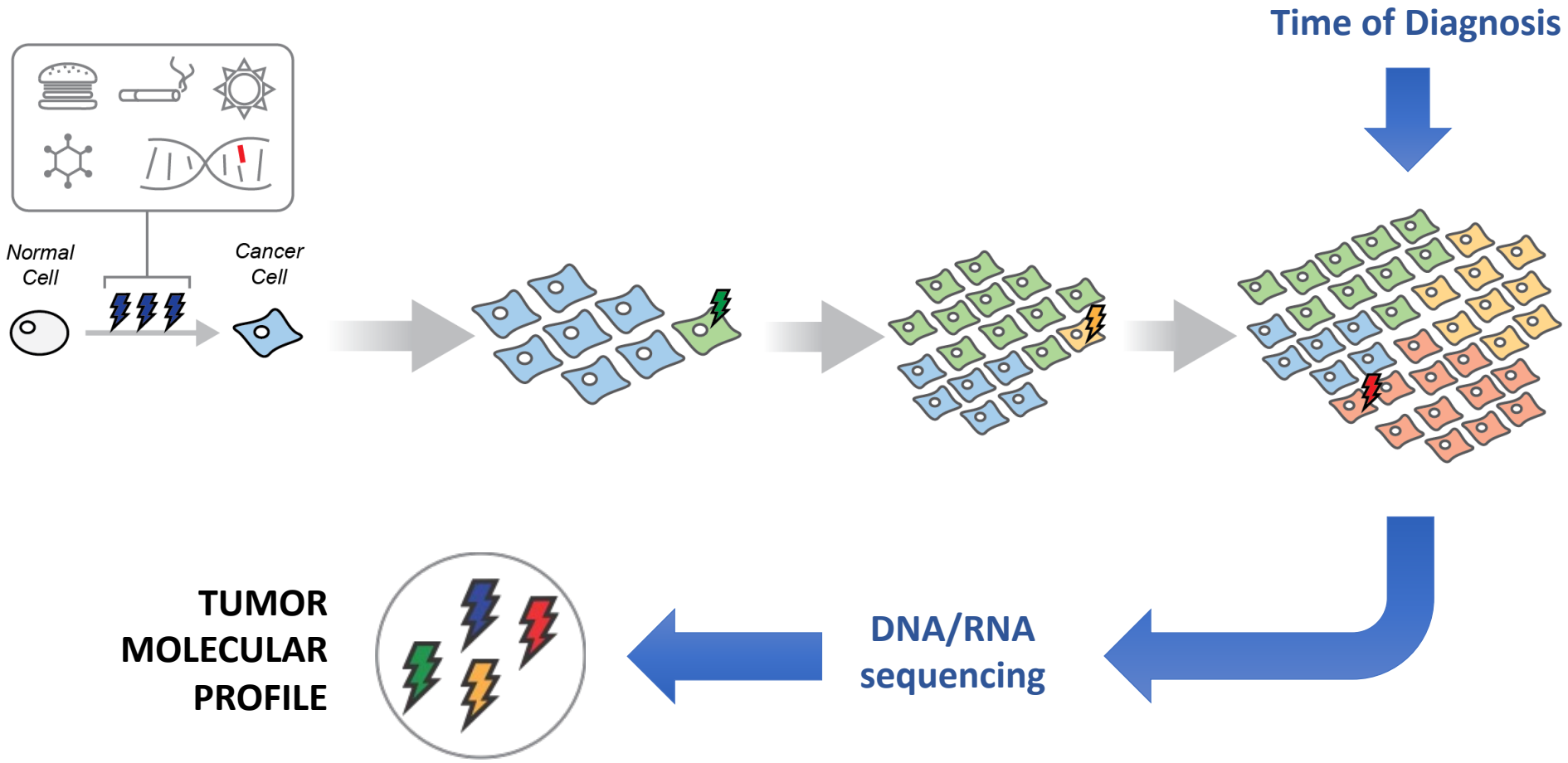
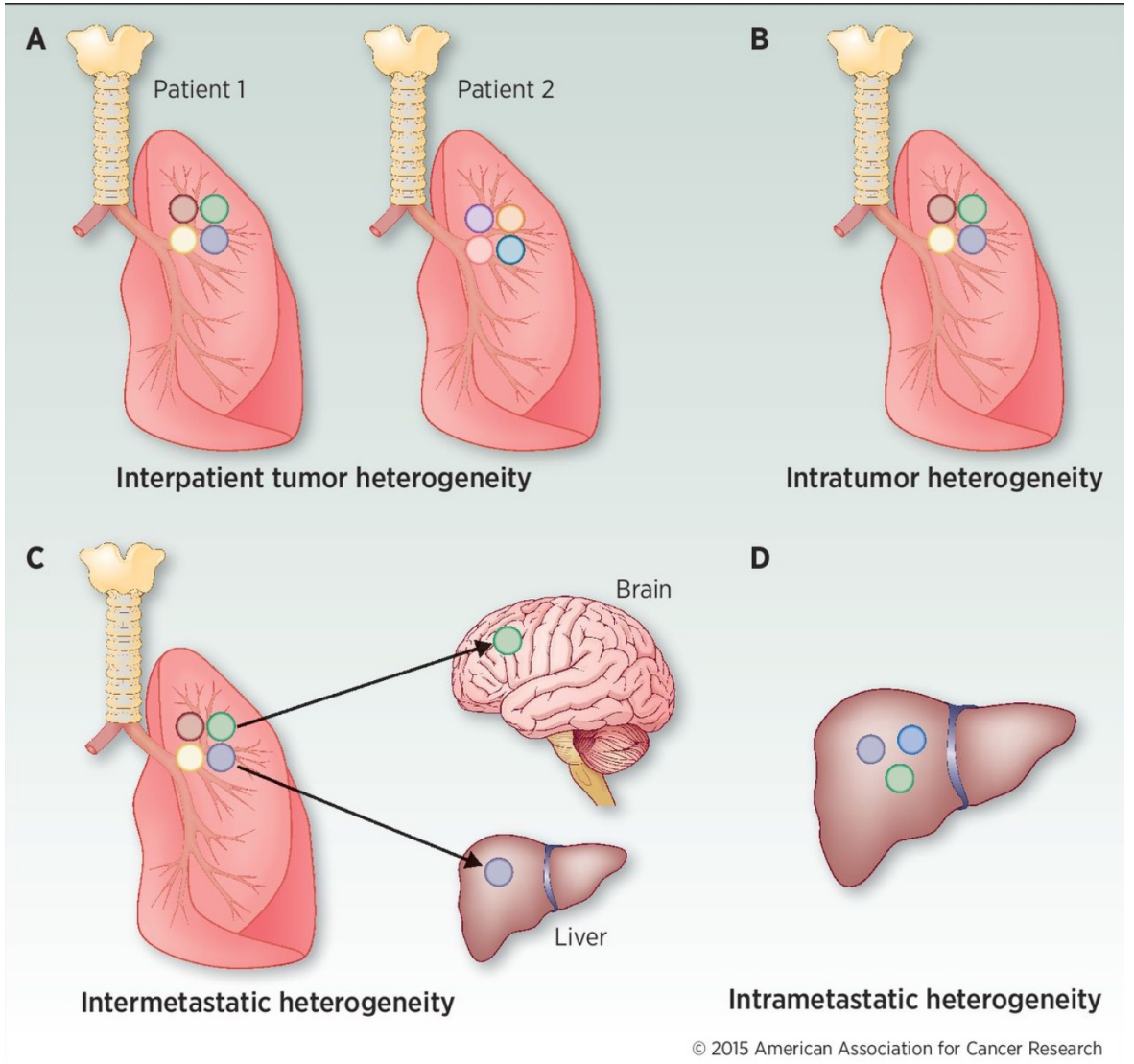
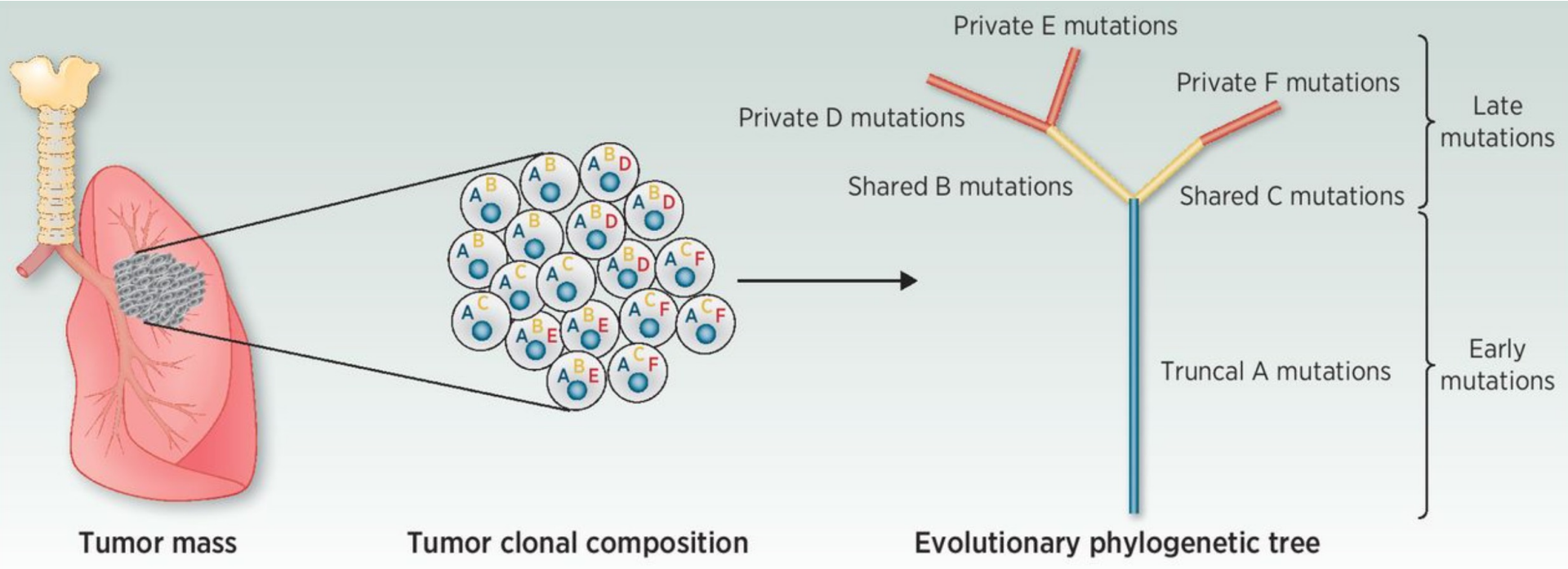


Intra-tumor heterogeneity and metastasis

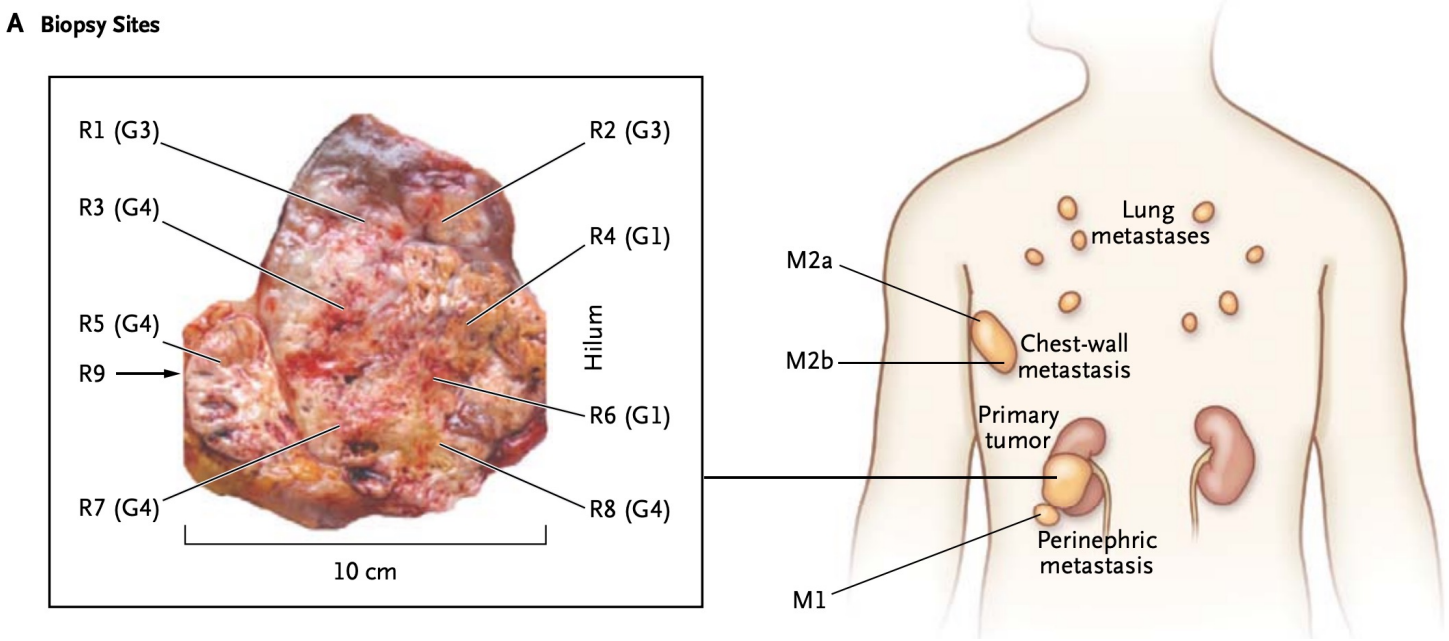


Intra-tumor heterogeneity

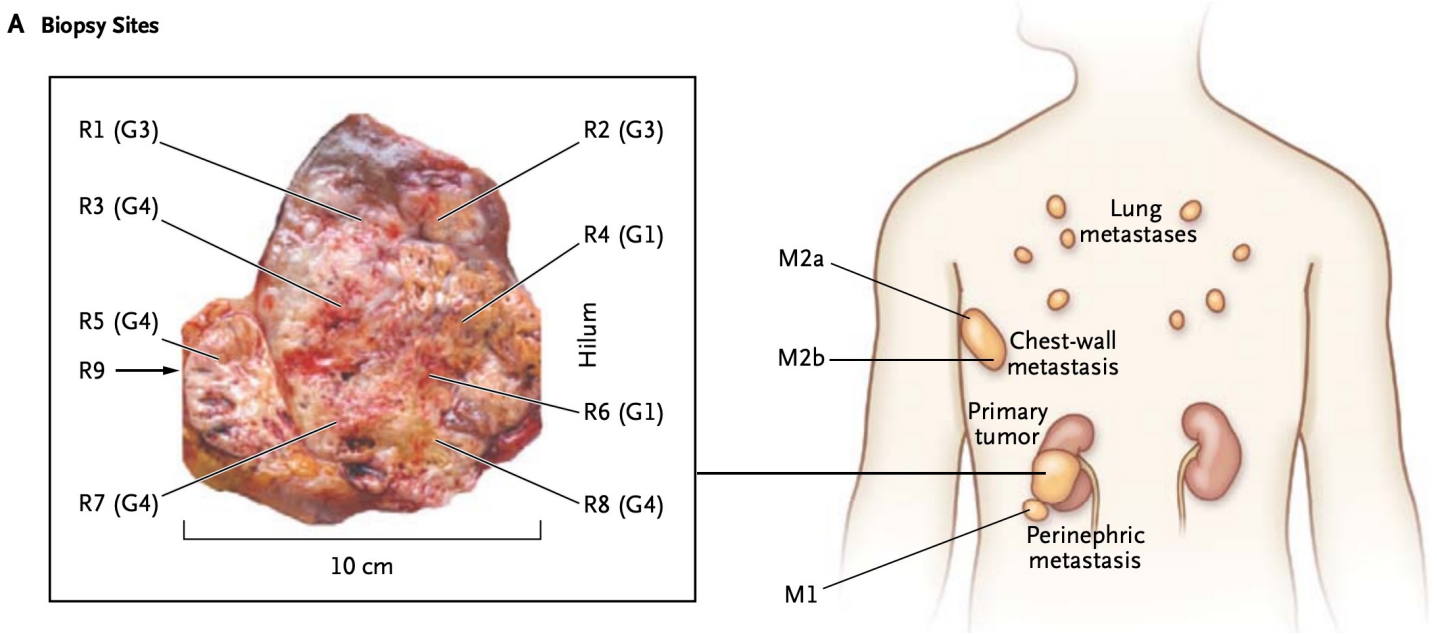


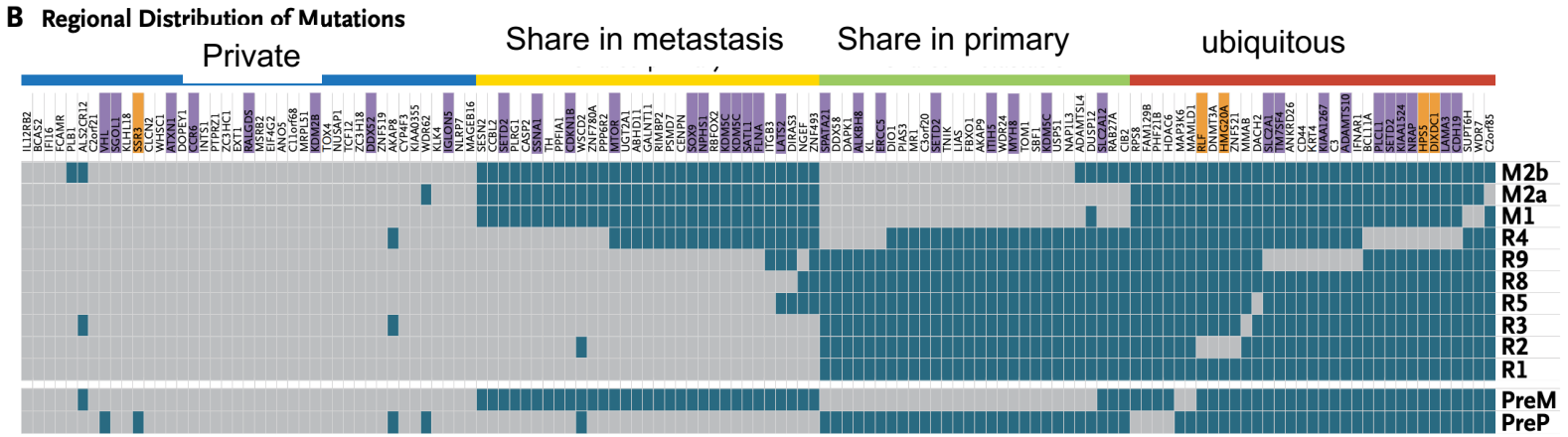
Phylogenetic tree analyses: study of cancer evolution driven by accumulation of genetic mutations

Multi-regional sampling

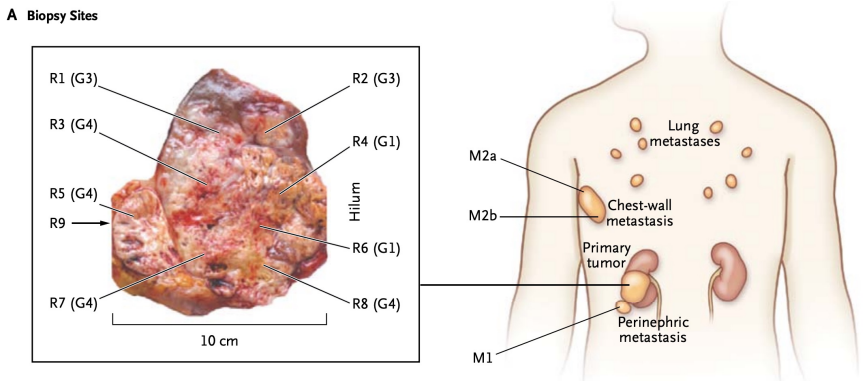


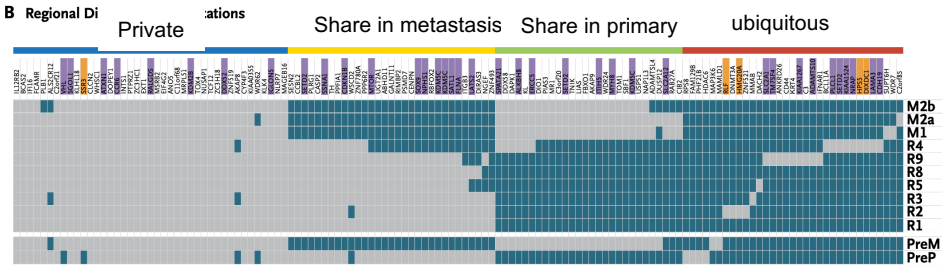
Multi-regional sampling





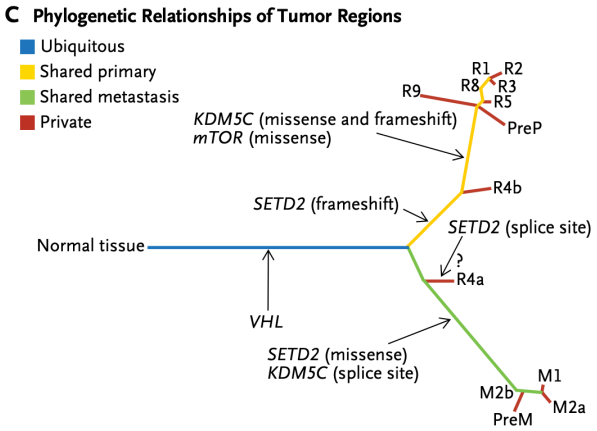
Multi-regional sampling



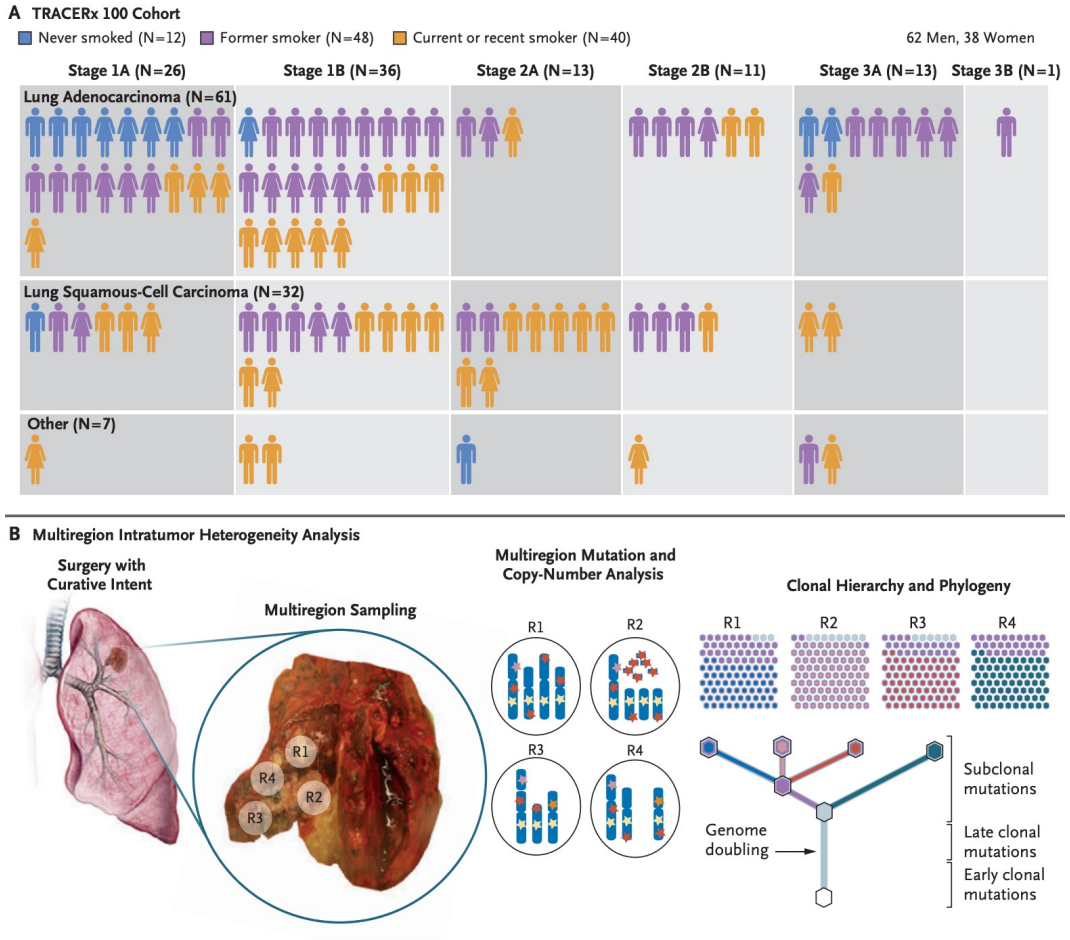


Tumor phylogenetic trees

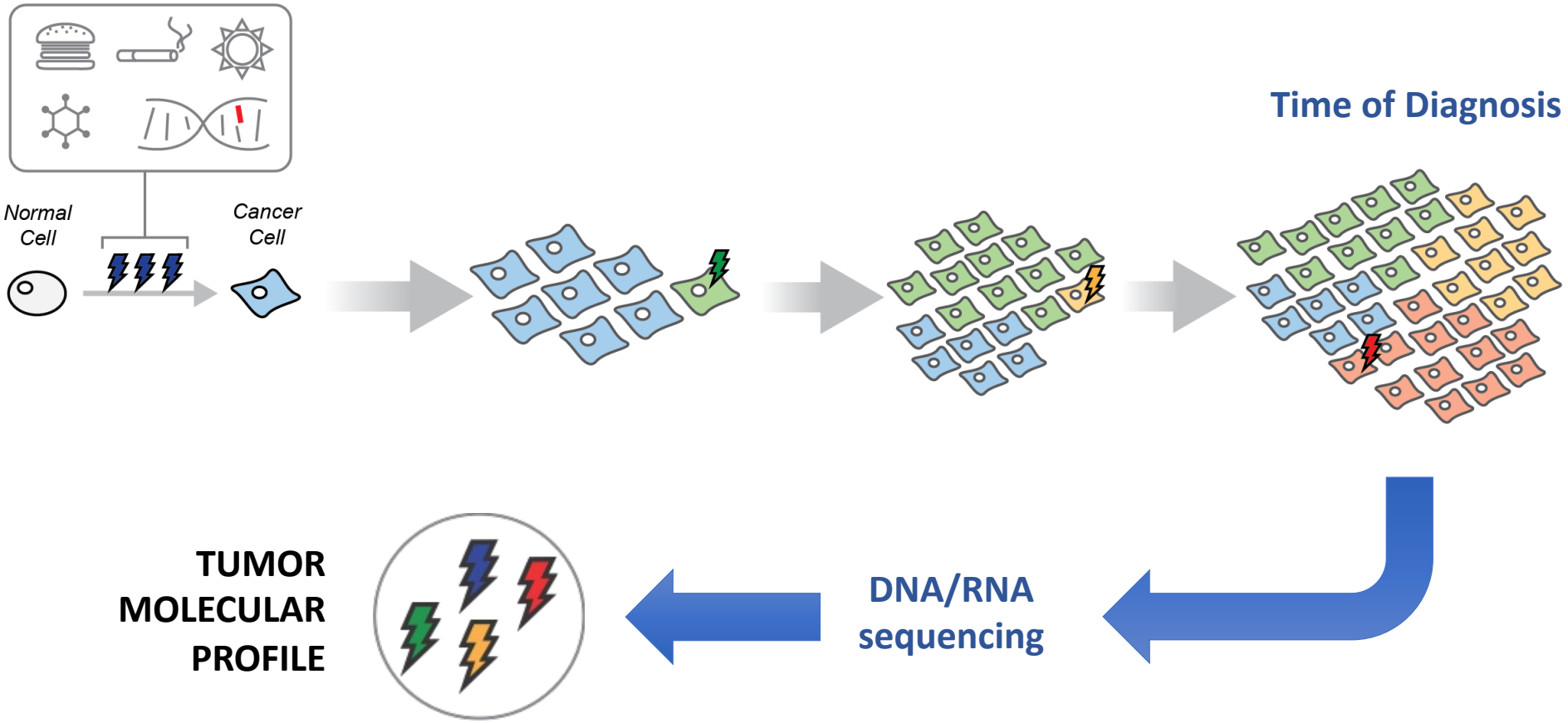
Ubiquitous / Shared /Private
mutations allows to reconstruct the evolutionary history of the tumor



Tracking tumor evolution



(Jamal-Hanjani et al. NEJM 2017)

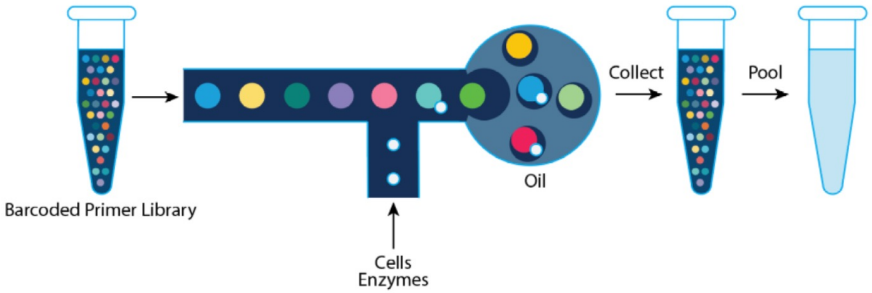


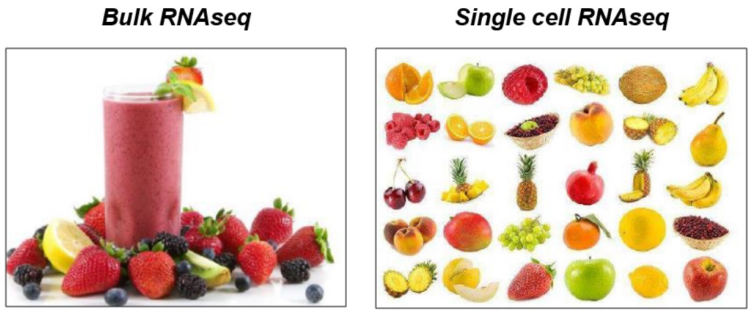
How can we analyze
intra tumor heterogeneity?

What is the problem of bulk analyses?

Single-cell molecular profiles

scRNA: Cell barcoding allows to determine which transcript come from which cells

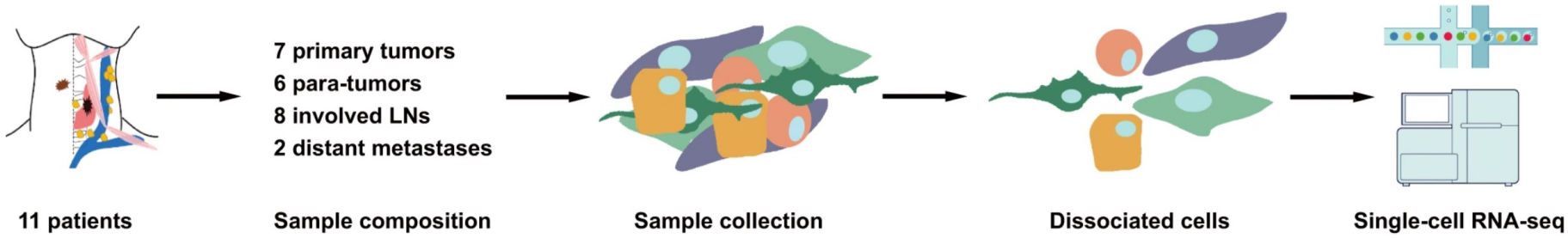




Single-cell molecular profiles

Single cell omics has revolutionized our ability to study **intra-tumor heterogeneity**

- Diversity among difference cancer cells within the same tumor
- Diversity of non-tumor cells (e.g., immune cells) surrounding the tumor (tumor microenvironment)



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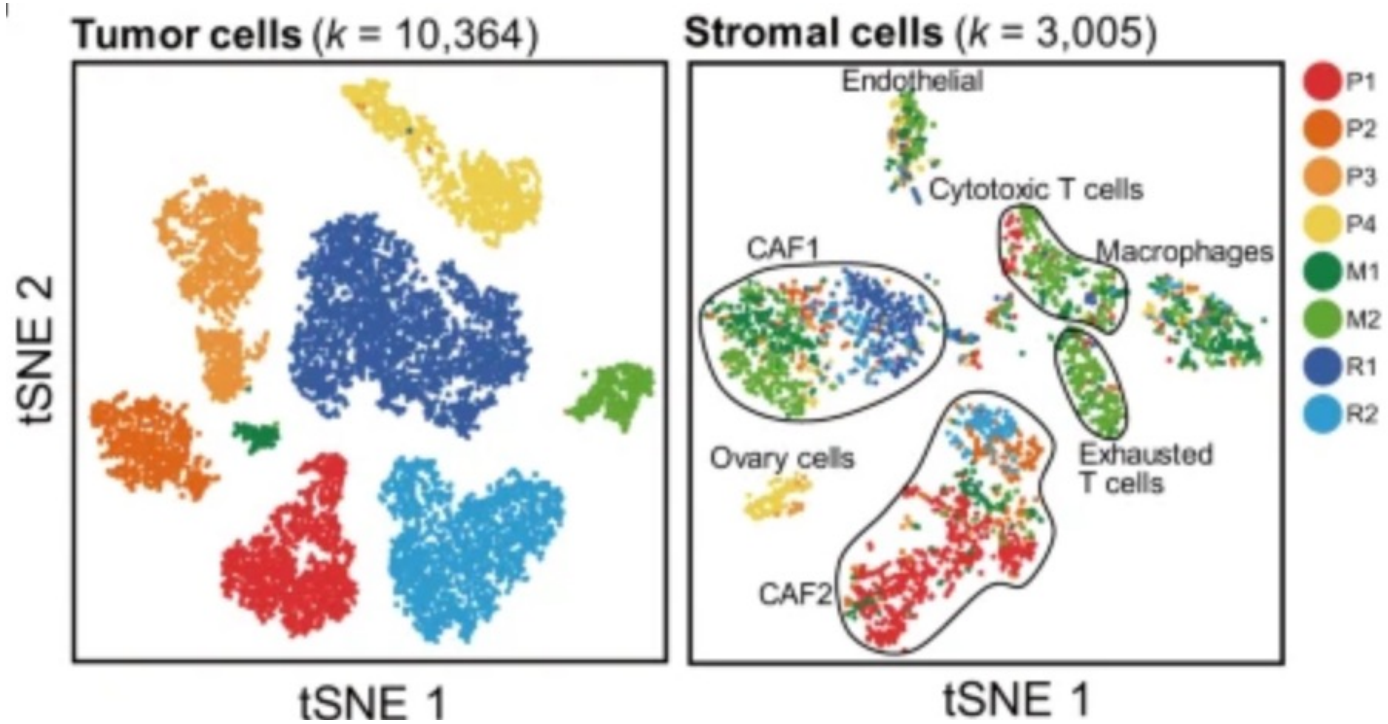
Ovarian cancer



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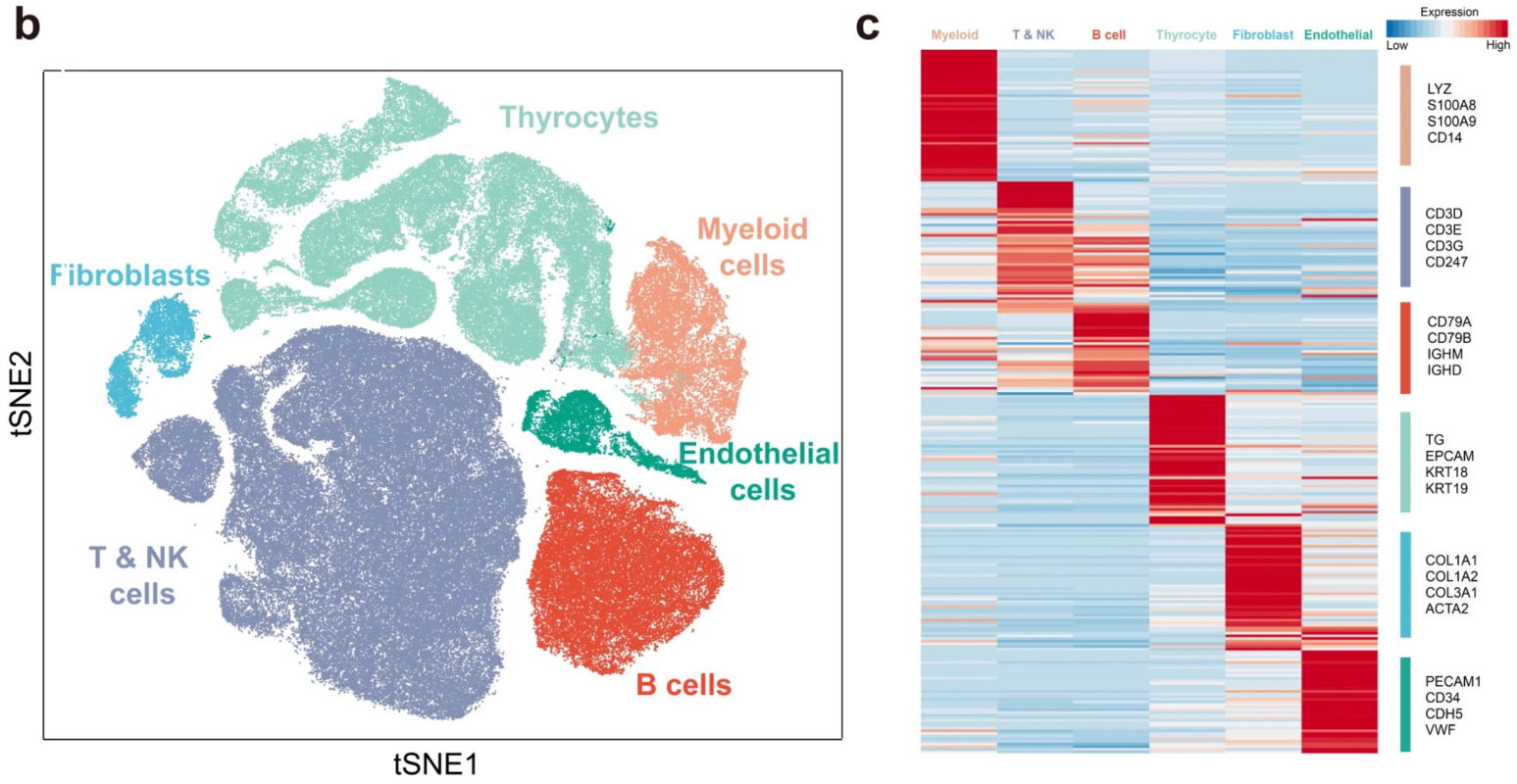
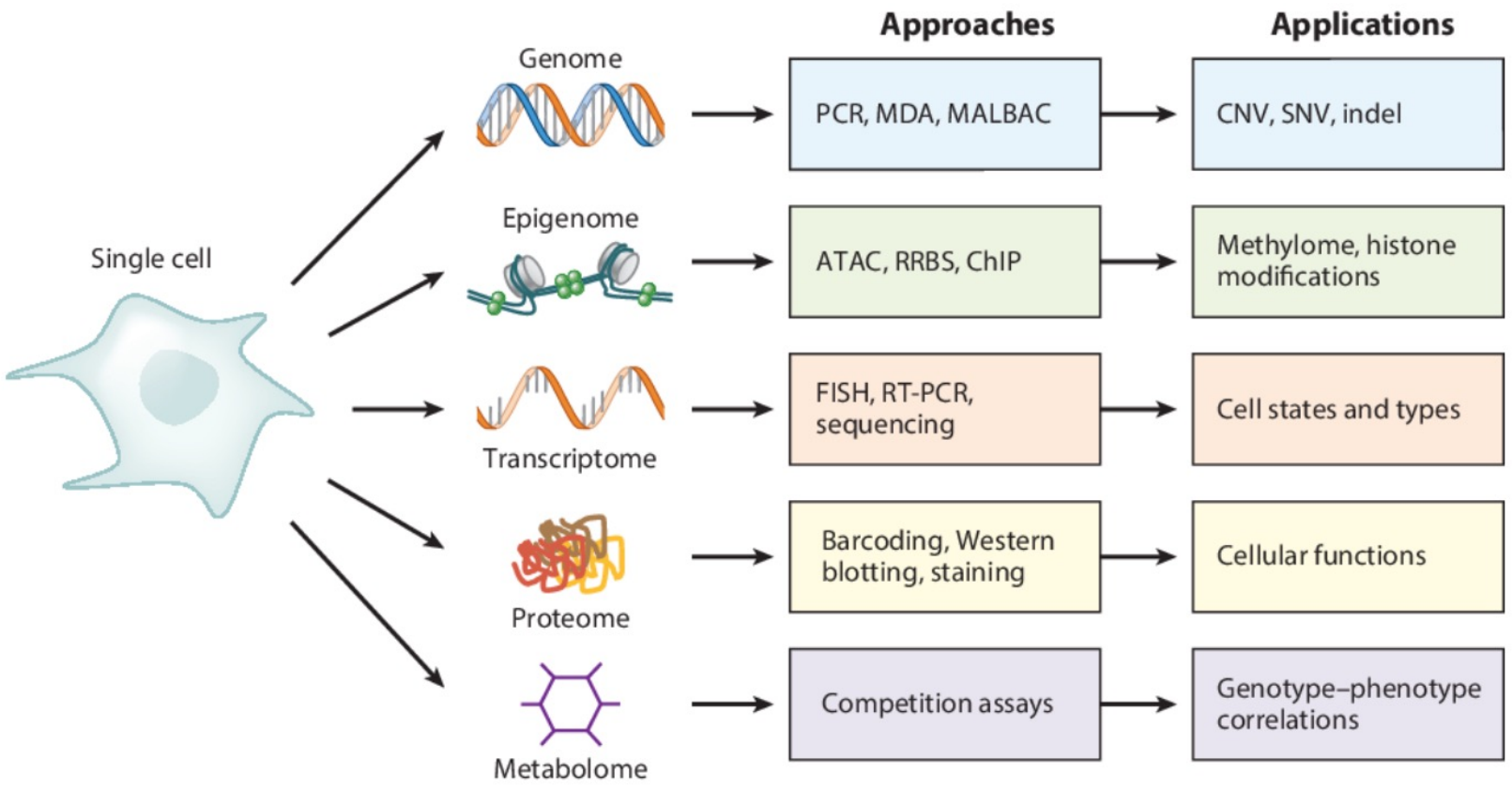


(Pu et al. Nature Comm 2021)

Single-cell molecular profiles

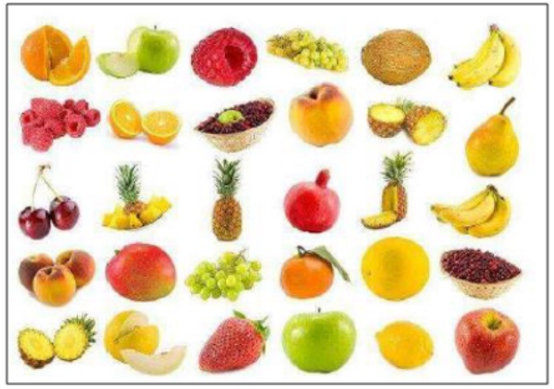
Single cell omics: Nowadays (almost) all genomic data can be generated at the single cell level



Spatial omics

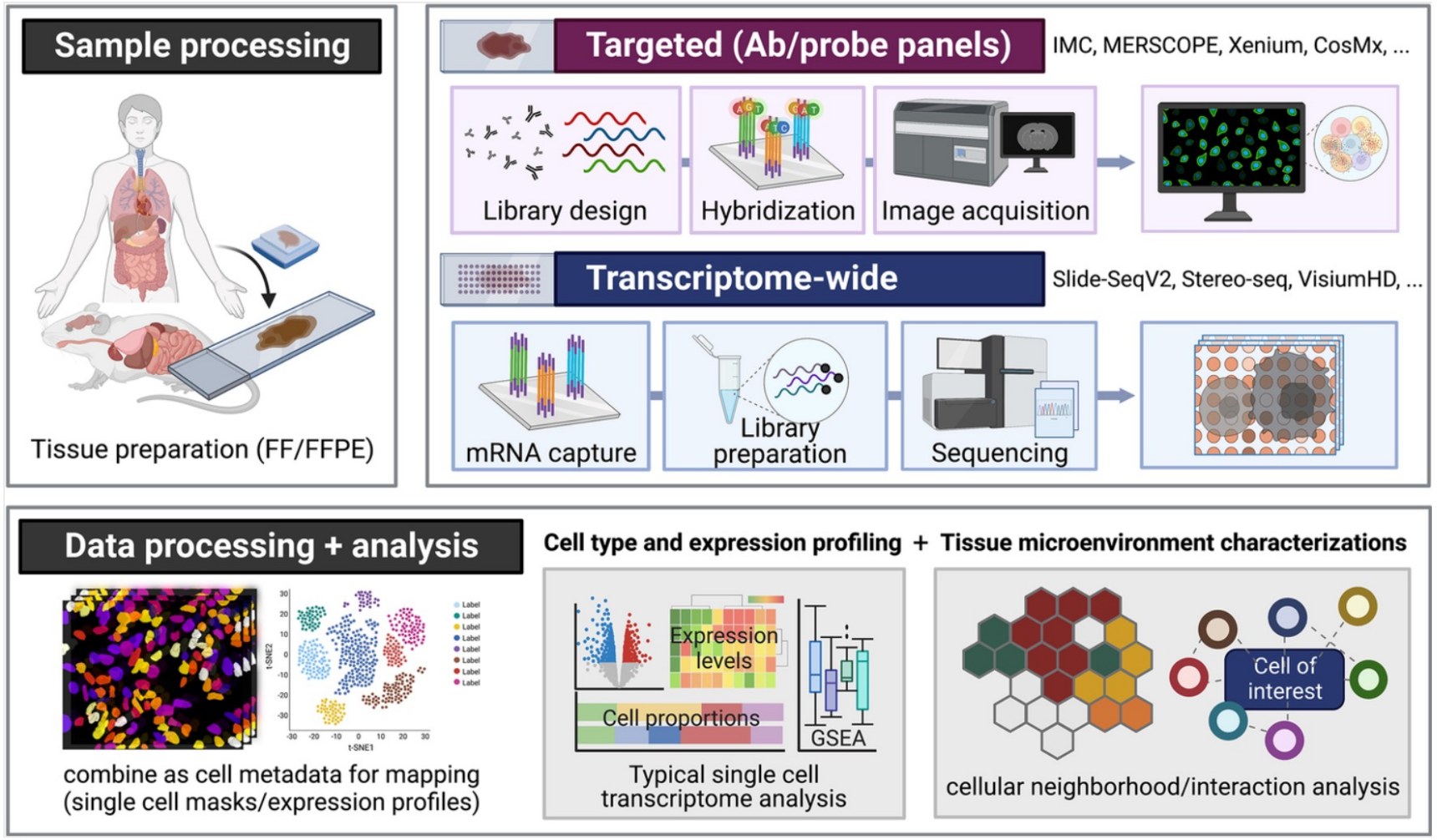
Bulk RNAseq

Single cell RNAseq



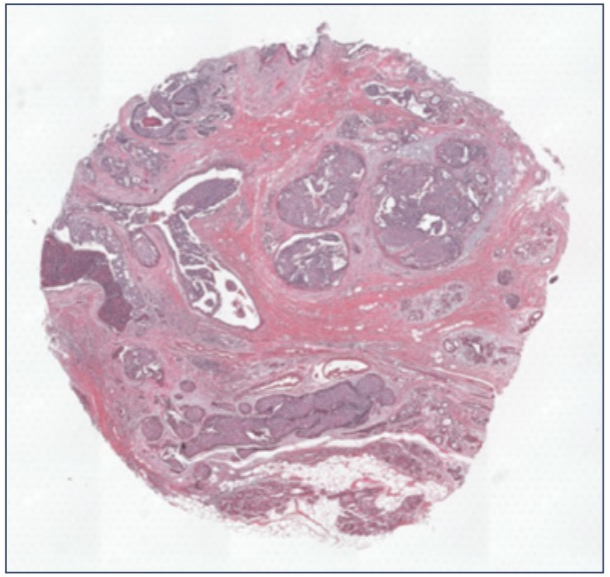
Spatial Transcriptomics

Spatial transcriptomics



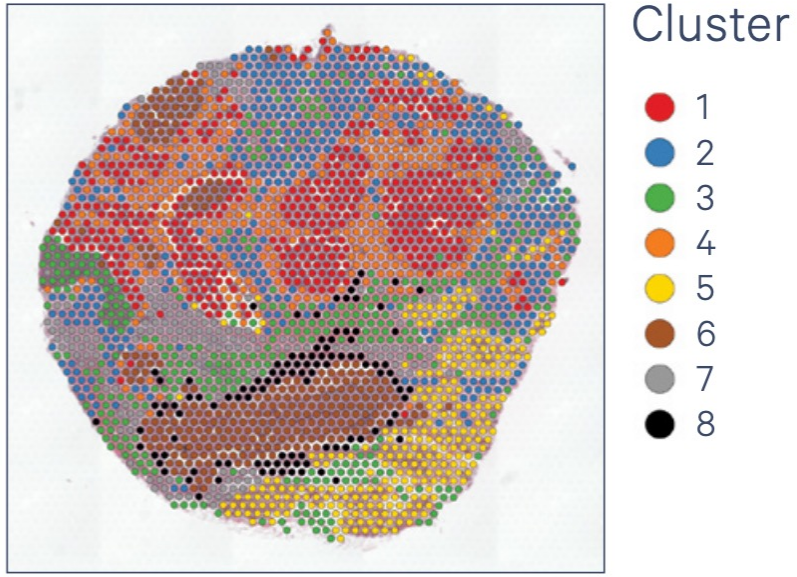
Spatial transcriptomics

A. H&E



Tumor tissue

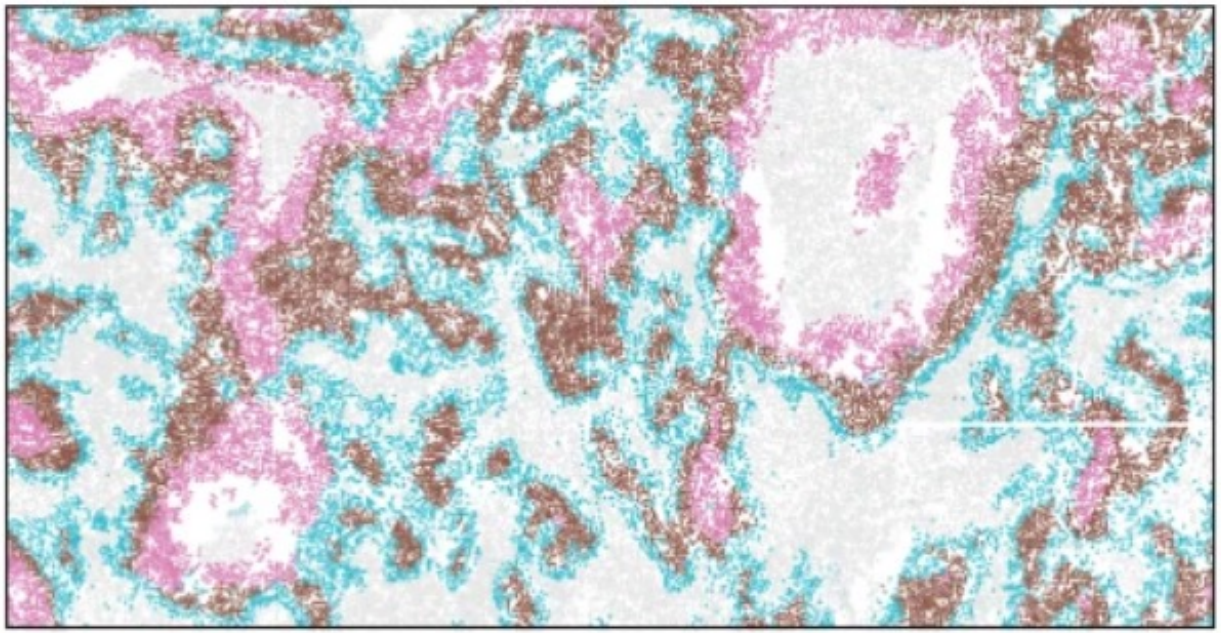
C. Spot clusters



spatial clusters based on gene expression

Spatial transcriptomics

Lung adenocarcinoma- tumor cells

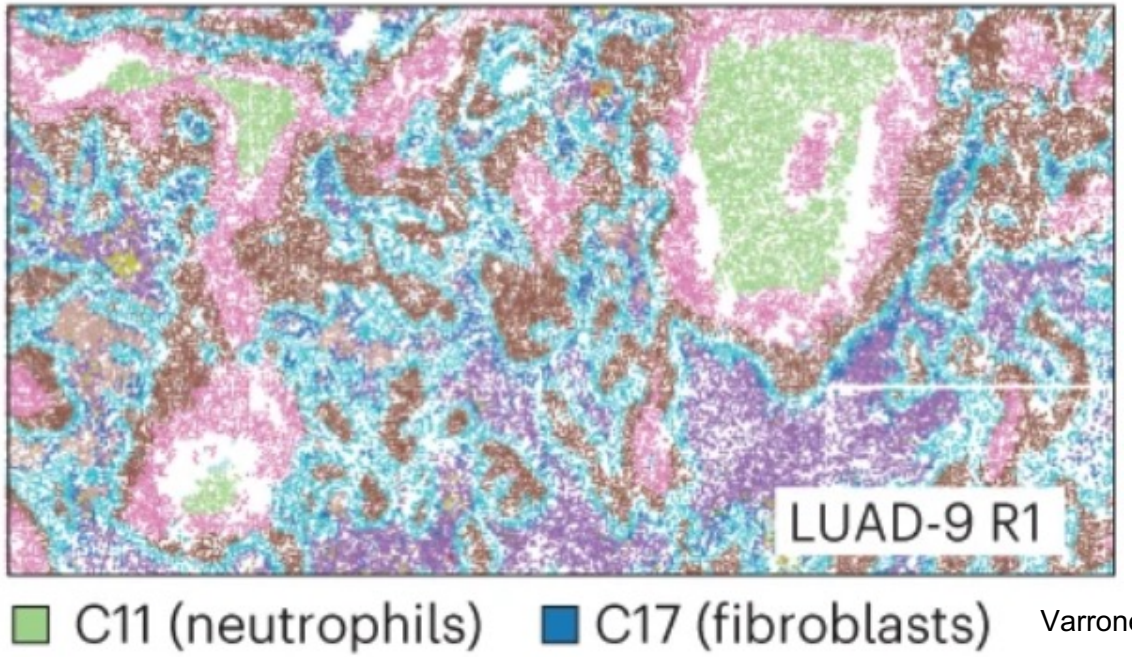


Varrone et al. 2023

3 categories of tumor cells
pink
Brown
clear-blue

Tumor cells spatially distribute have a distinct expression profile

Spatial transcriptomics



Varrone et al. 2023

The gene expression of the tumor cells might be influenced by their proximity
With the tumor microenvironment and vice versa

Paper for Wednesday

https://www.nejm.org/doi/pdf/10.1056/NEJMoa1616288

Pdf will be in the moodle with a list of questions to guide the discussion