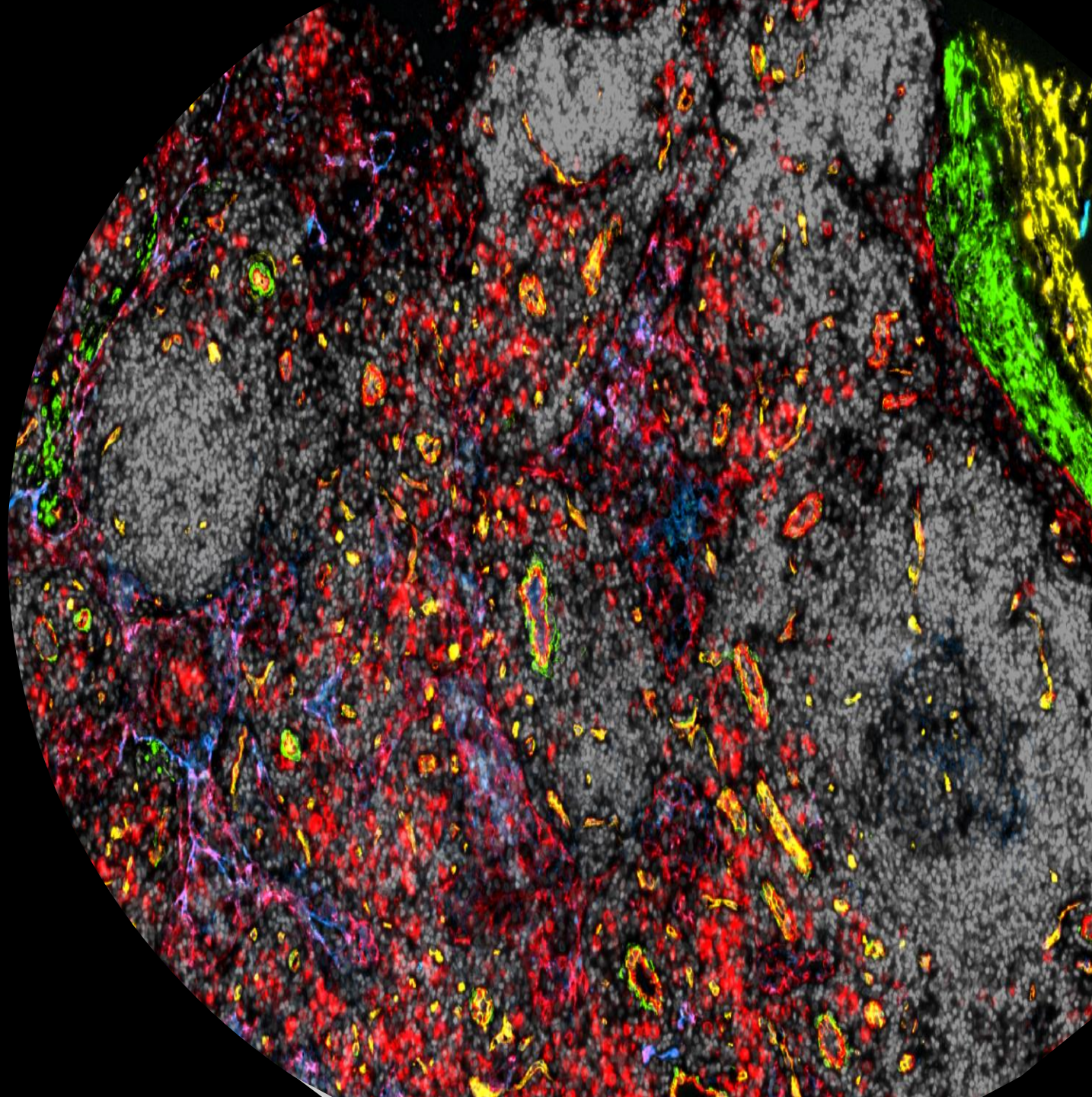
Cancer Biology I

Part-II

Week 9



AGENDA

Nov 3rd: Cancer genomics- mutations

Nov 10th: Cancer genomics-copy number alterations, heterogeneity, tumor evolution

Nov 17th: Cancer Epigenetics- chromatin 3D structure, cell plasticity

Nov 24th: – Major signaling pathways leading to cancer

Dec 1st: Cancer Therapies – chemo and targeted therapies

Dec 8th: Introduction to immunotherapies –

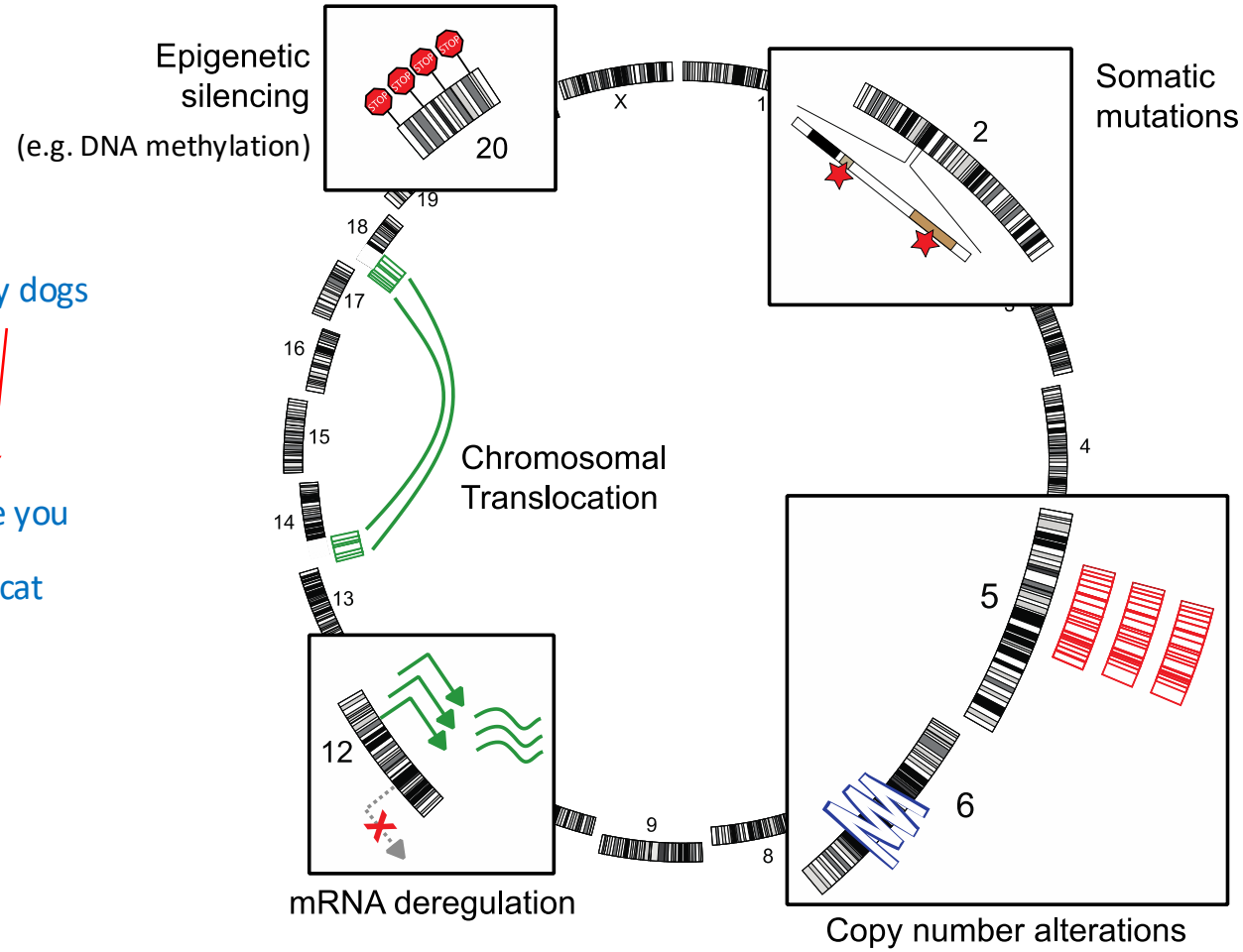
Dec 15th: discussion of unclear points and career development discussion towards a PhD

Dec 17th: Exam 2-4 PM (room to be decided)

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

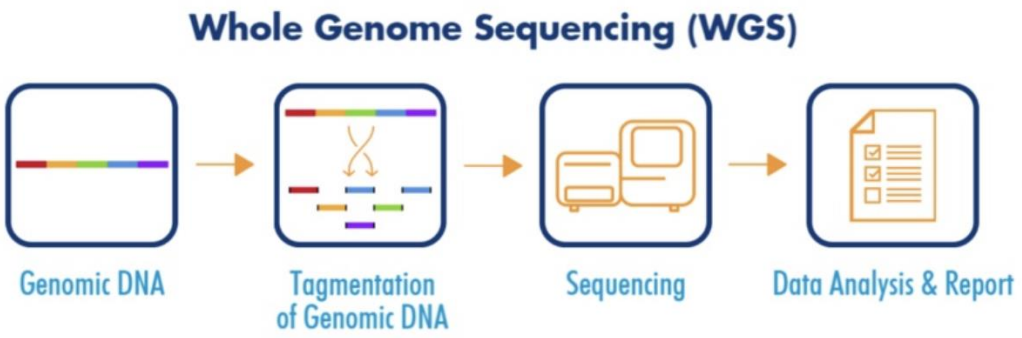
You like my dogs

You like __ dogs

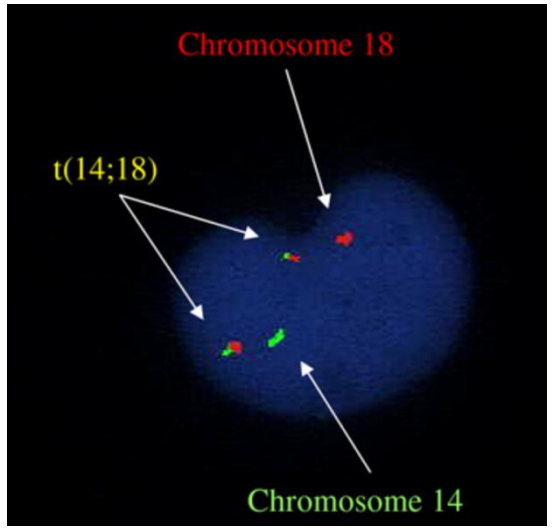
You like like my dogs

How can we detect copy number alterations?

Copy Number Alterations:



vs



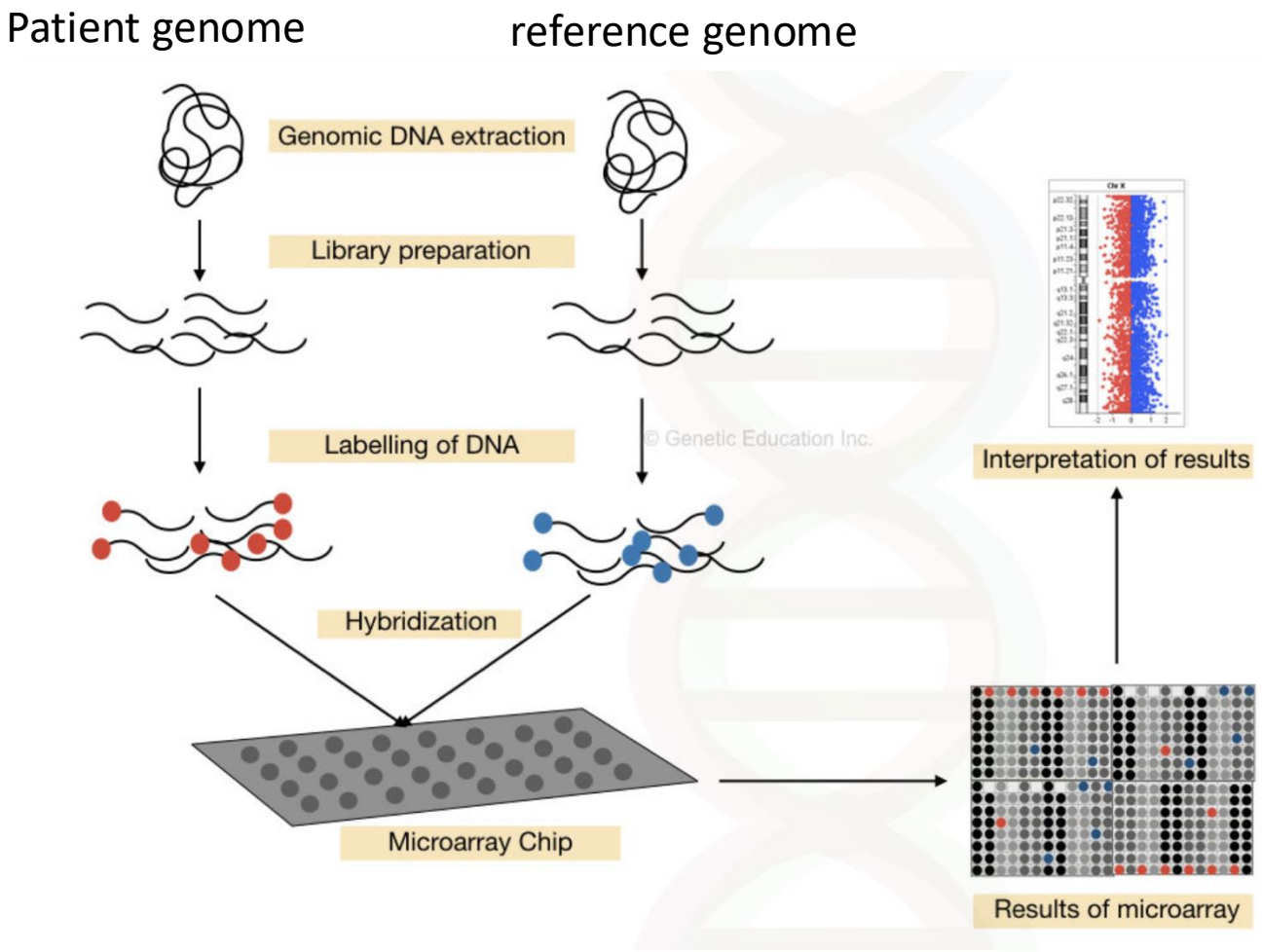
whole genome sequencing
or SNP array

FISH
Fluorescent *in-situ* hybridization

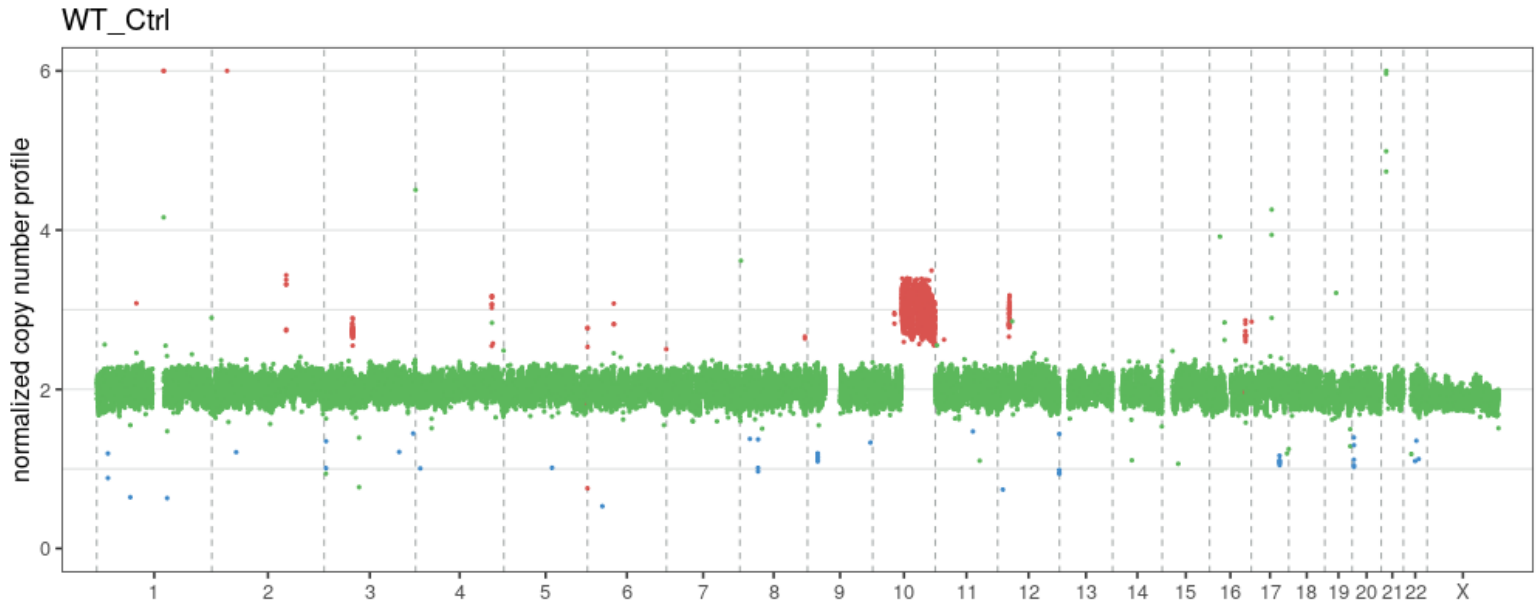
What is the major difference between these two approaches?

SNP array:

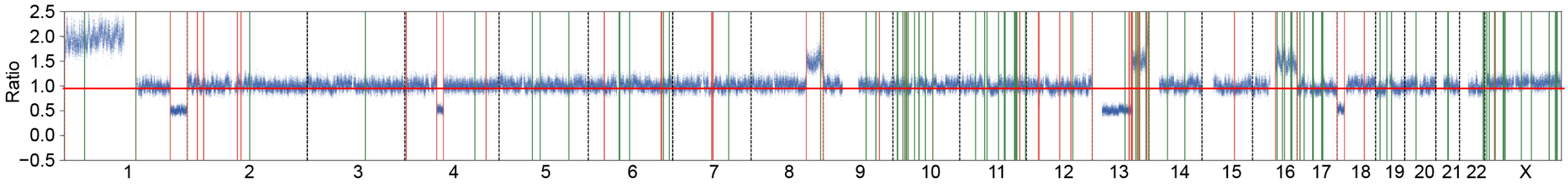
SNPs in an individual's genome, occurring on average once every 1,000 nucleotides.



Copy Number Alterations: whole genome sequencing or SNP array for each patient



Copy Number Alterations: whole genome sequencing or SNP array for each patient

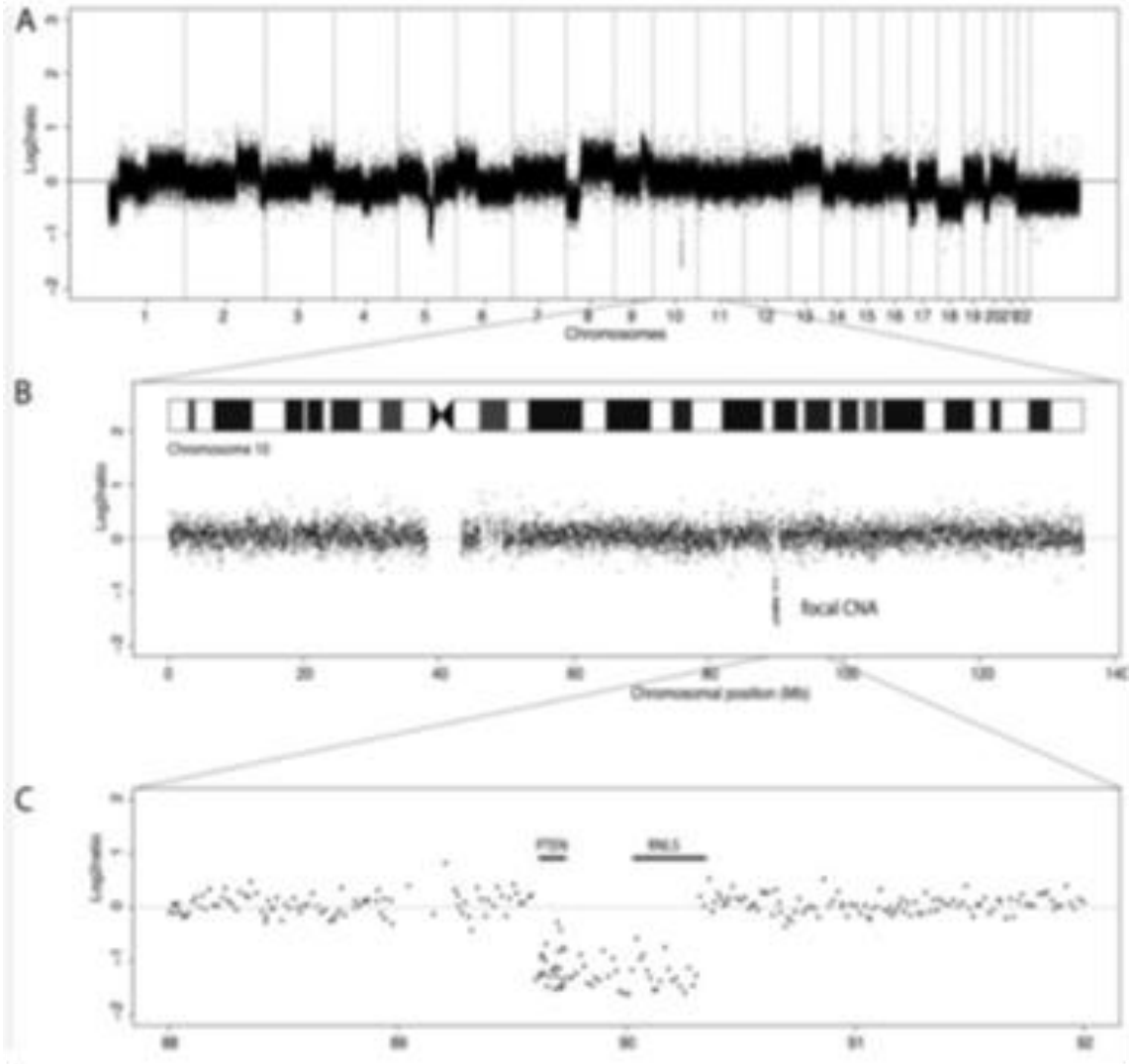


Copy Number Alterations profile for each patient

Whole genome

Whole chromosome

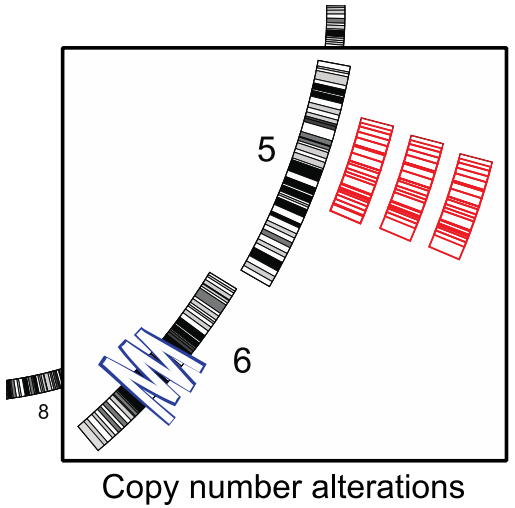
A region
in the chromosome



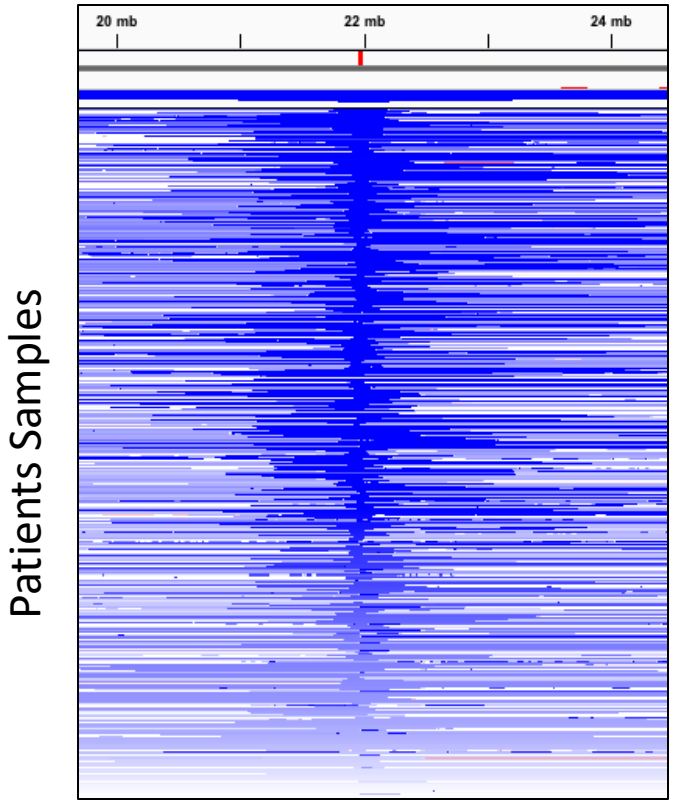
Copy Number Alterations (CNA)

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

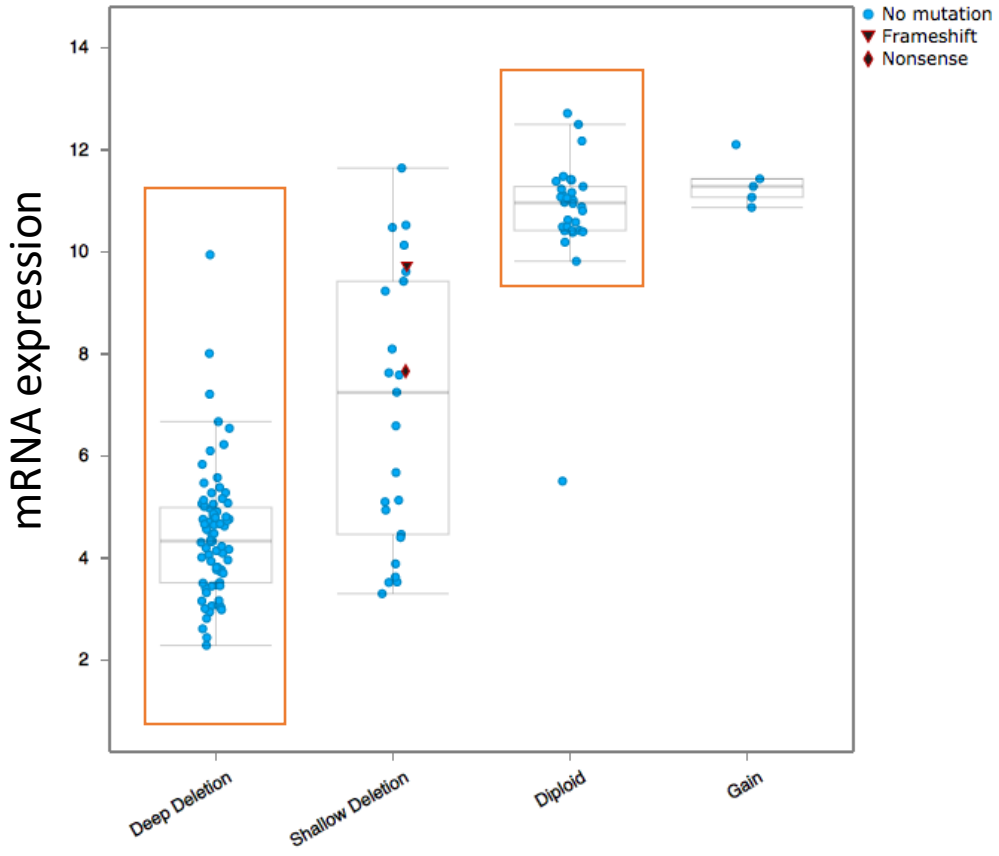
Why do we have heterozygous or homozygous CNA?



Focal Deletions derived from multiple cancer patients

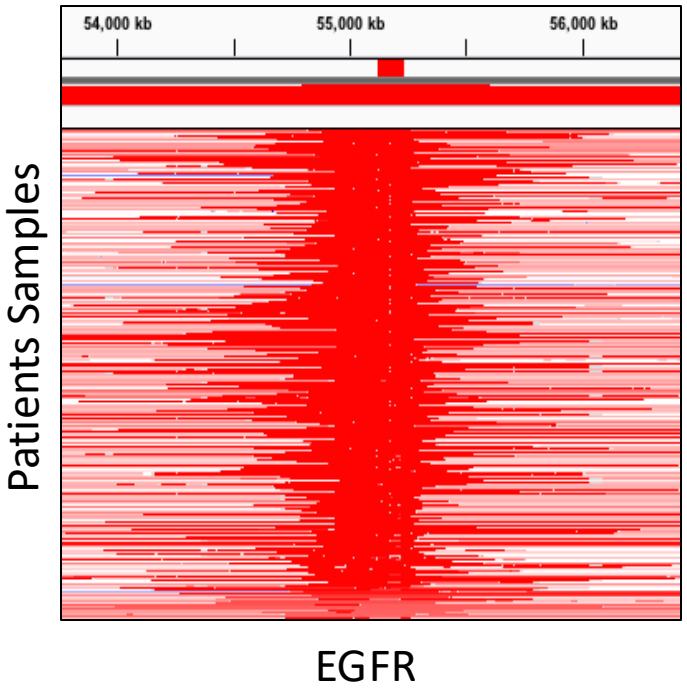


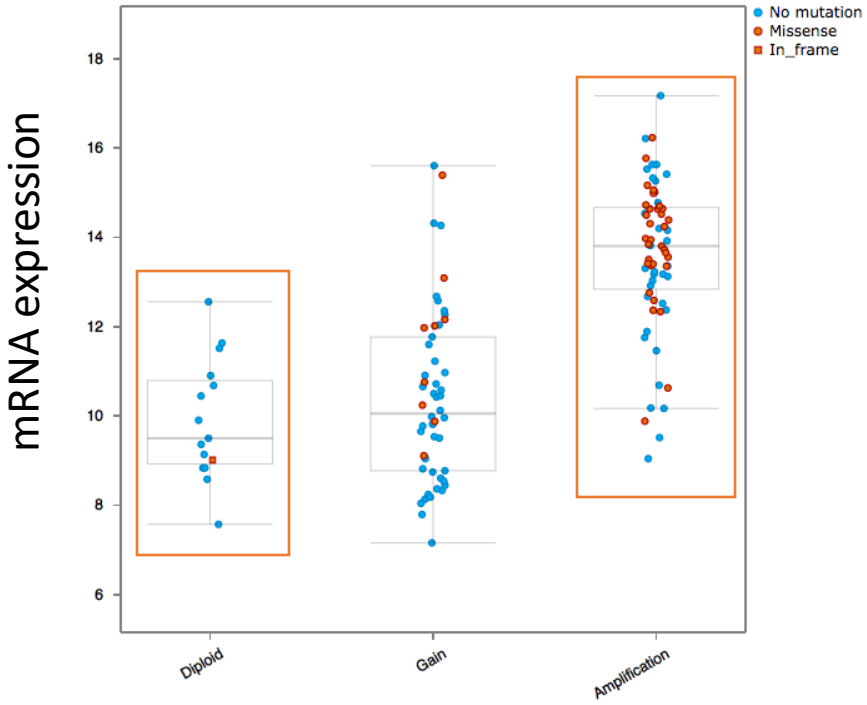
CDKN2A
(ARF/p16)



inactivating a **tumor suppressor**

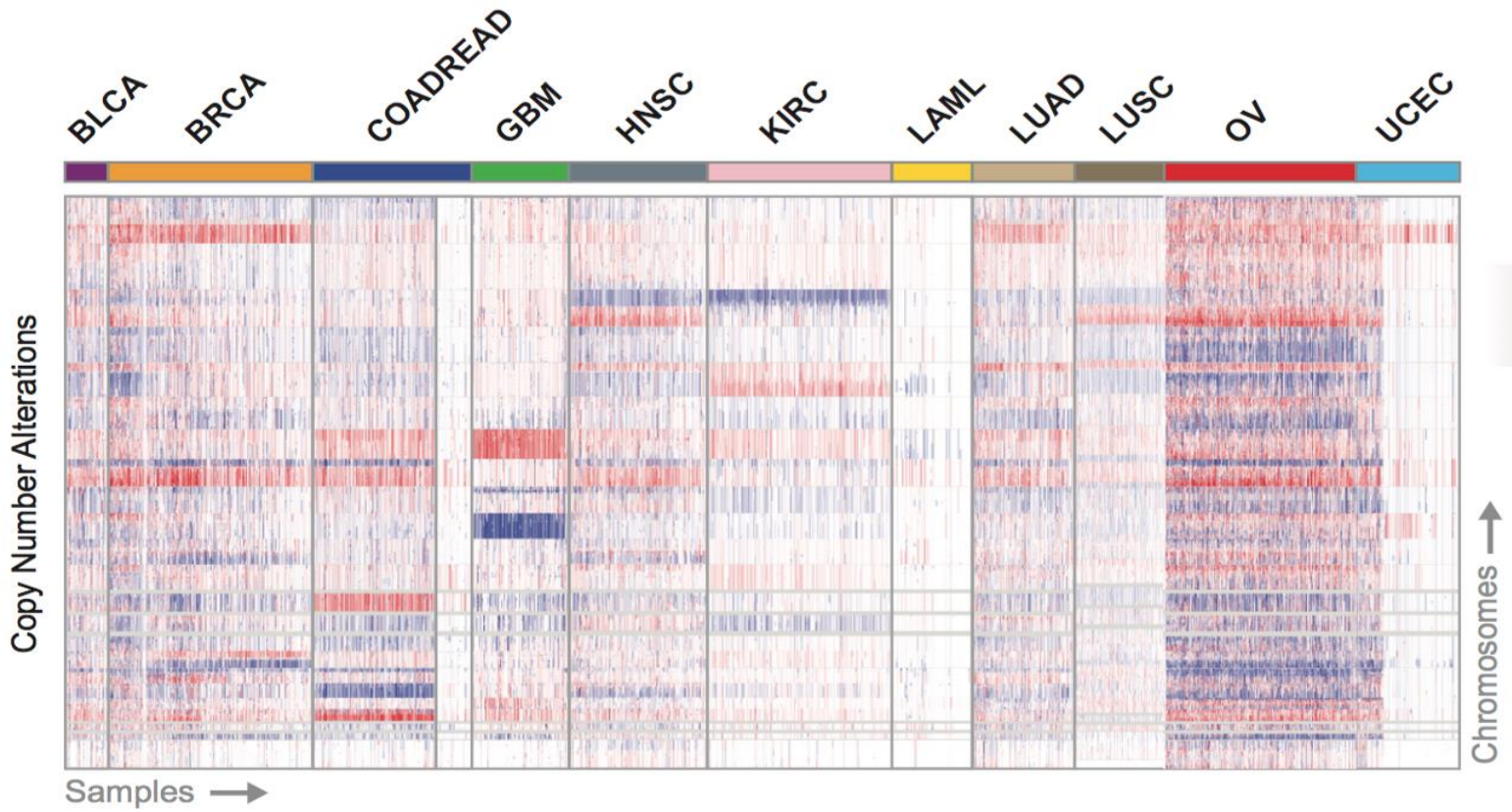
Focal Amplifications





(activating an **oncogene**)

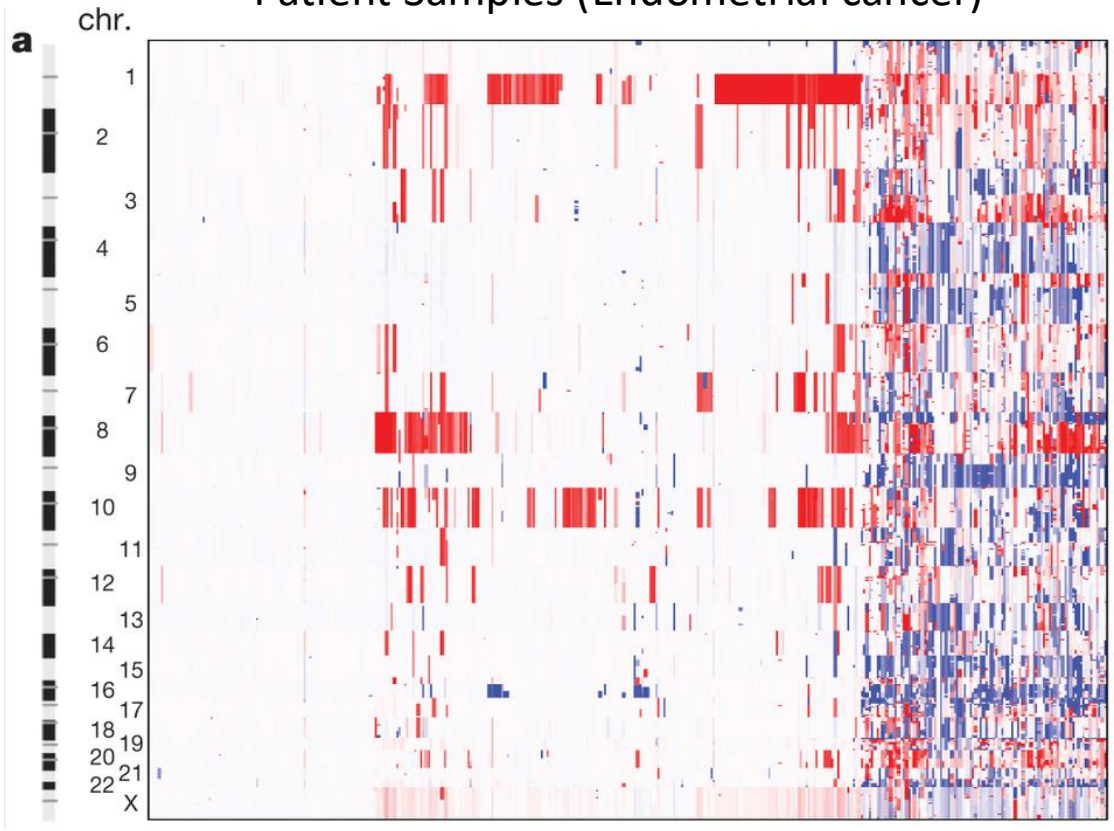
Copy Number Alterations inter-tumor heterogeneity

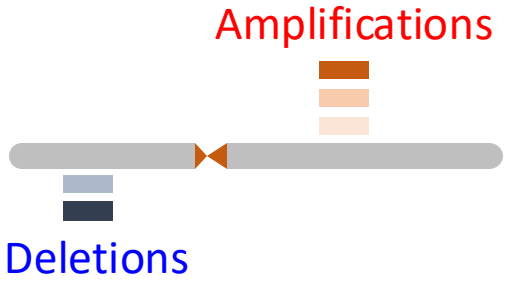


Copy Number Alterations inter patient heterogeneity

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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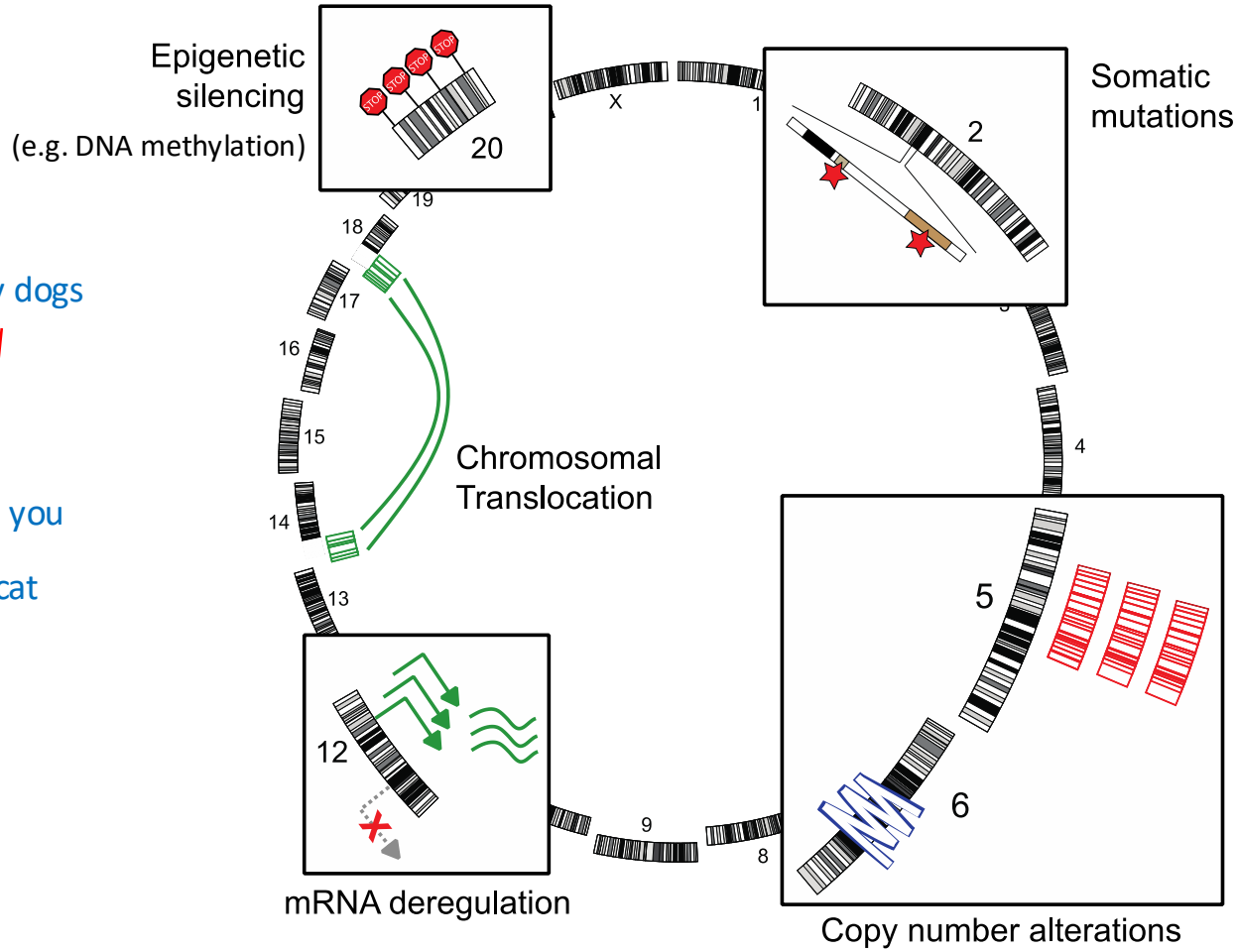
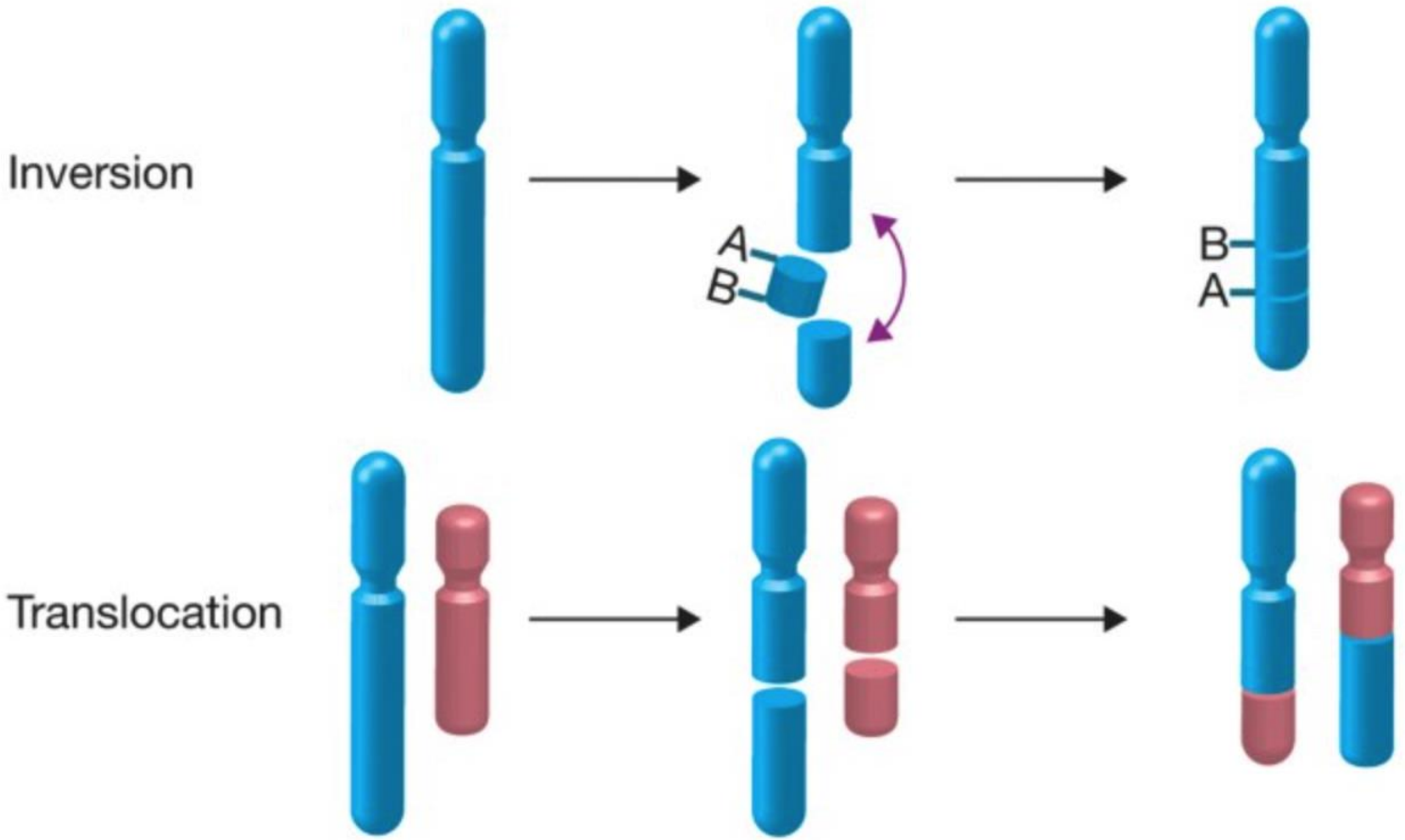
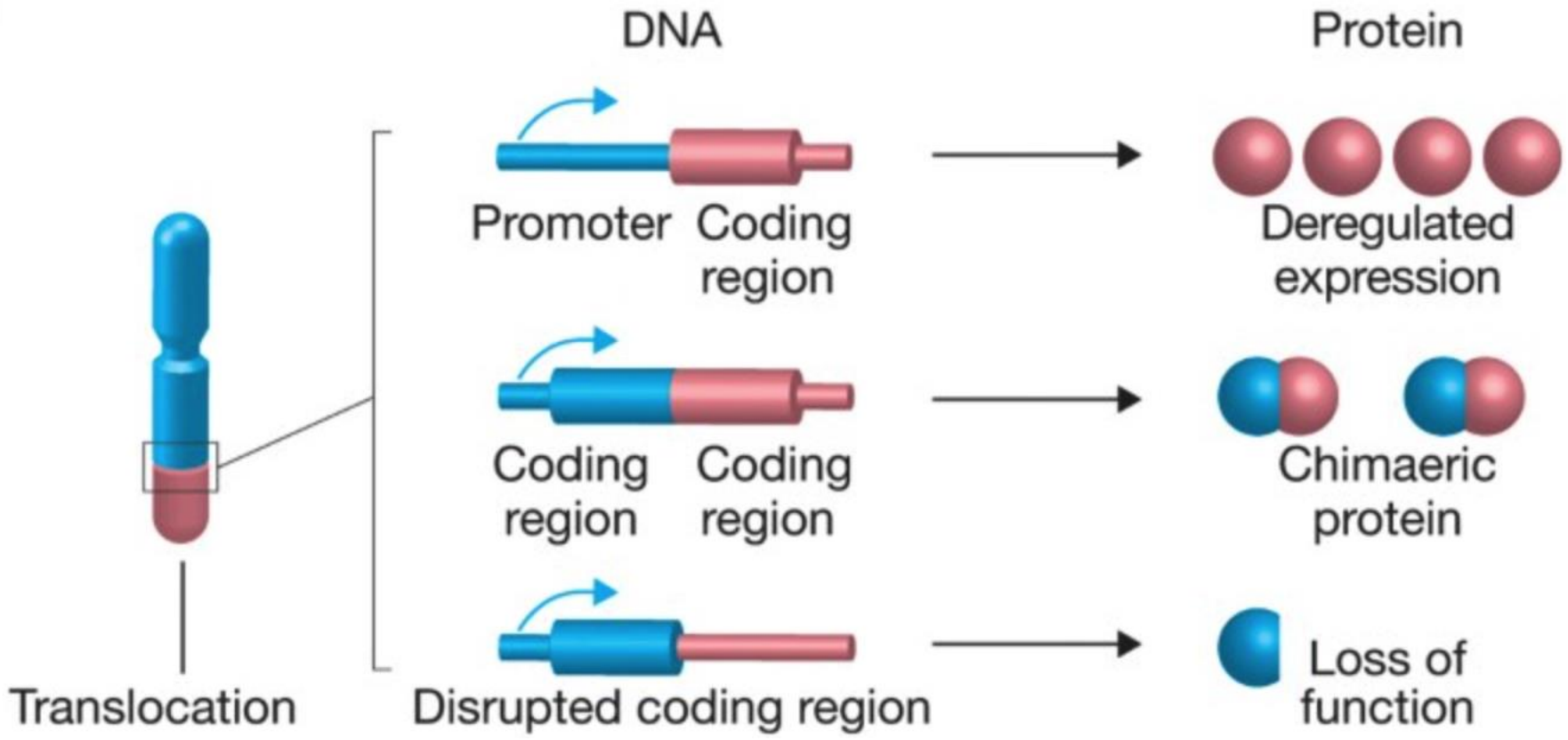
change the meaning



Chromosomal Structural Variants

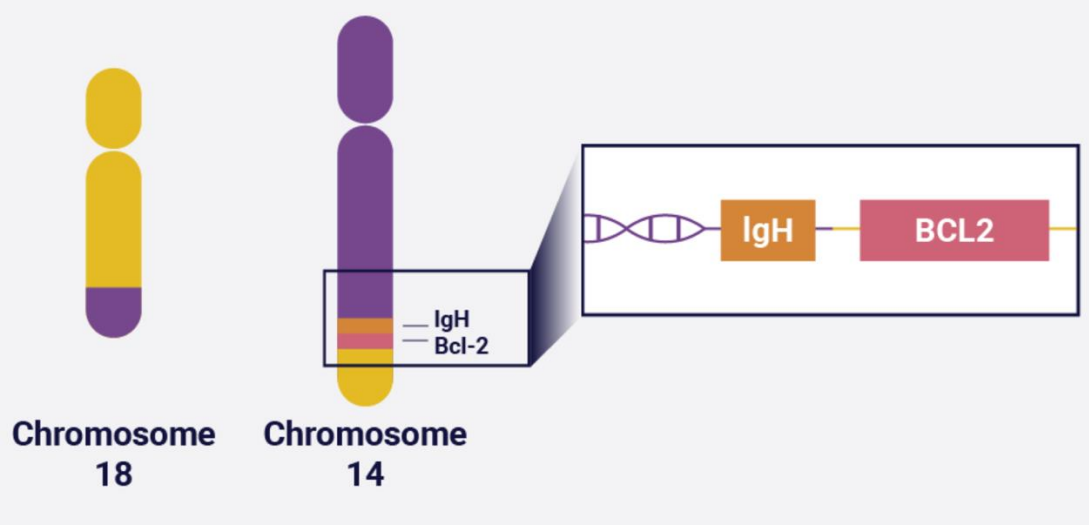


Chromosomal Structural Variants

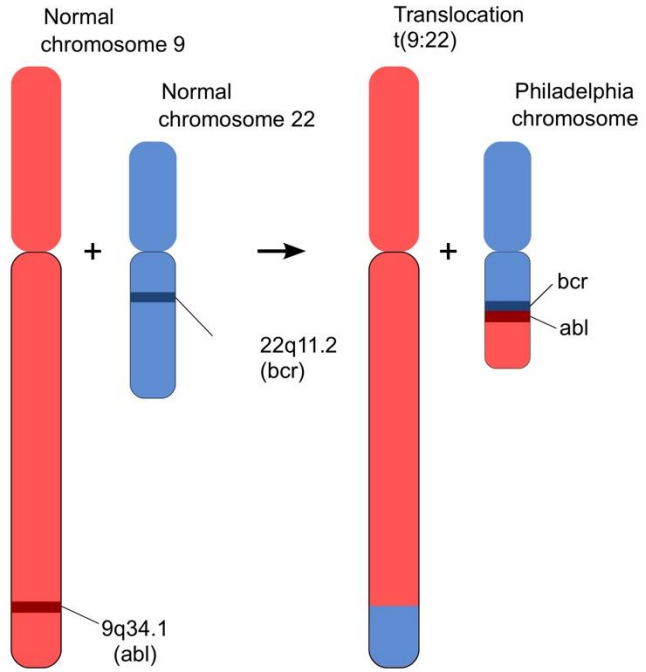


Chromosomal Structural Variants

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



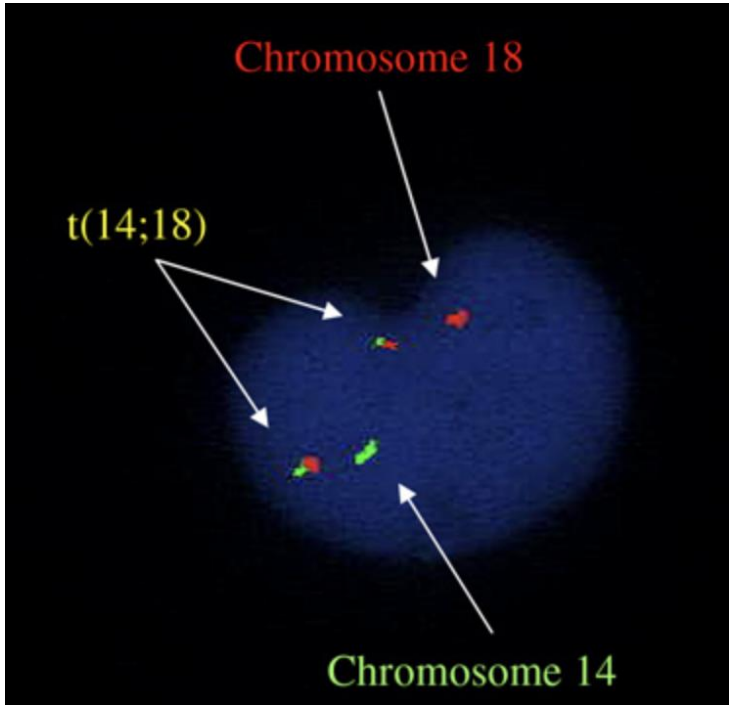
BCR-ABL fusion protein: fusion generate a new protein with hyper-active kinase activity

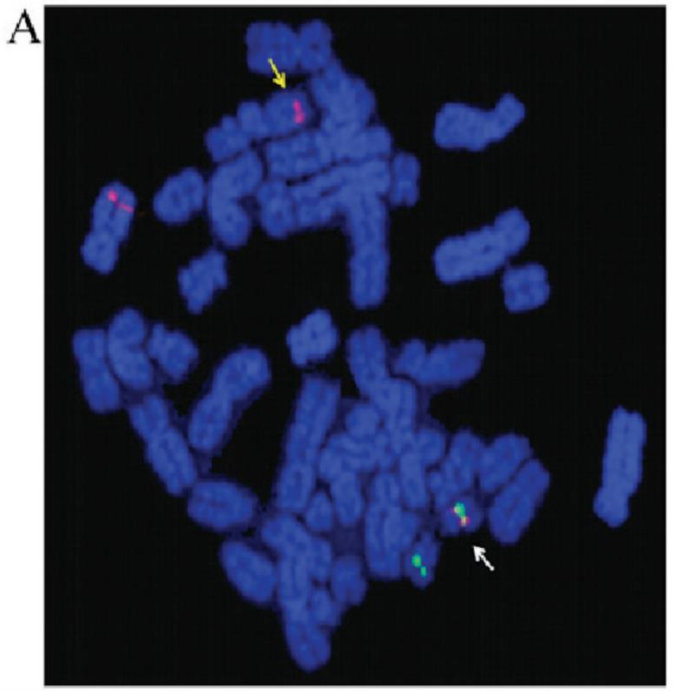


Can we use whole genome sequencing to Identify chromosomal translocation?

Chromosomal Structural Variants: individual genomic loci

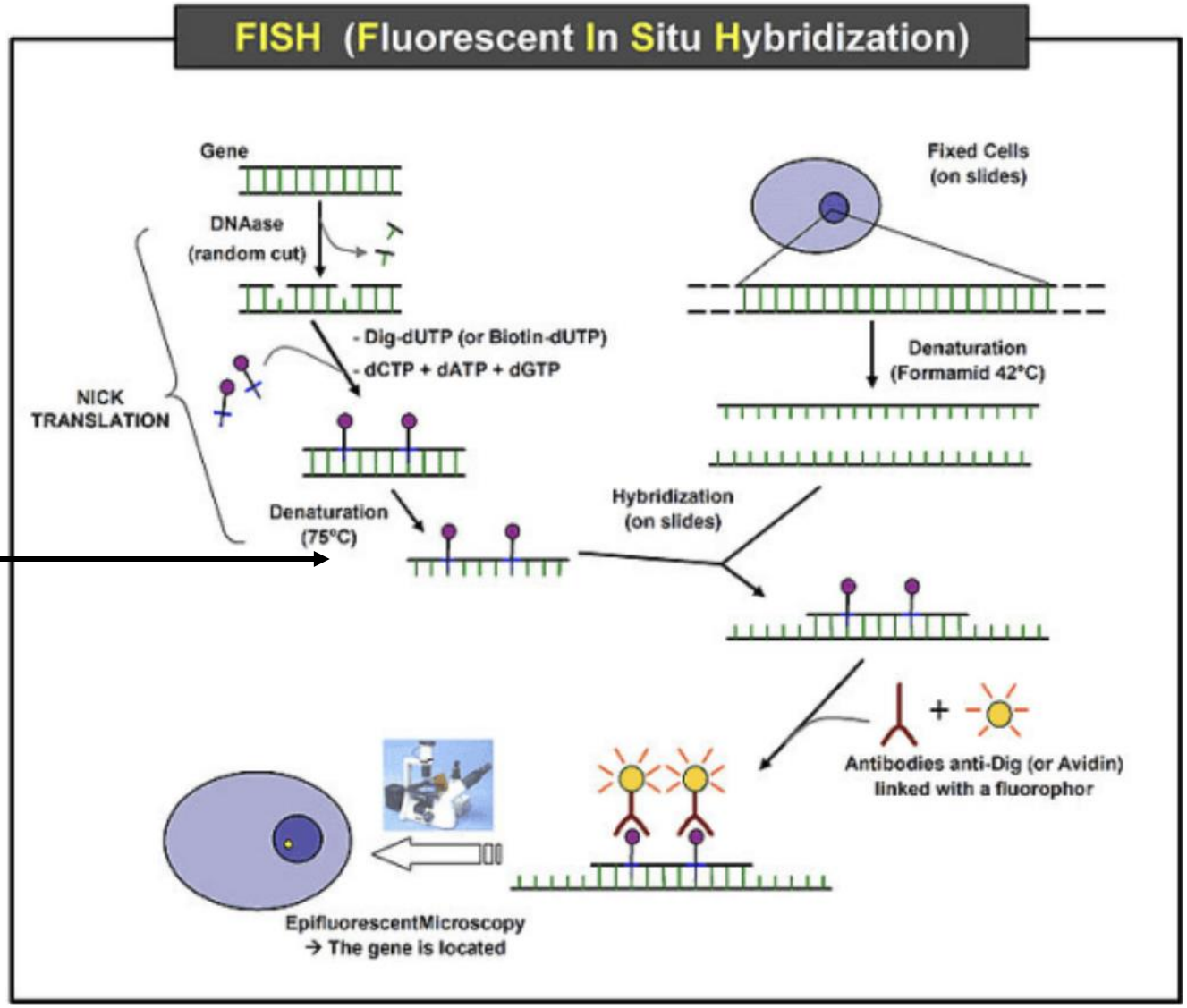
Translocations became apparent from FISH (long before NGS techniques)





Fluorescent in situ hybridization for a single genomic locus

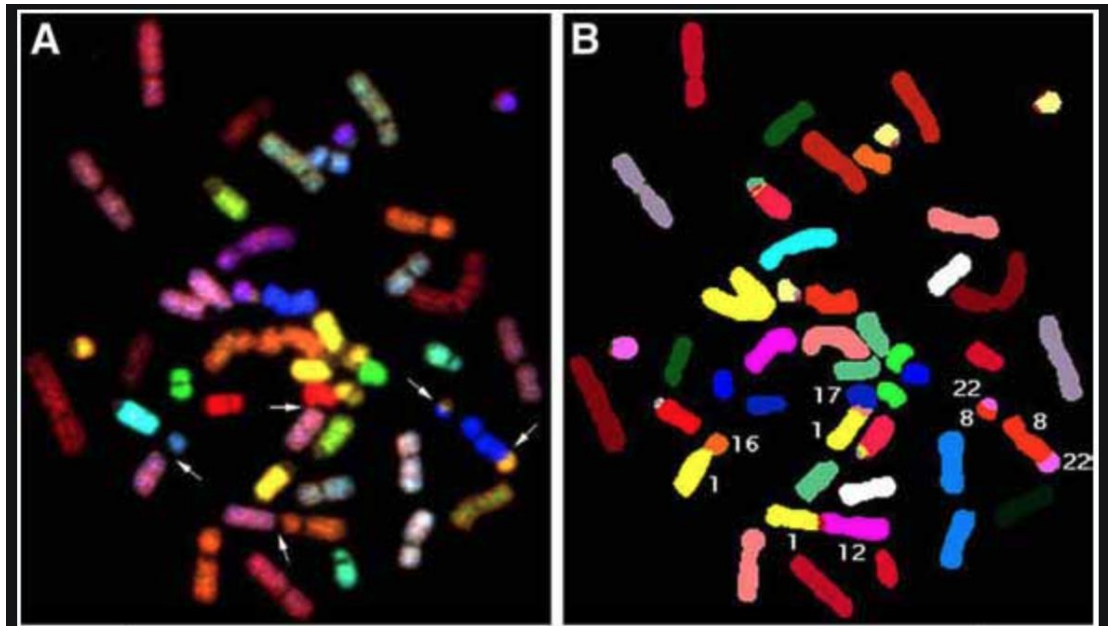
Synthesis of an fluorescent label oligonucleotide probe

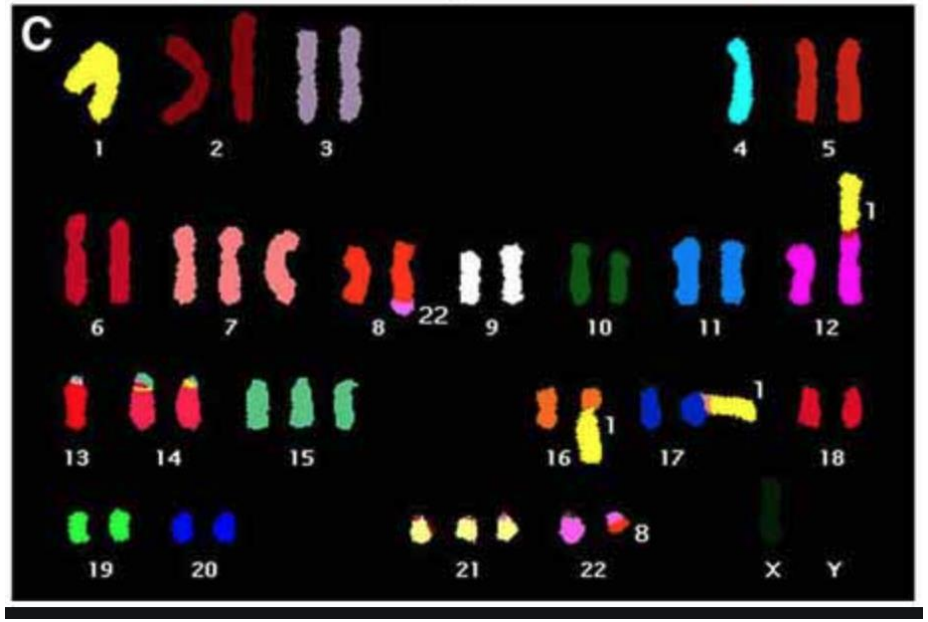


Synthesis of an fluorescent label oligonucleotide probe

Chromosomal Structural Variants: Chromosome painting

Translocations became apparent from “chromosome painting”





Patterns of genomic alterations

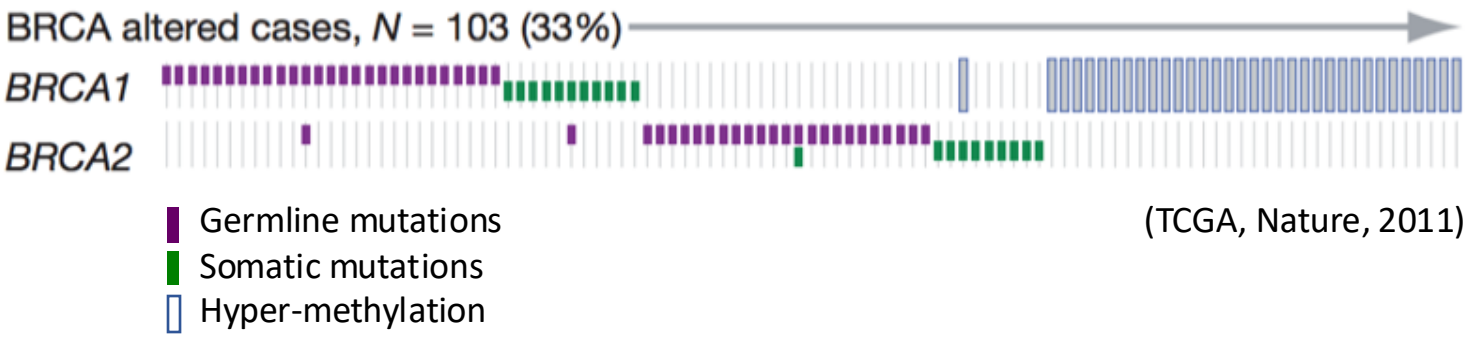
Considering both mutations and copy number changes:

MUTUALLY EXCLUSIVE: rarely occur together

CONCURRENT ALTERATIONS: frequently occur together

Mutual Exclusivity

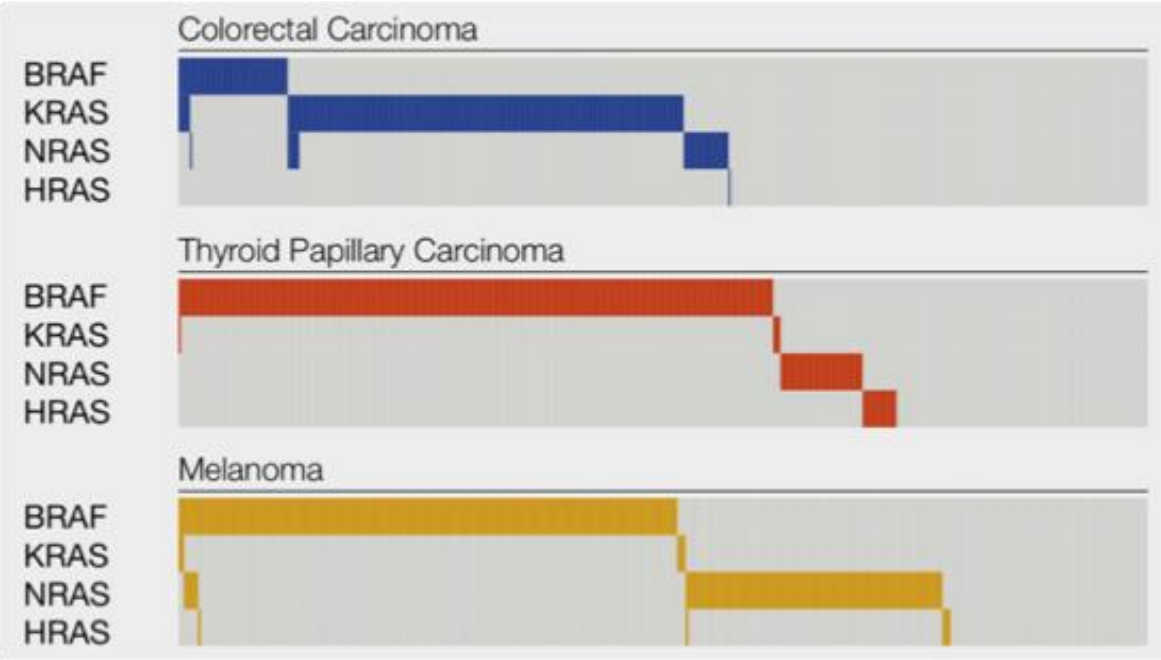
- Observations of mutually exclusive alterations



(TCGA, Nature, 2011)

Mutual Exclusivity

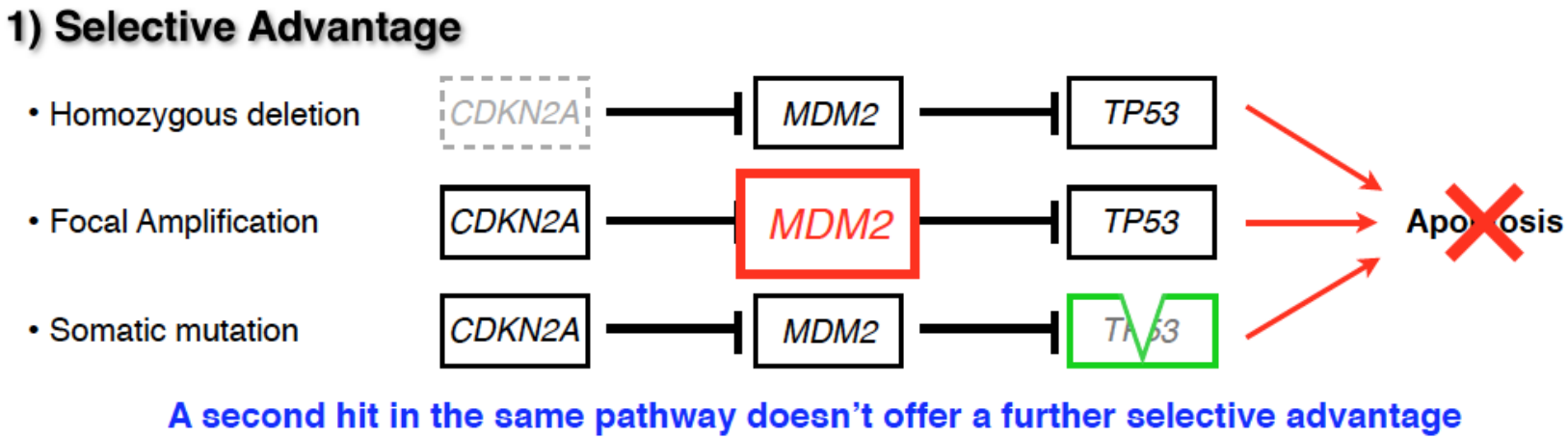
- Observations of mutually exclusive alterations



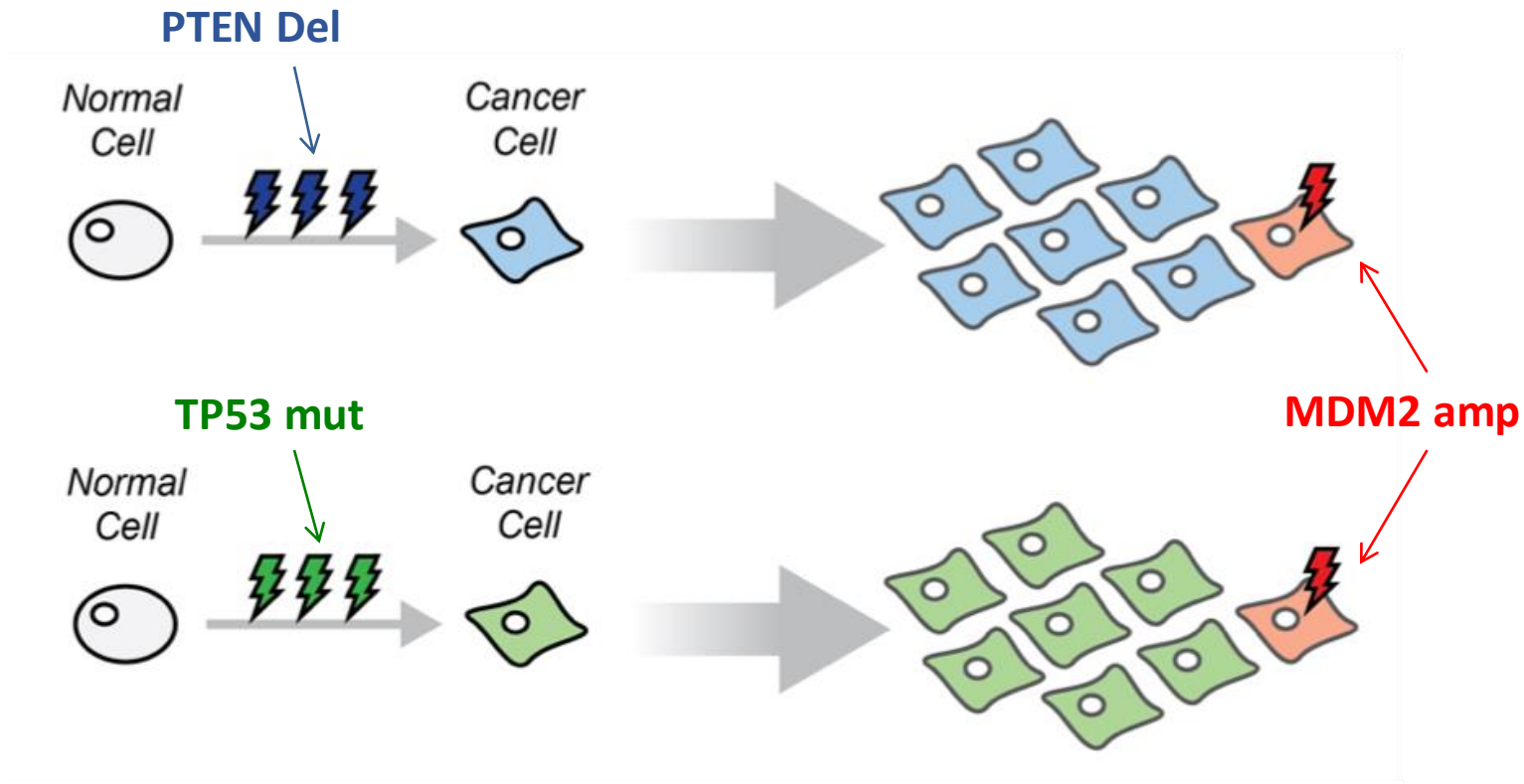
Patient Samples

Why Mutual Exclusivity?

Why Mutual Exclusivity?



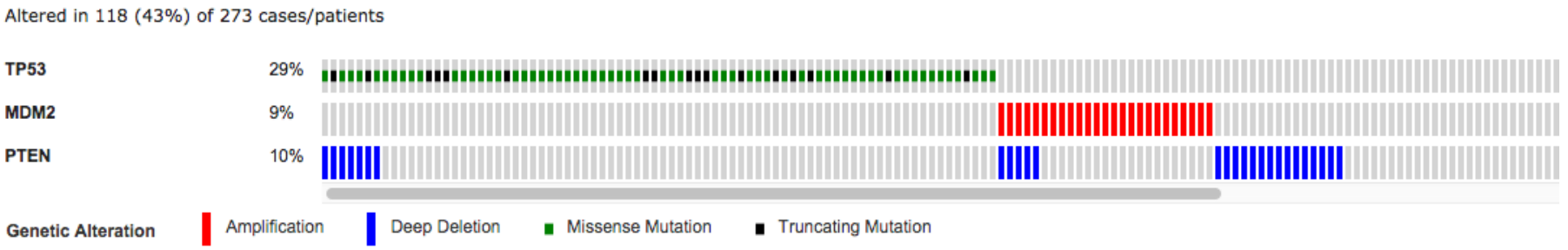
Mutual Exclusivity reflects Selection



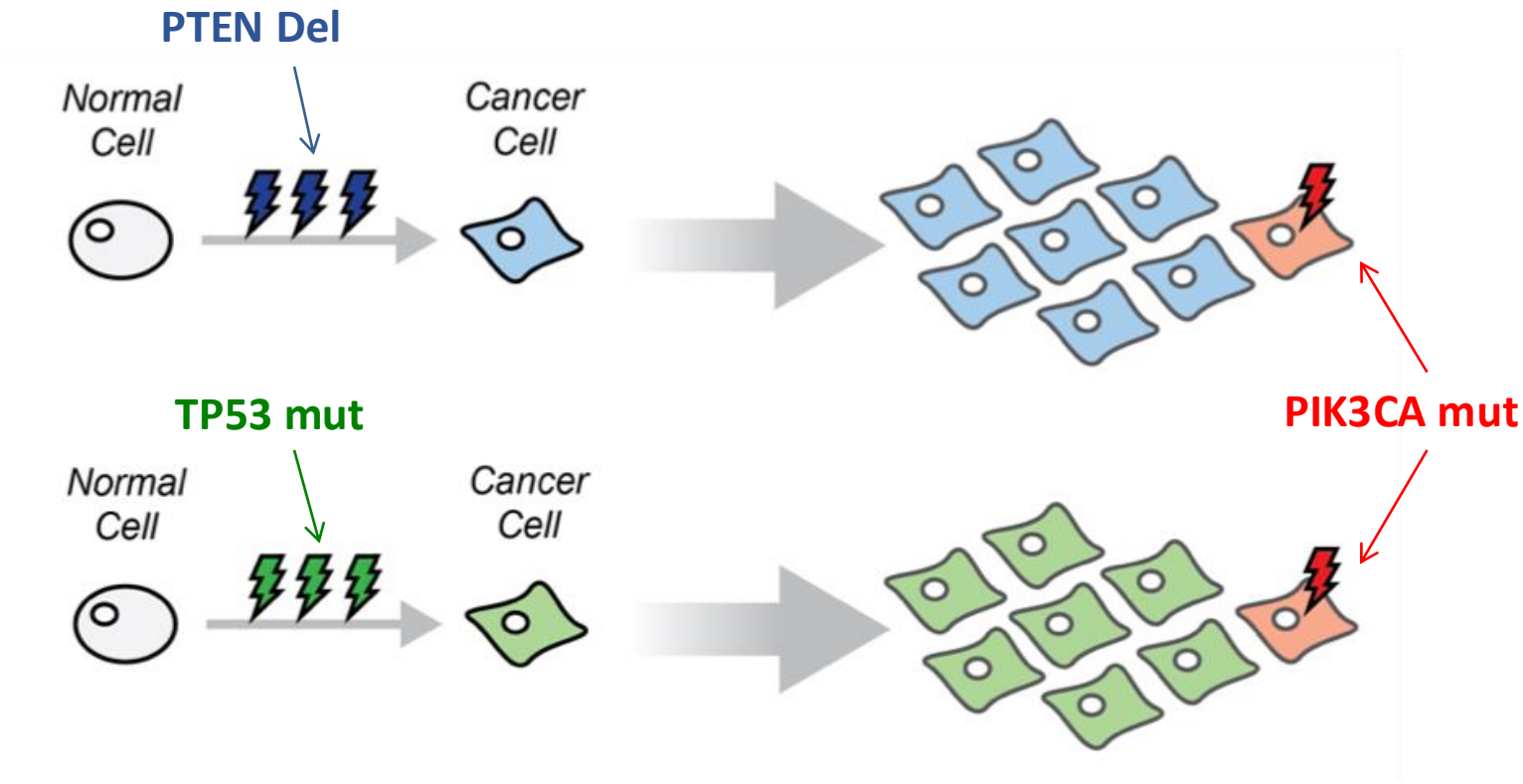
Is MDM2 amplification giving the same advantage in the 2 cases?

Mutual Exclusivity reflects Selection

TCGA Glioblastoma Dataset



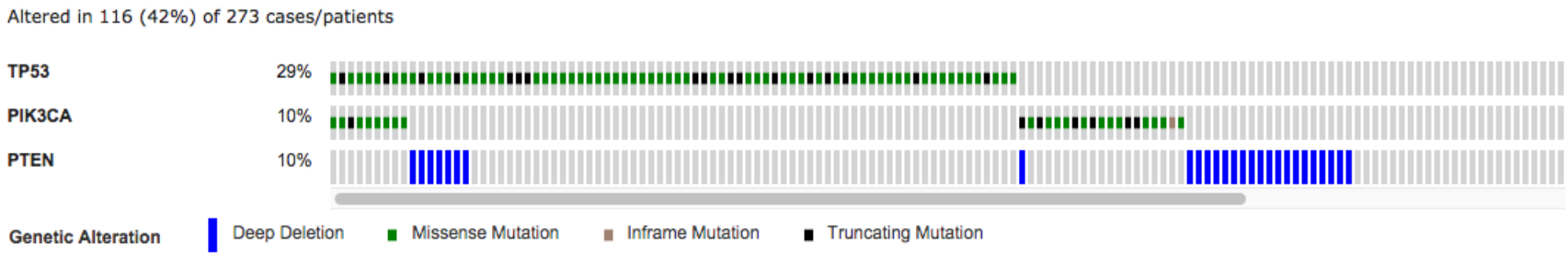
Mutual Exclusivity reflects Selection



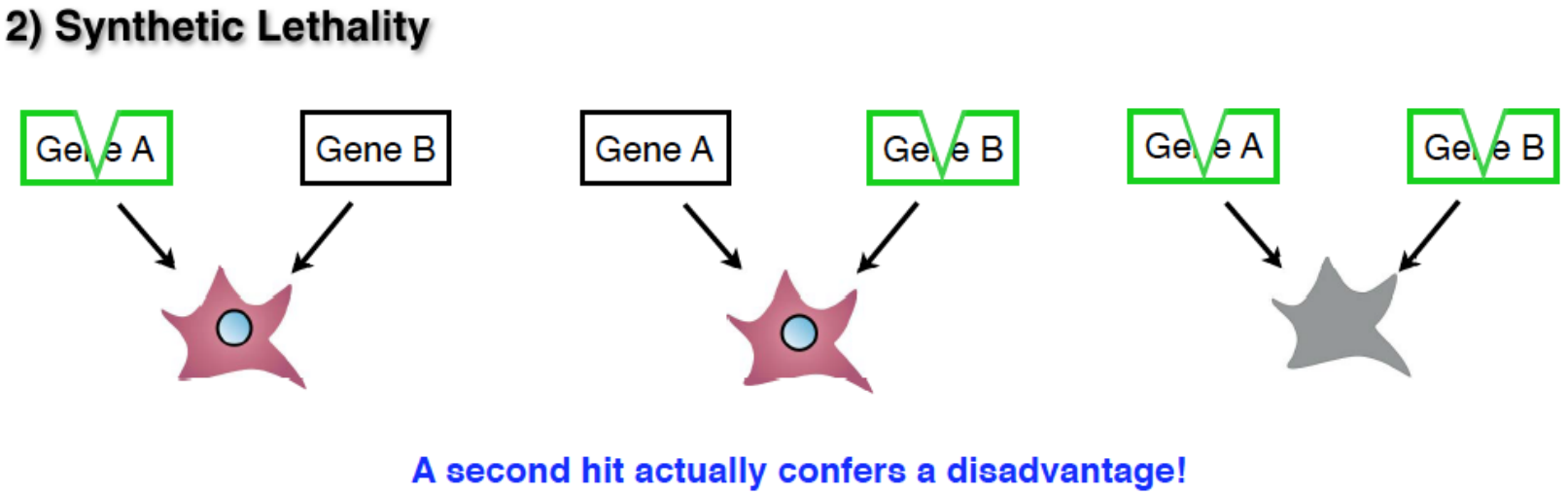
Is PIK3CA mutation giving the same advantage in the 2 cases?

Mutual Exclusivity reflects Selection

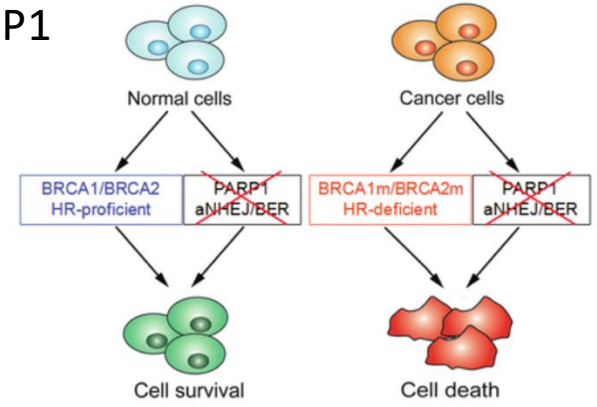
TCGA Glioblastoma Dataset (source cBioPortal)



Why mutual exclusivity?



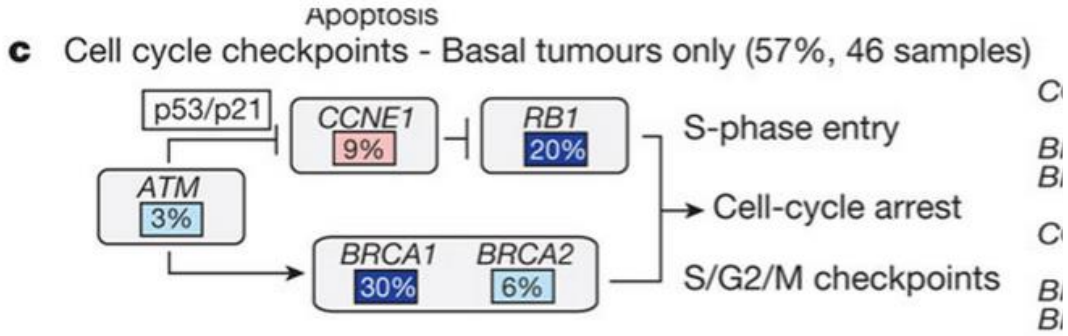
e.g. BRCA1/2 and PARP1



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)



(TCGA, Nature 2012)

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(Ciriello et al. Genome Res. 2012)

(PNAS, 2013)

(TCGA, Nature 2012)

Why is it important to find pairs of genomic alterations that are synthetic lethal?

Laboratories working on cancer genomics EPFL/UNIL

Sebastian Martin Waszak

EPFL

Group of Giovanni Ciriello

UNIL

Computational Biology & Cancer Genomics group

We have open positions for postdoc candidates and phd students. Please check our website http://ciriellolab.org/

Research in our group focuses on computational and system biology approaches to study functional interrelationships between molecular alterations selected in cancer. **Computational biology** studies focus on the design and development of systematic approaches to nominate candidate functional alterations from molecular profiles of human tumors, how these events are

What are the challenges?

- **Prioritize the multitude of genetic aberrations**

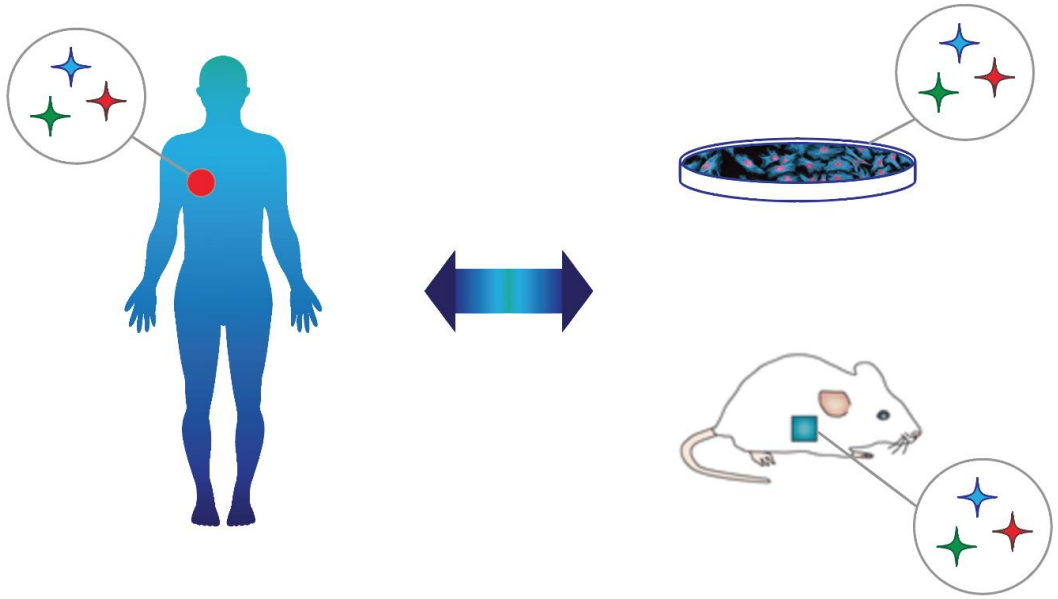
  Several studies classified genomic alteration based on **statistical analyses**

- **Functional Annotations of Genomic Alterations**

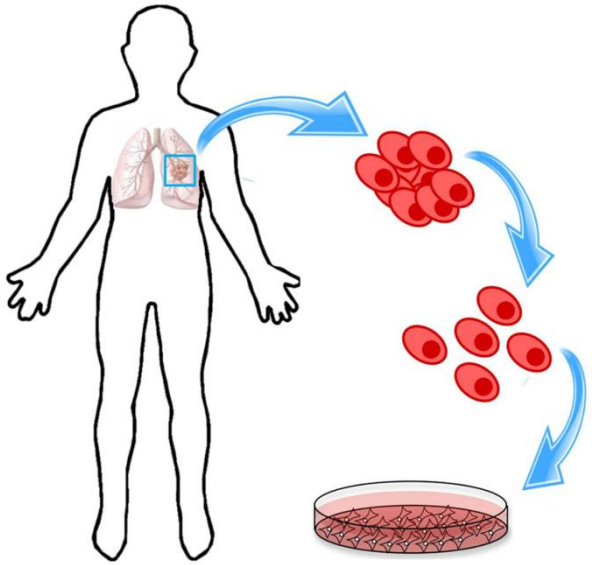
  Define the biological impact of genetic alteration in the tumor development

How to study this complexity?

Disease-model matching



Multiple cell lines isolated from different tumors

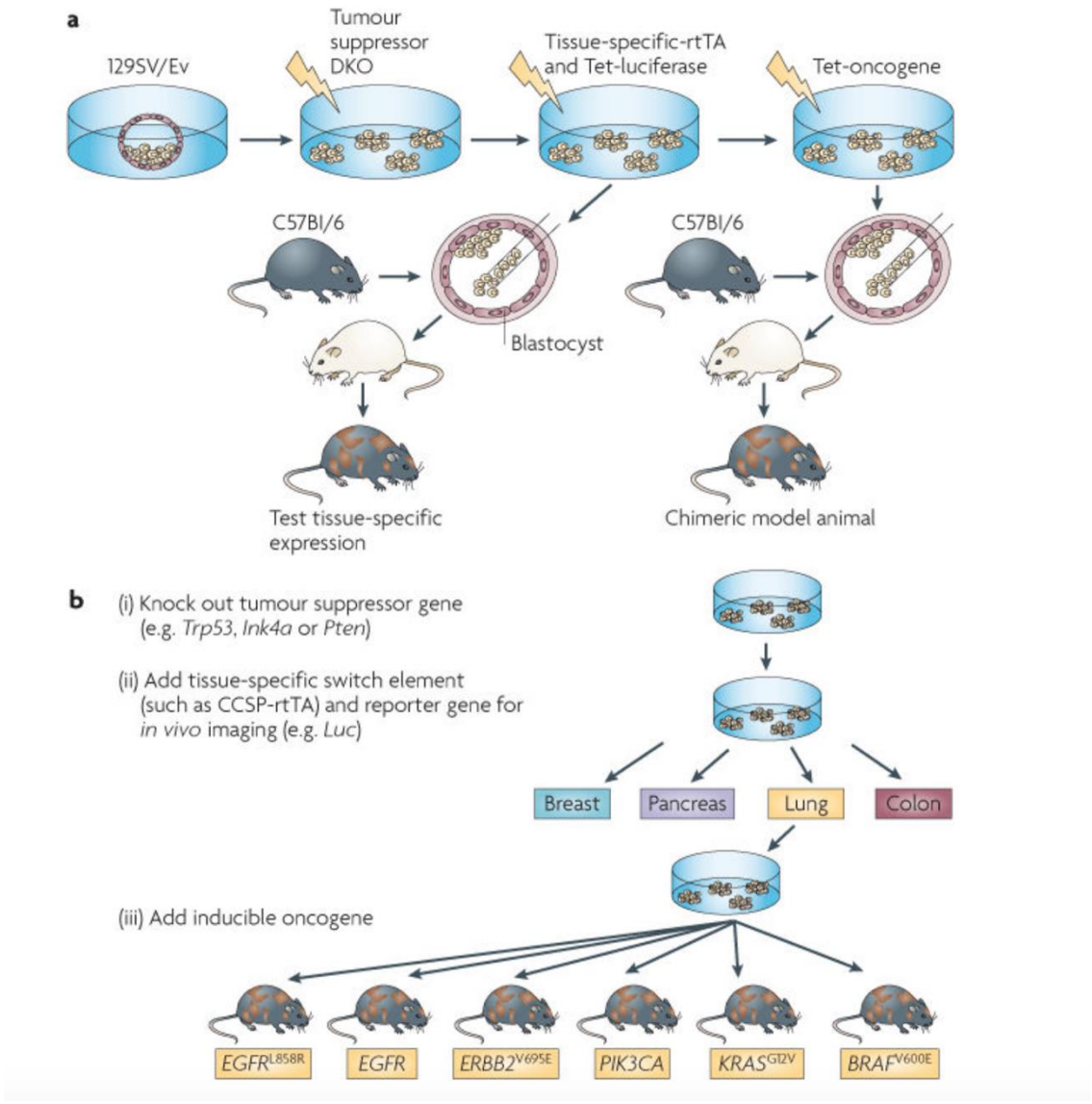


Cancer cells grow for forever

Cancer cell line encyclopedia

https://portals.broadinstitute.org/ccle

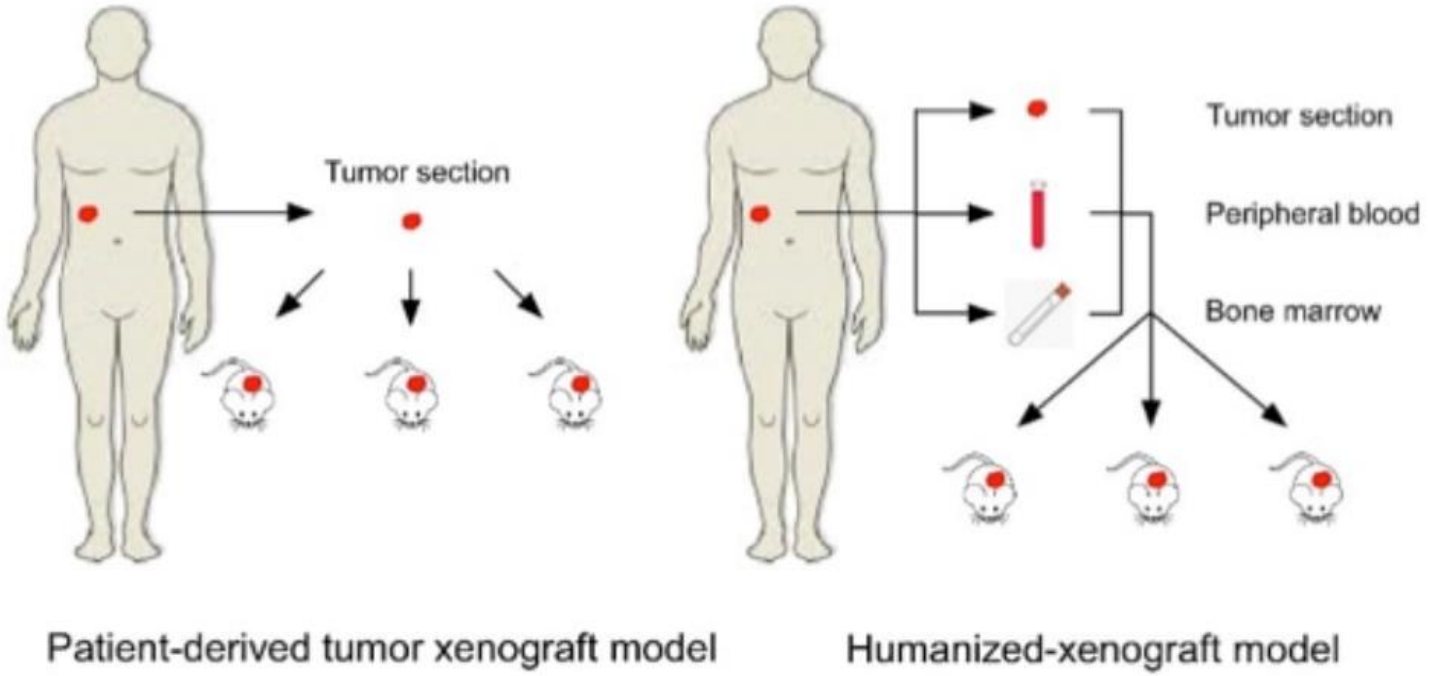
Transgenic animal models



Heyer et al. Nature Rev. Cancer, 2013

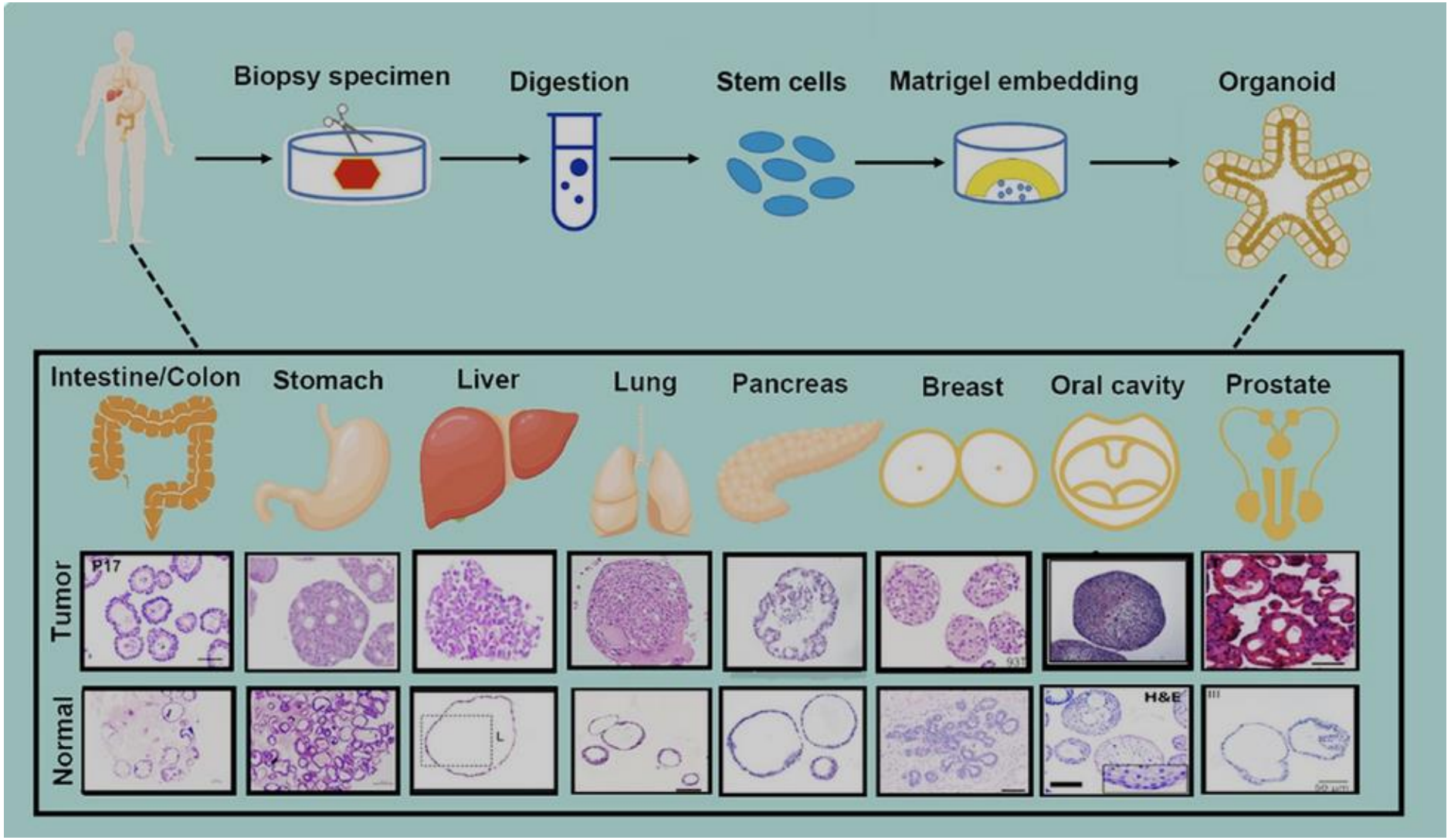
The Human Relevance

Patient derived xenograft
and
Humanized-xenogaft model



What is the difference between these two models?

Organoids


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

Laboratories working on organoids EPFL

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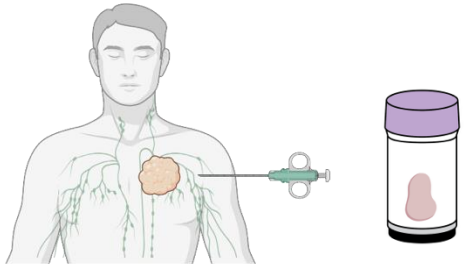
EPFL › VPA › VPA-AVP-DLE › AVP-DLE-EDOC › EDMS-GE

https://go.epfl.ch/phd-edms

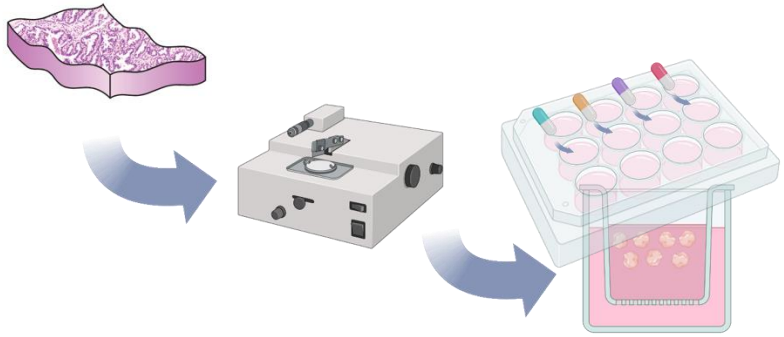
Fragments of tumors: tissue explants

Hospitals (CHUV)



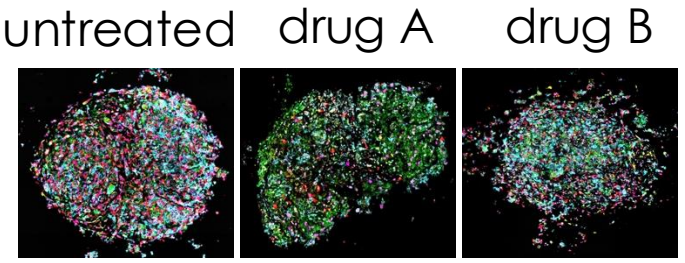
1. Obtain a fresh tumor tissue

Laboratory

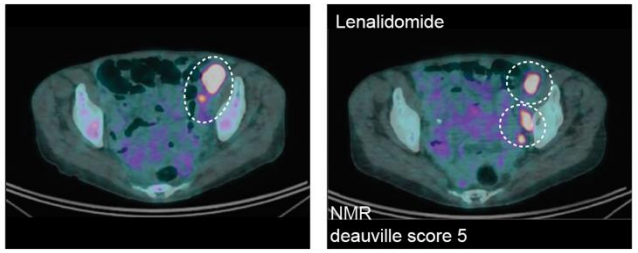


2. Reduce it in small fragments

3. Test different therapies



4. Assess response to therapies using image-based analyses



5. Matches with clinical response

Laboratories working on tissue explants in EPFL

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Oricchio lab: for new model development and Albert for clinical development

Patient avatars

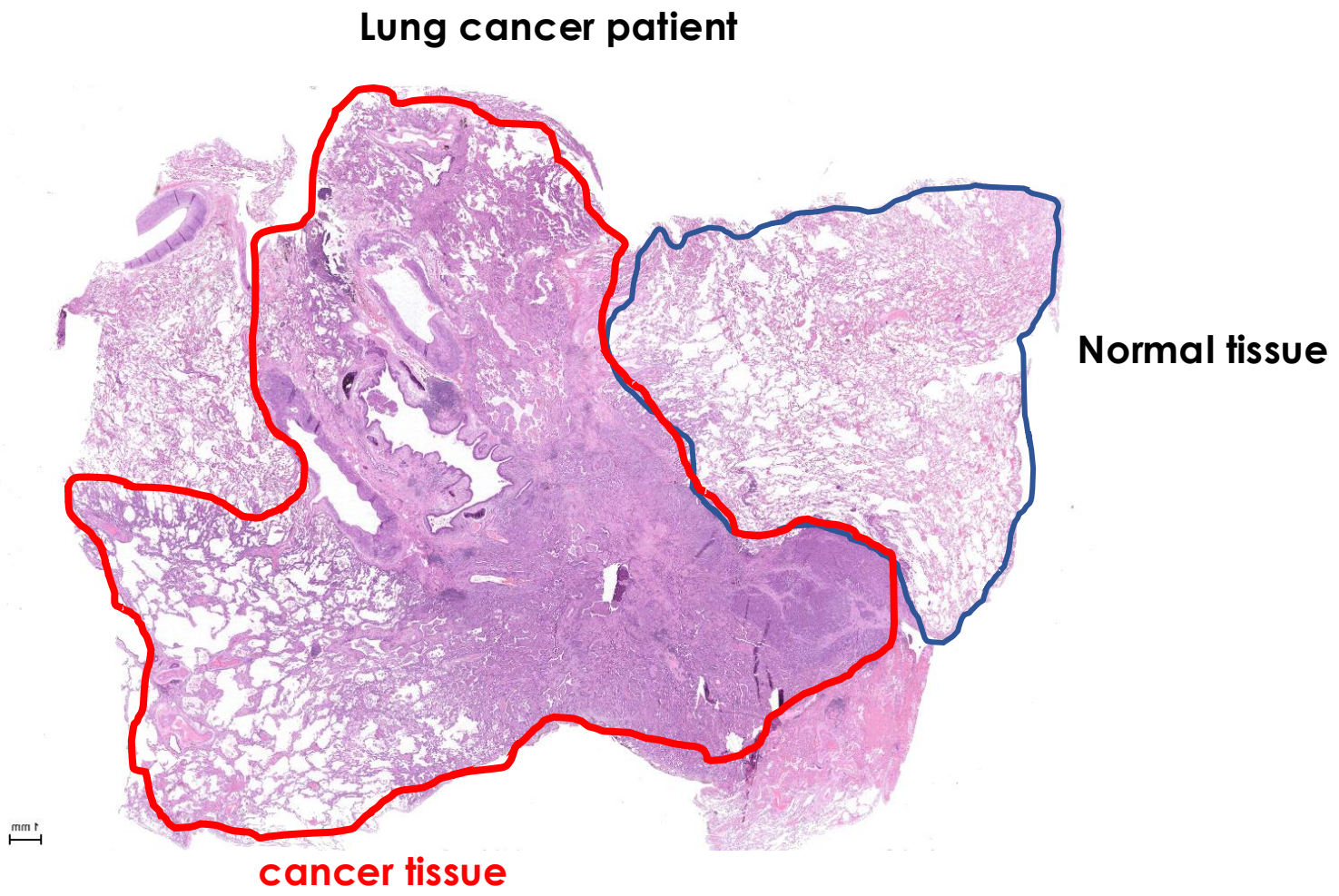
A

	 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	+	+	+	+++	++	++	+

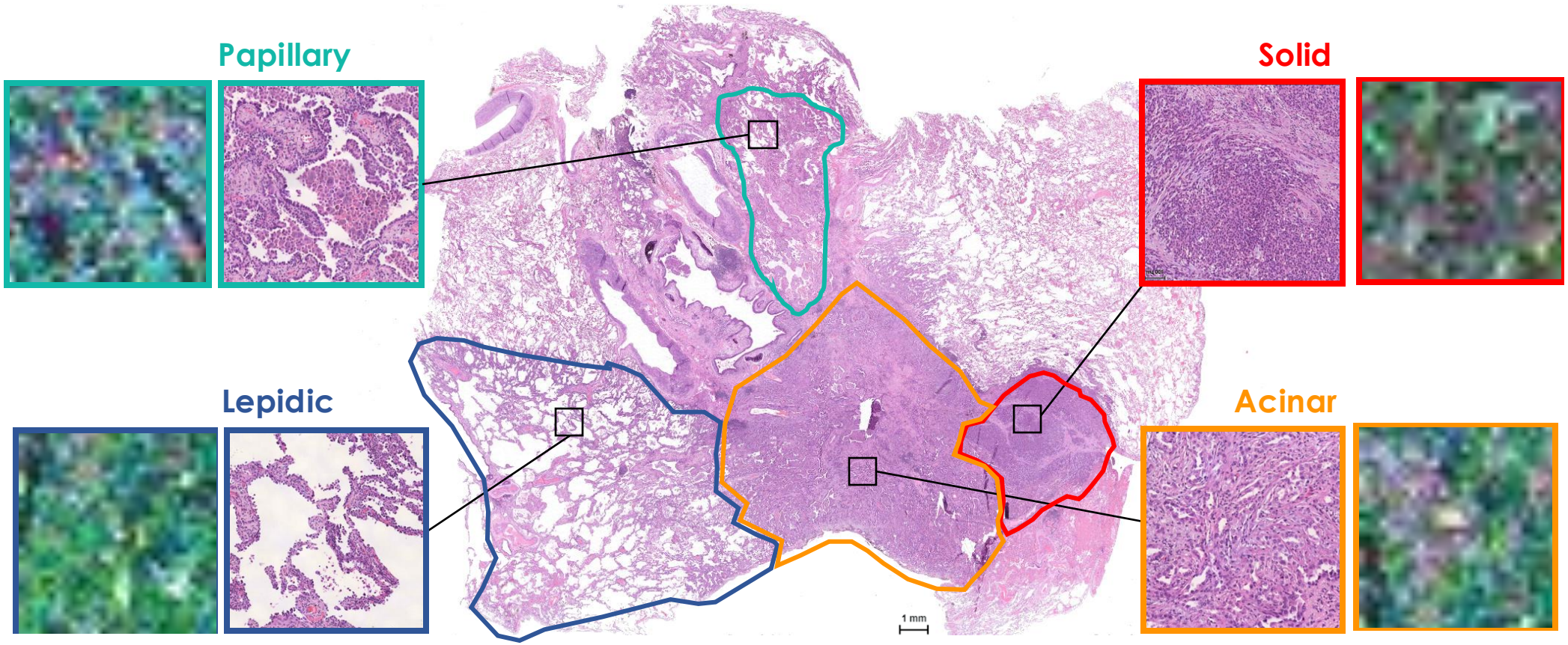
T = Targeted Therapies, C = Chemotherapies, R = Radiation, IO = Immuno-oncology Therapies, TME = Tumor Microenvironment
*PDX models include mouse stromal cells in the TME and require immune reconstitution with humanized mouse models to adequately recapitulate IO therapies.

Cancer intra-tumor heterogeneity and its evolution

Cancer is an heterogenous disease

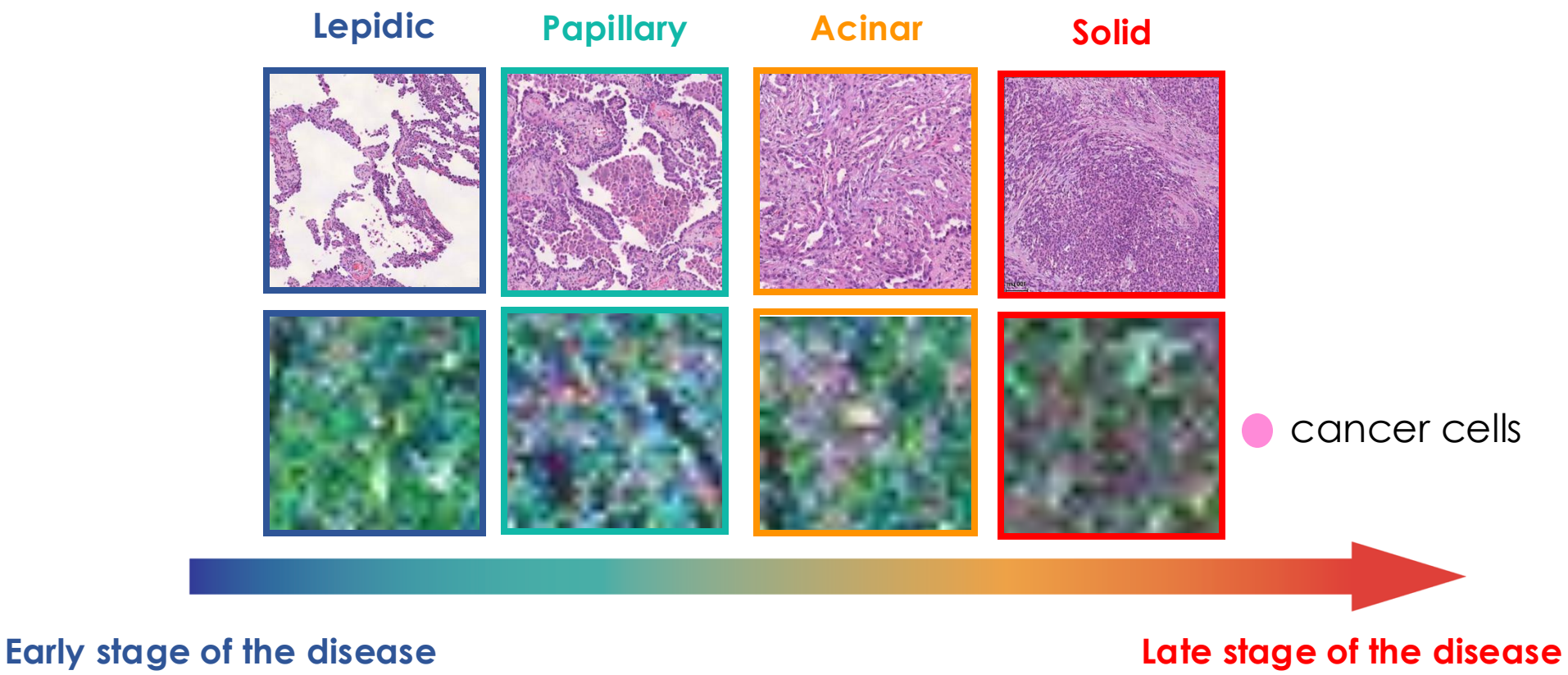


Cancer is an heterogenous disease

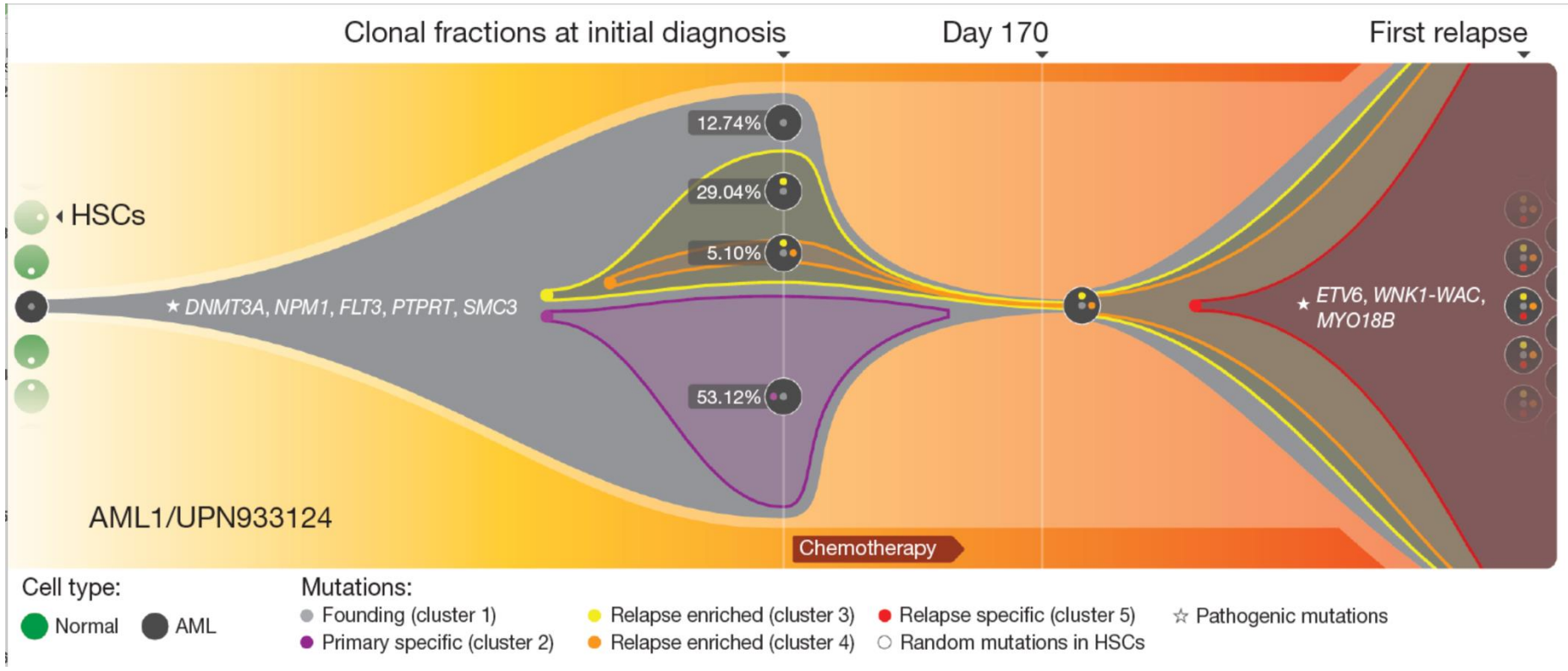


cancer cells

Cancer is an heterogenous disease **that evolves over time**

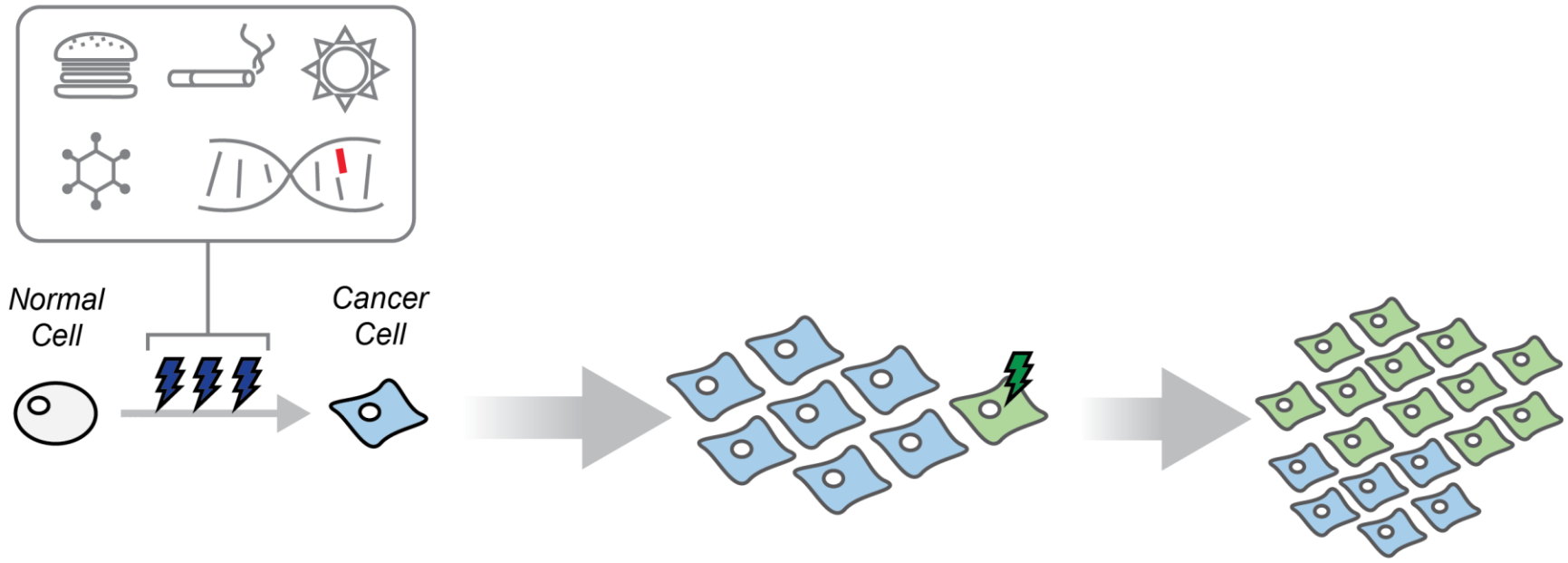


Cancer is a disease that evolves following the principle of species evolution

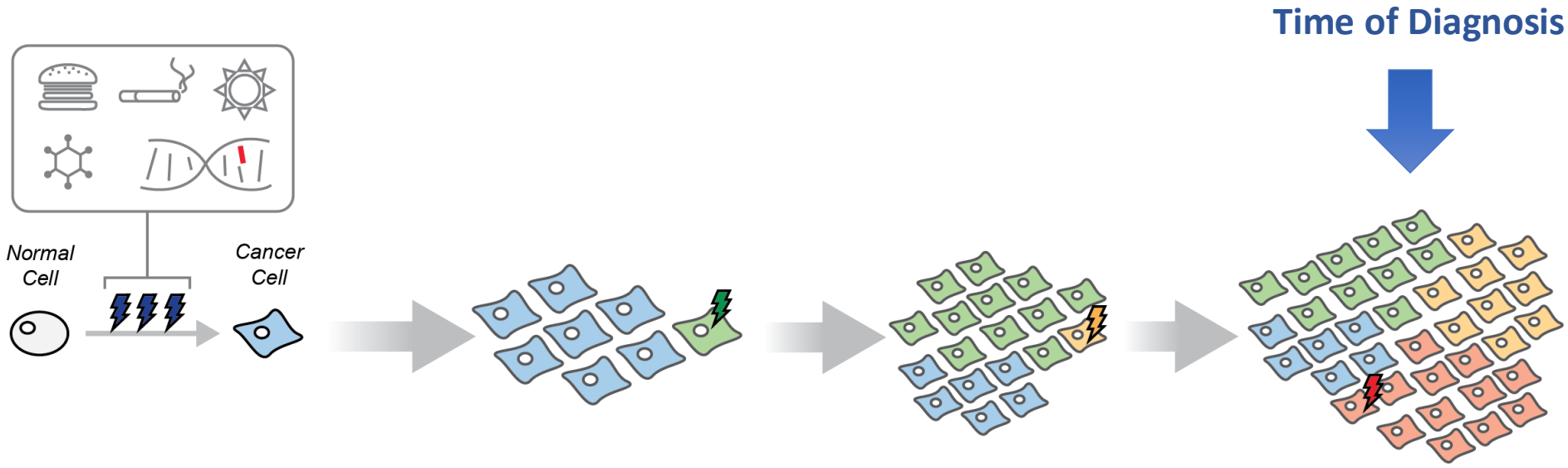


What happens during the time of chemotherapy treatment to tumor evolution?

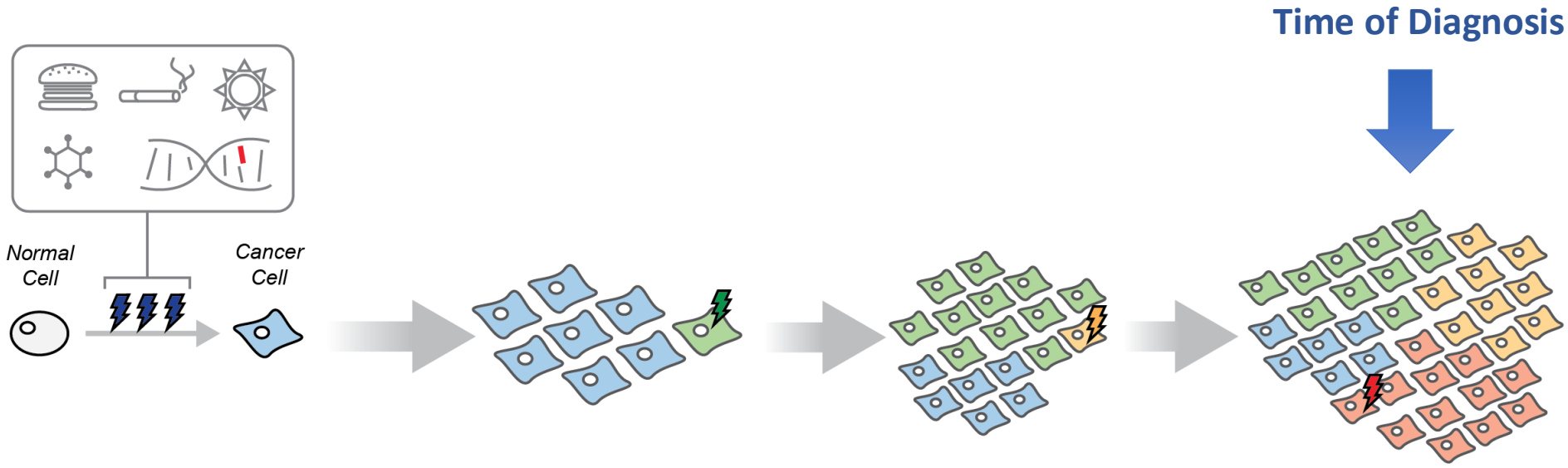
A simplified model of cancer evolution



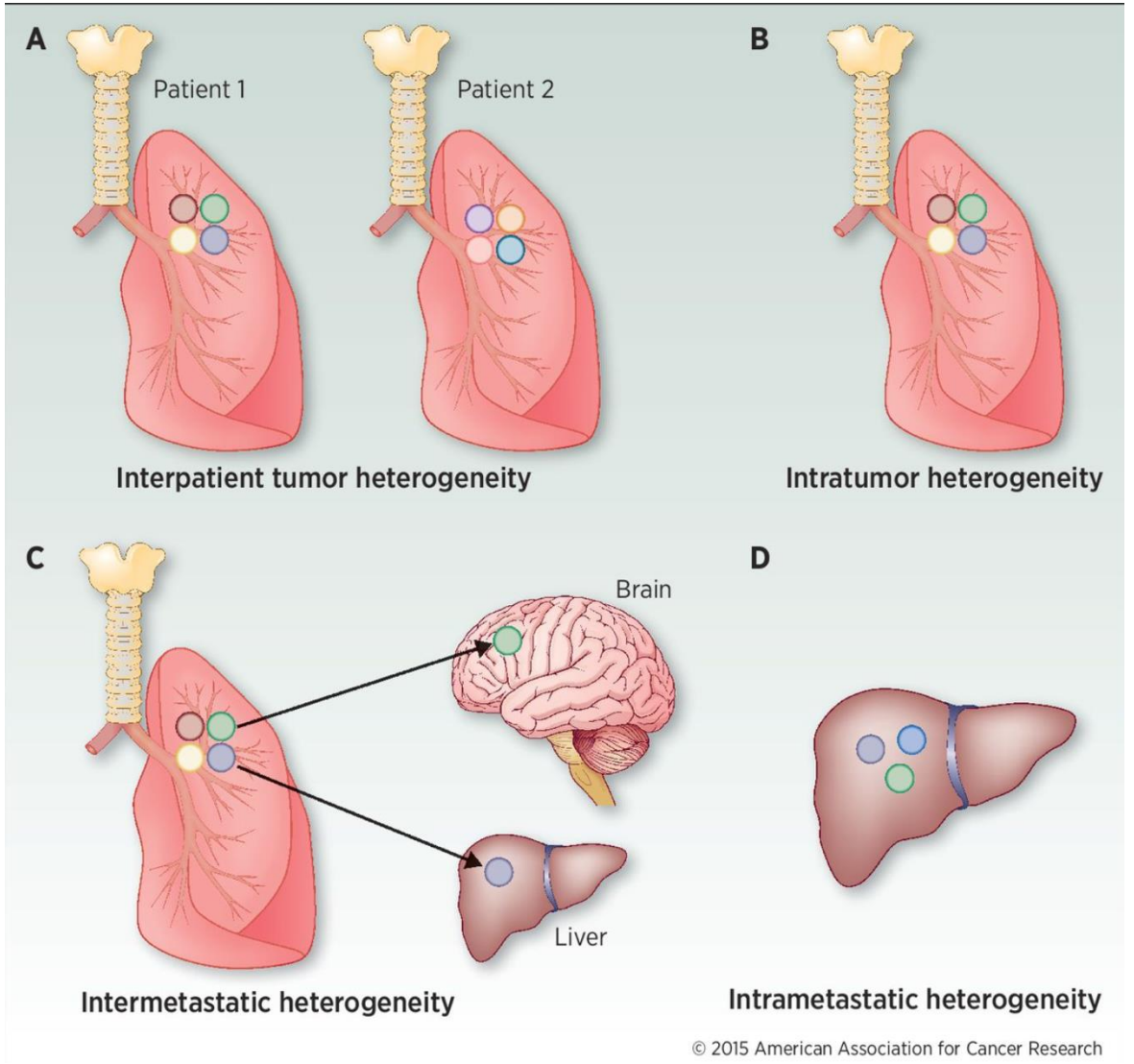
A simplified model of cancer evolution



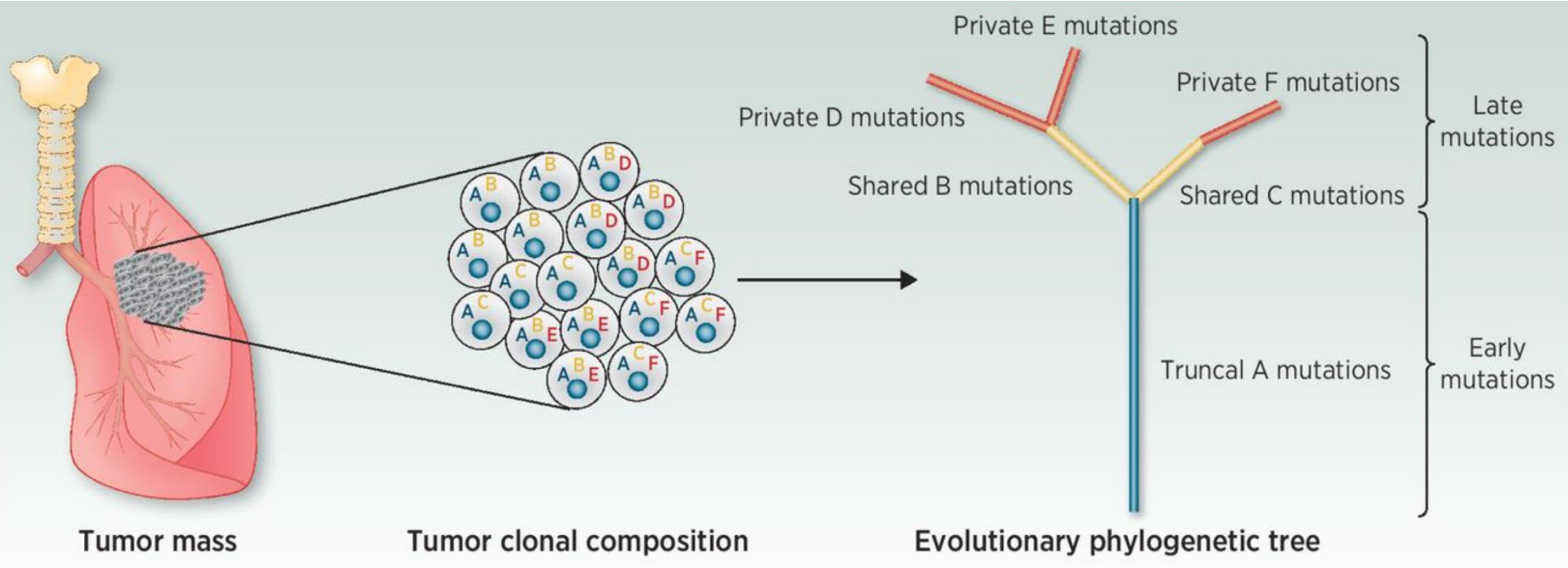
A simplified model of cancer evolution



Intra-tumor heterogeneity and metastasis



Intra-tumor heterogeneity



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

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