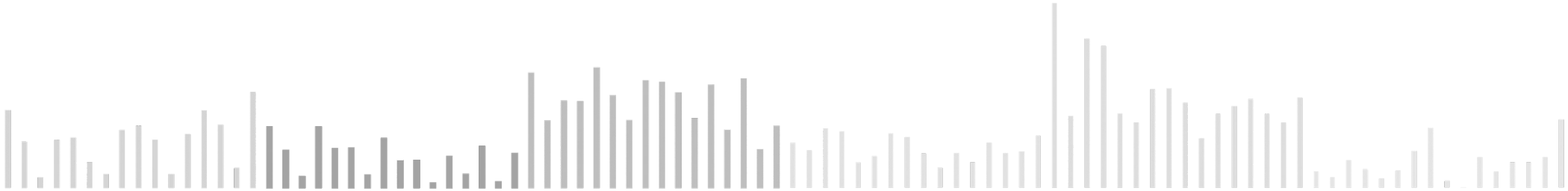
BIMM 143 – Class 18 Lab

Mutational Signatures in Cancer



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Alexandrov Lab

A long journey to San Diego and the States…

UNIVERSIDADE
DA CORUÑA

Galicia, Spain

A long journey to San Diego and the States…

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… pivoting from civil engineering to computational biology

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New paradigm of civil engineering

Apply the same mathematical framework, but for cancer research

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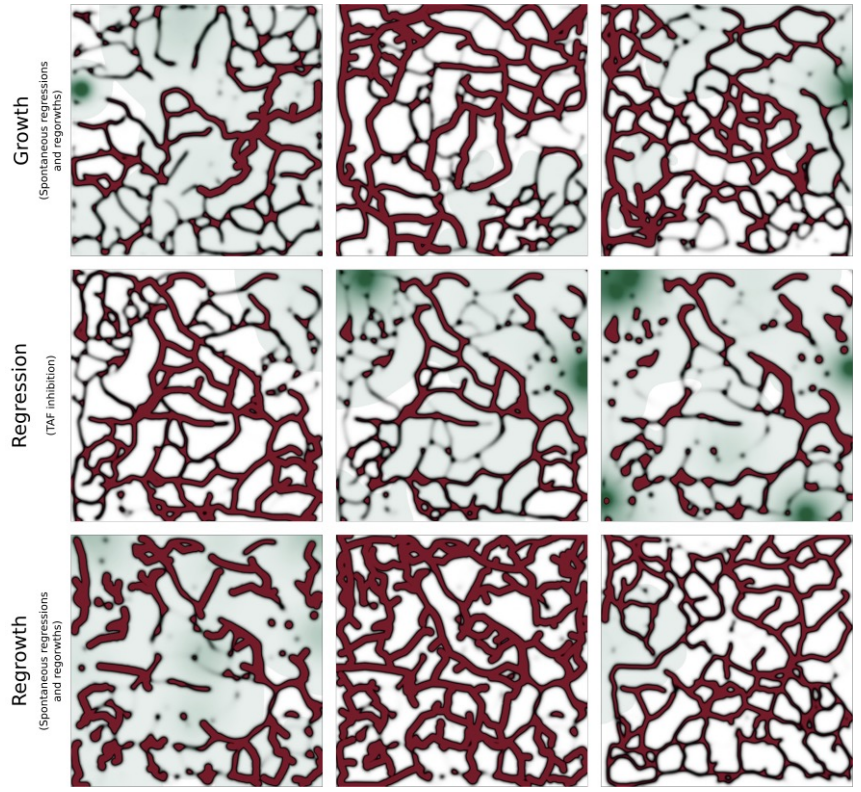

… pivoting from civil engineering to computational biology

New paradigm of civil engineering

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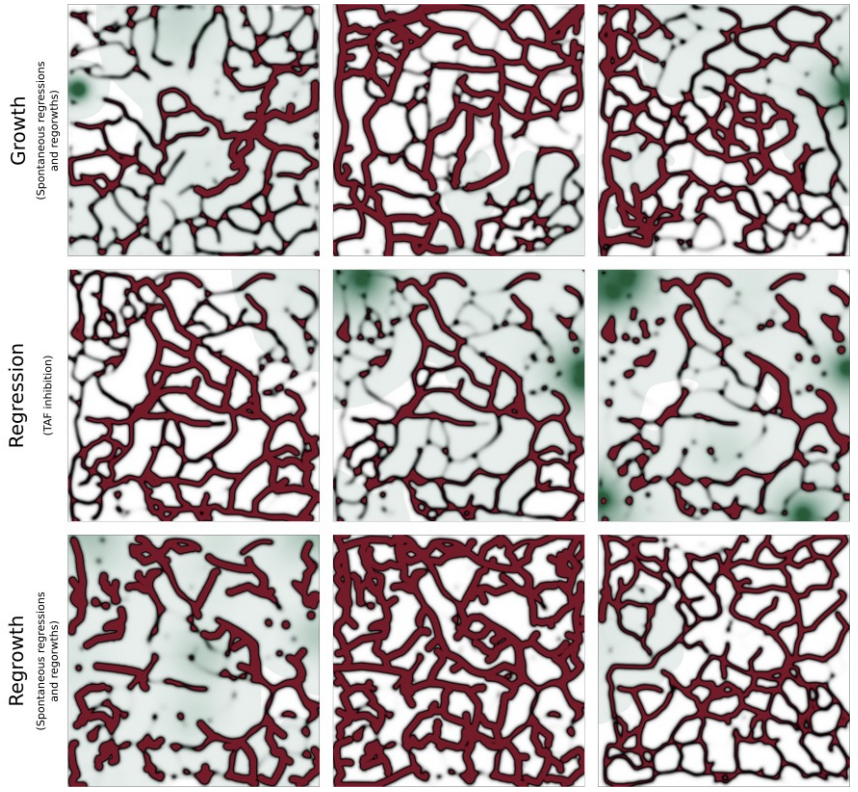
MSc in Biomedicine

The first step



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New paradigm of civil engineering
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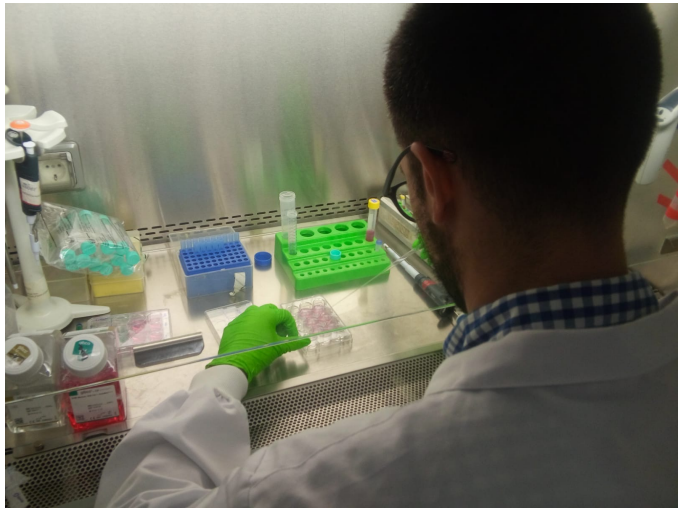
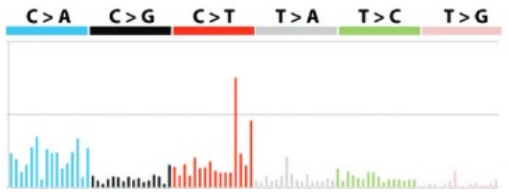
MSc in Biomedicine
The first step

PhD in Translational Medicine
A new biomedical researcher



Spoiler alert!



Pattern of mutations (DNA changes) found in a sequenced lung cancer

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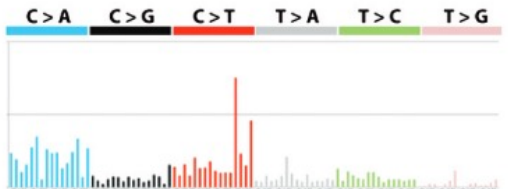

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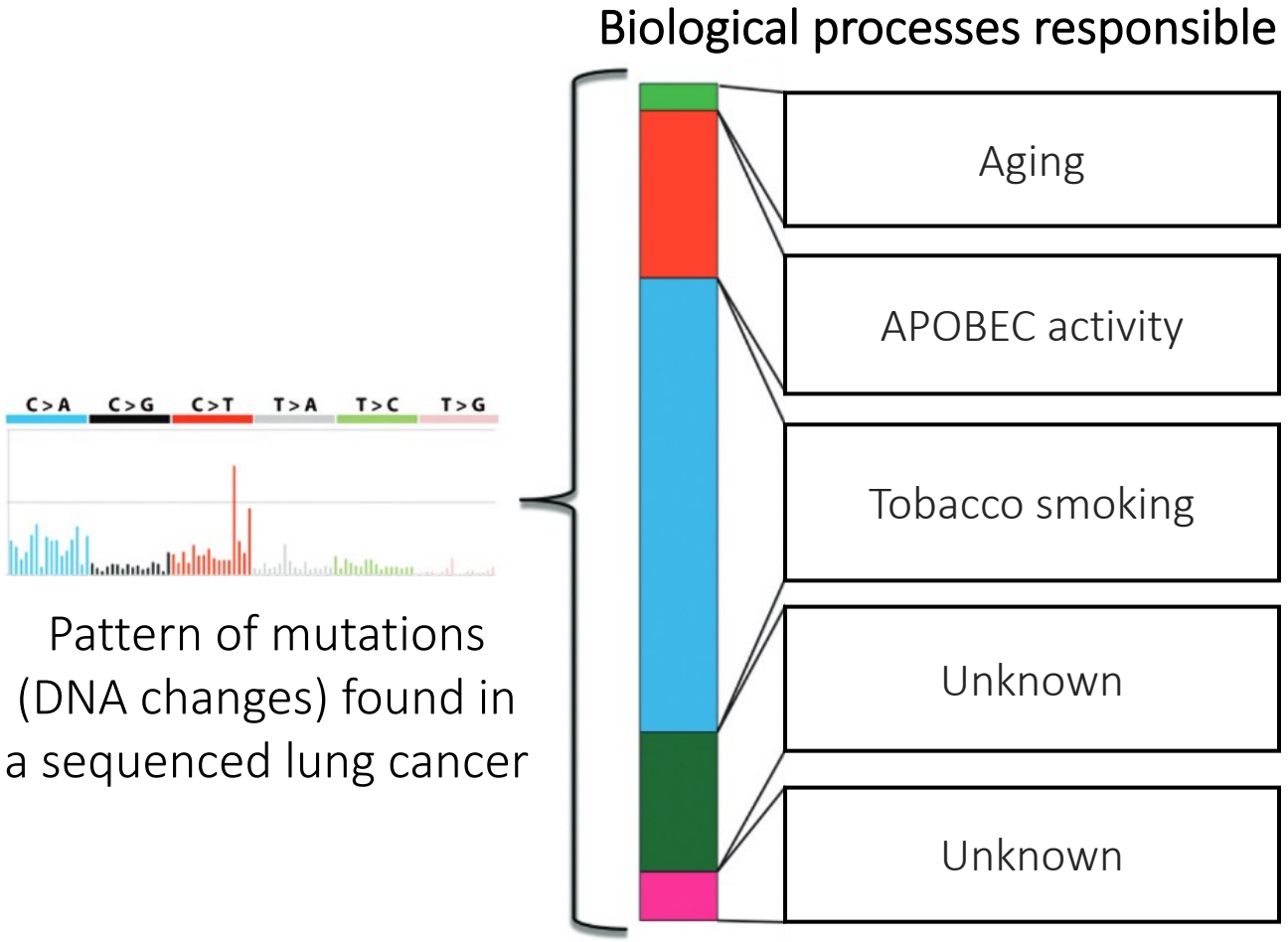

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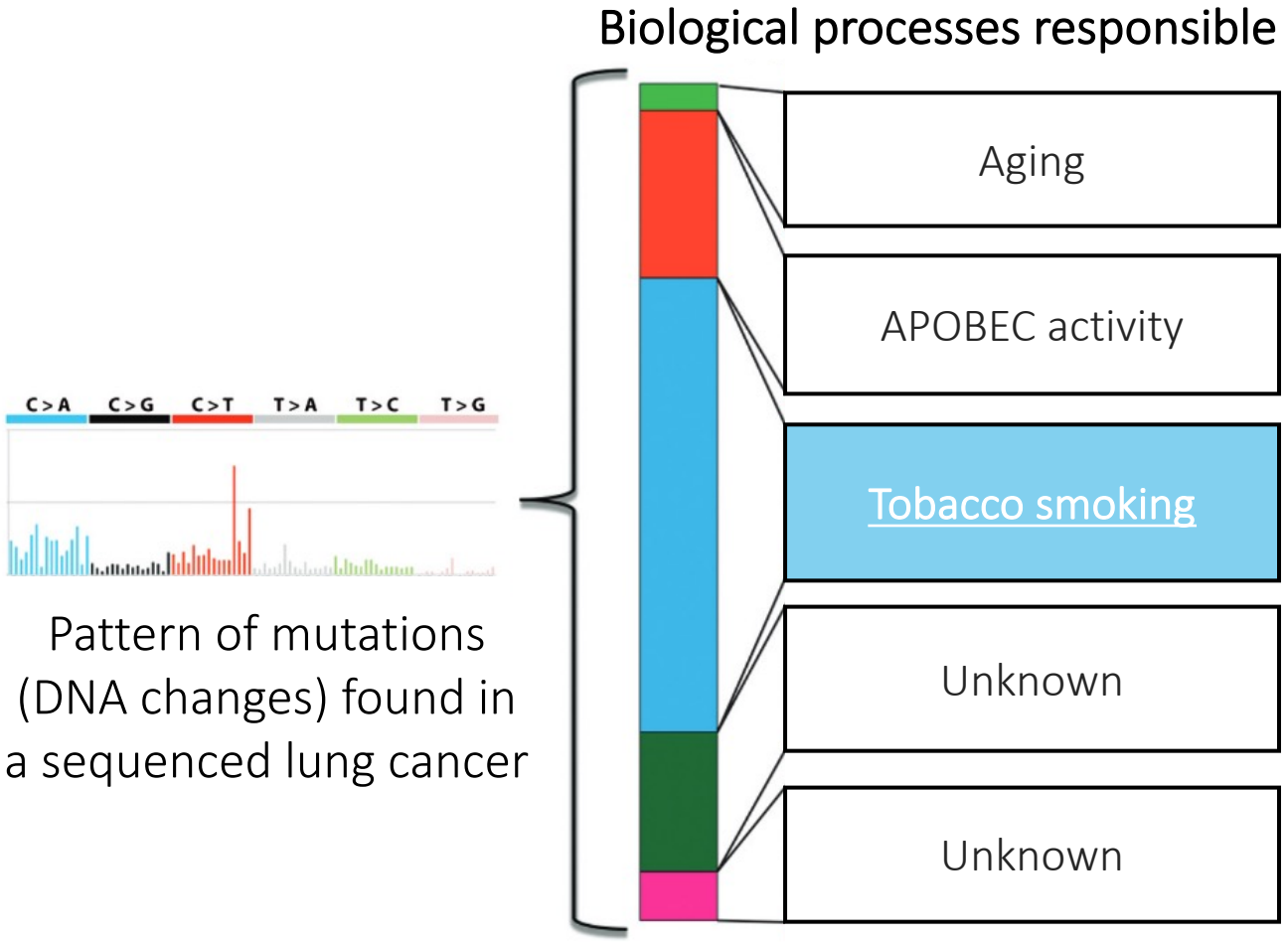

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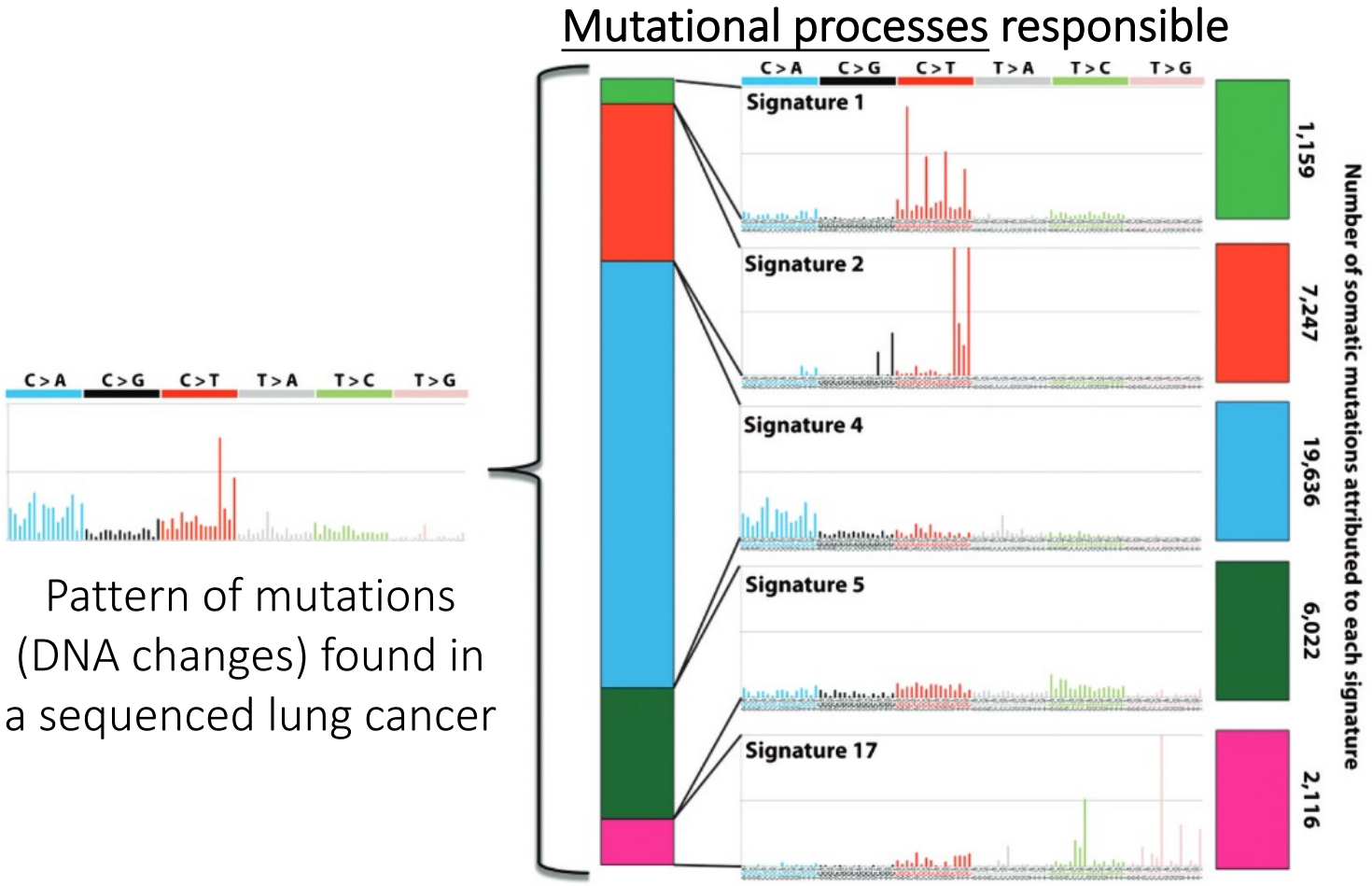

Pattern of mutations (DNA changes) found in a sequenced lung cancer

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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Overview of cancer

- All cancers originate from a single cell that starts to behave abnormally, dividing uncontrollably and invading adjacent tissues
- The reason that this single cell begins to behave abnormally is because of acquired changes in its genome known as somatic mutations
- Cancer is a disease of the genome and the most common human genetics disease

Types of mutations

- DNA molecules in our cells are targeted by diverse mutagenic processes that can occur in:
  - **germ** cells, contributing to species evolution
  - or in **somatic** cells, accumulating with age and contributing to diseases, especially cancer

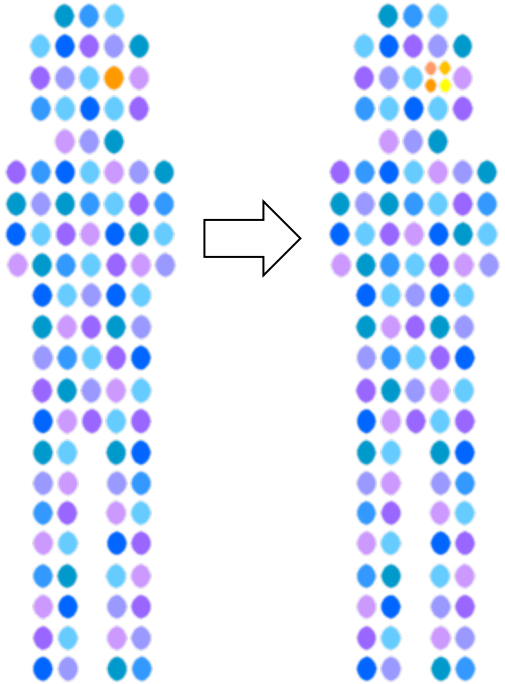
- Recent mutation rate studies of tumors have focused on deciphering the **somatically acquired changes** in the DNA of cancer cells to advance our understanding of the relations among mutagenic exposures, DNA damage and repair, and outcomes (such as cancer and uncontrolled cell growth)

Cancer development

A cancer arises when a single cell acquires somatic mutations and begins to behave abnormally.
(dividing when it should be quiescent)

Cancer development

Benign tumor: a cell has evaded some controls on growth giving rise to a ‘clonal mass’, however they lack many of the aggressive characteristics of more advanced cancer (i.e. unlimited invasive growth).



Benign tumor

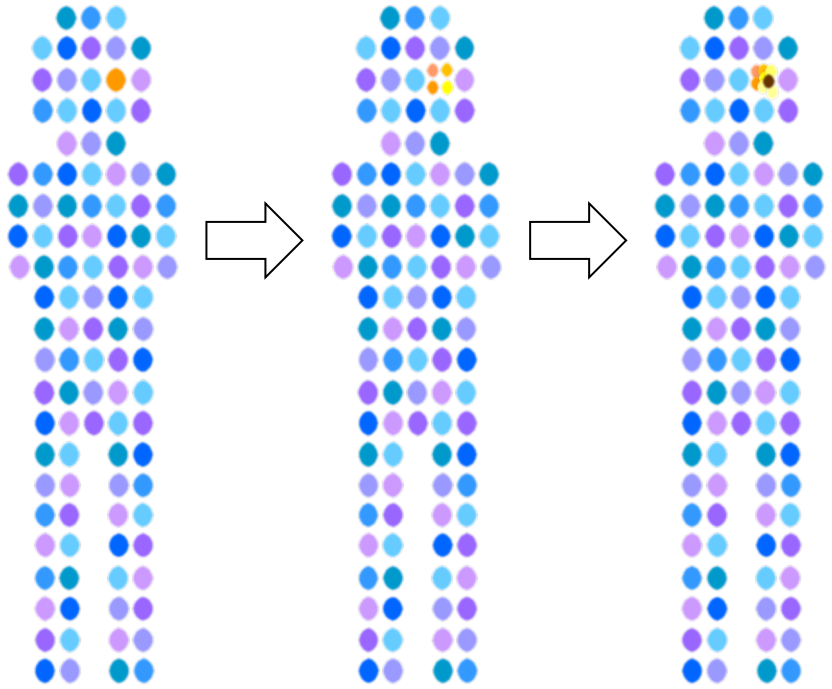
Moles (nevi) are an example of a benign tumor.

82% of nevi have a mutation of the known cancer gene *BRAF.*

BRAF mutations are thought to be the initiating event in melanoma.

Cancer development

***In situ* cancer:** the tumor has evaded controls on cell division and grows in a disorderly fashion.



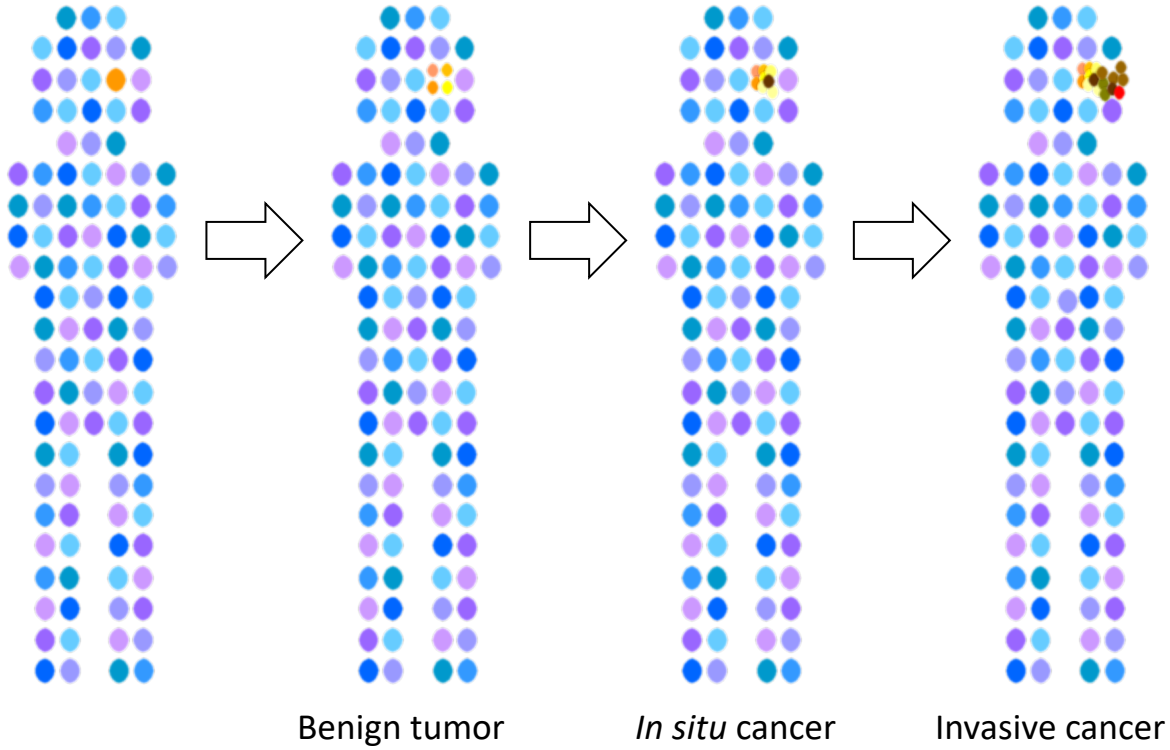
Benign tumor *In situ* cancer

"in situ" means "in its natural place".

The tumor cells are still confined to the site where they originated.

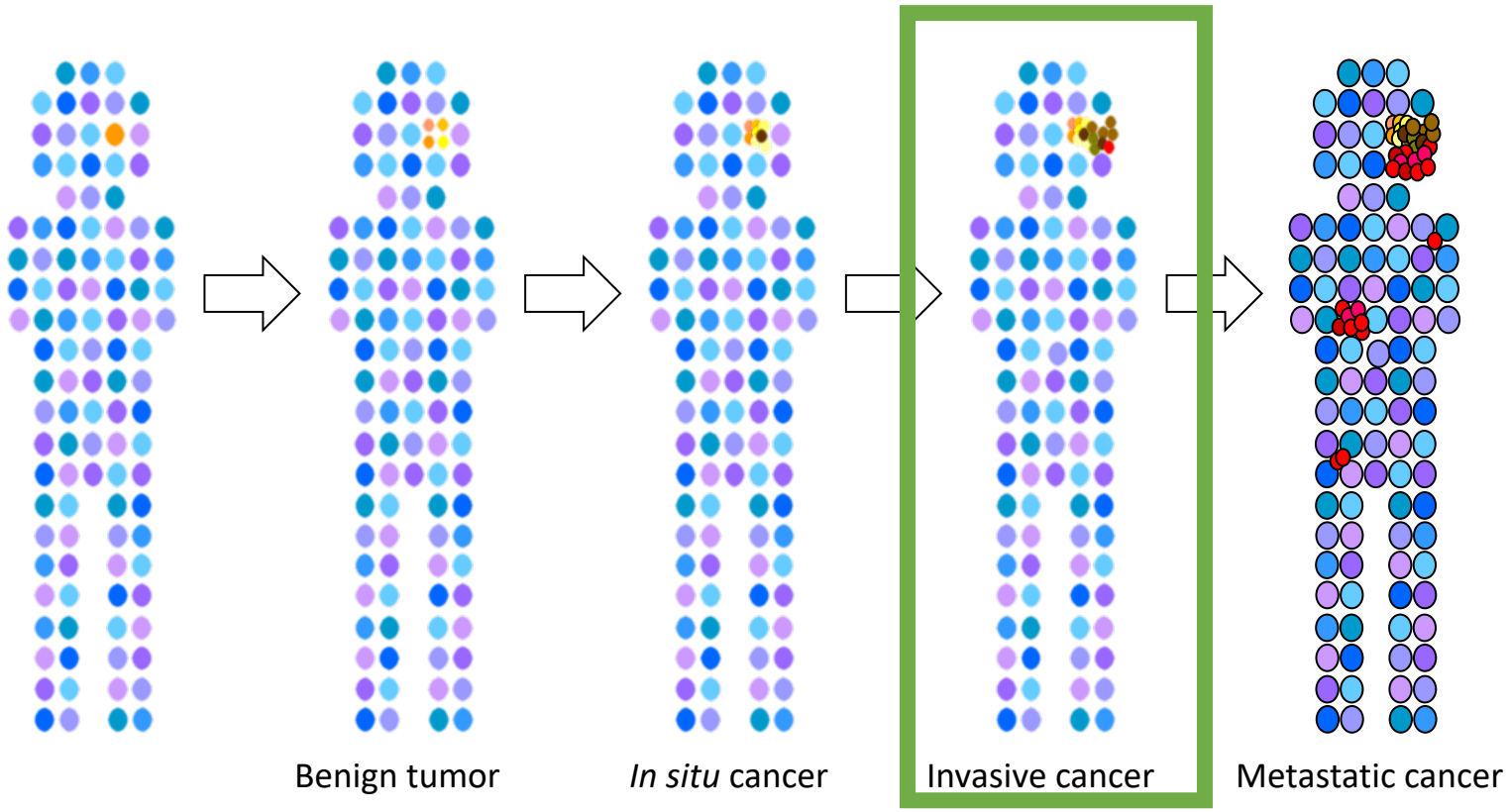
Cancer development

Invasive cancer: the tumor has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues.

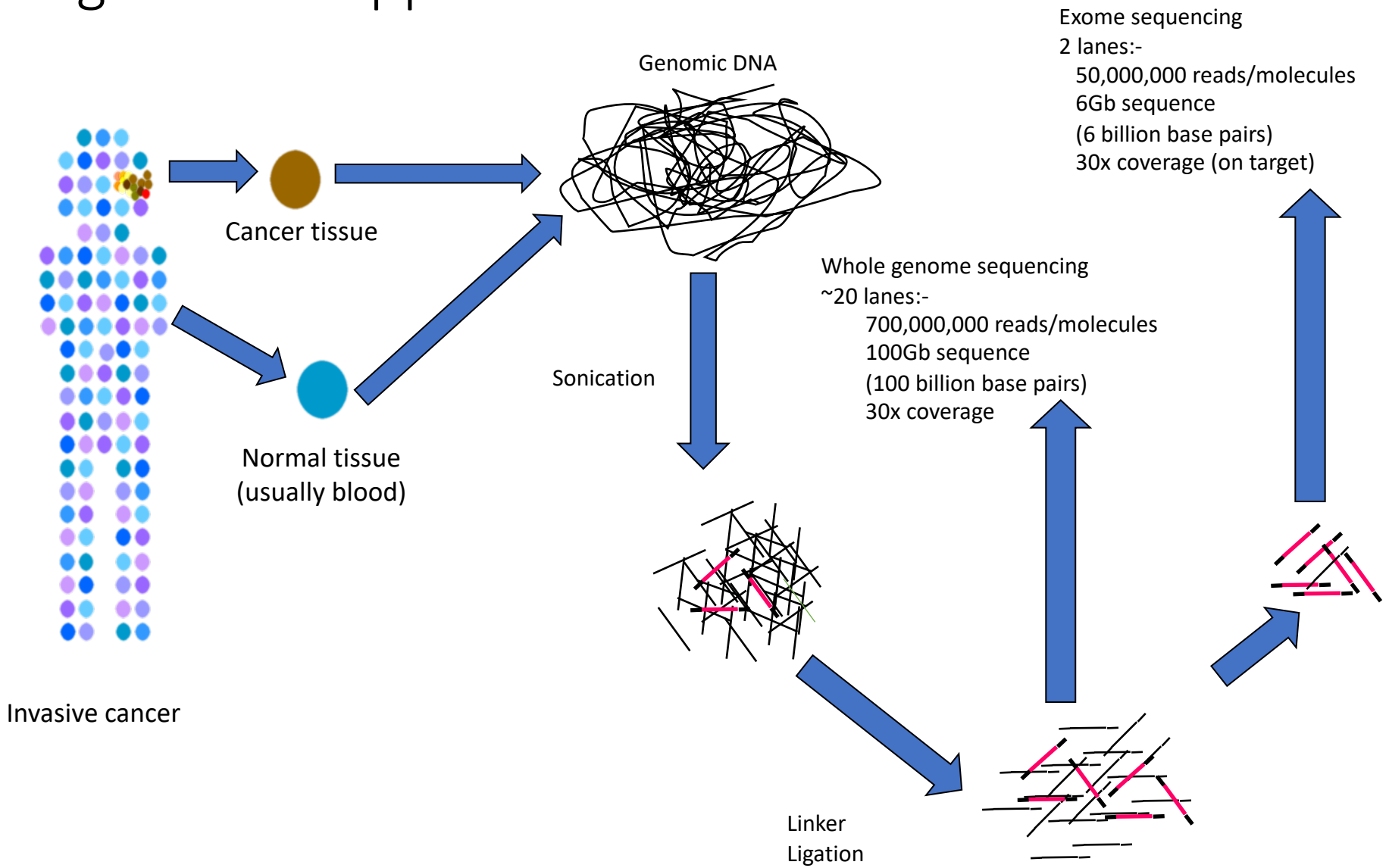


Cancer development

Metastatic cancer: the tumor has spread from the place where the cancer started to other parts of the body. Metastases are the cause of 90% of human cancer deaths.



Cancer genomics approach



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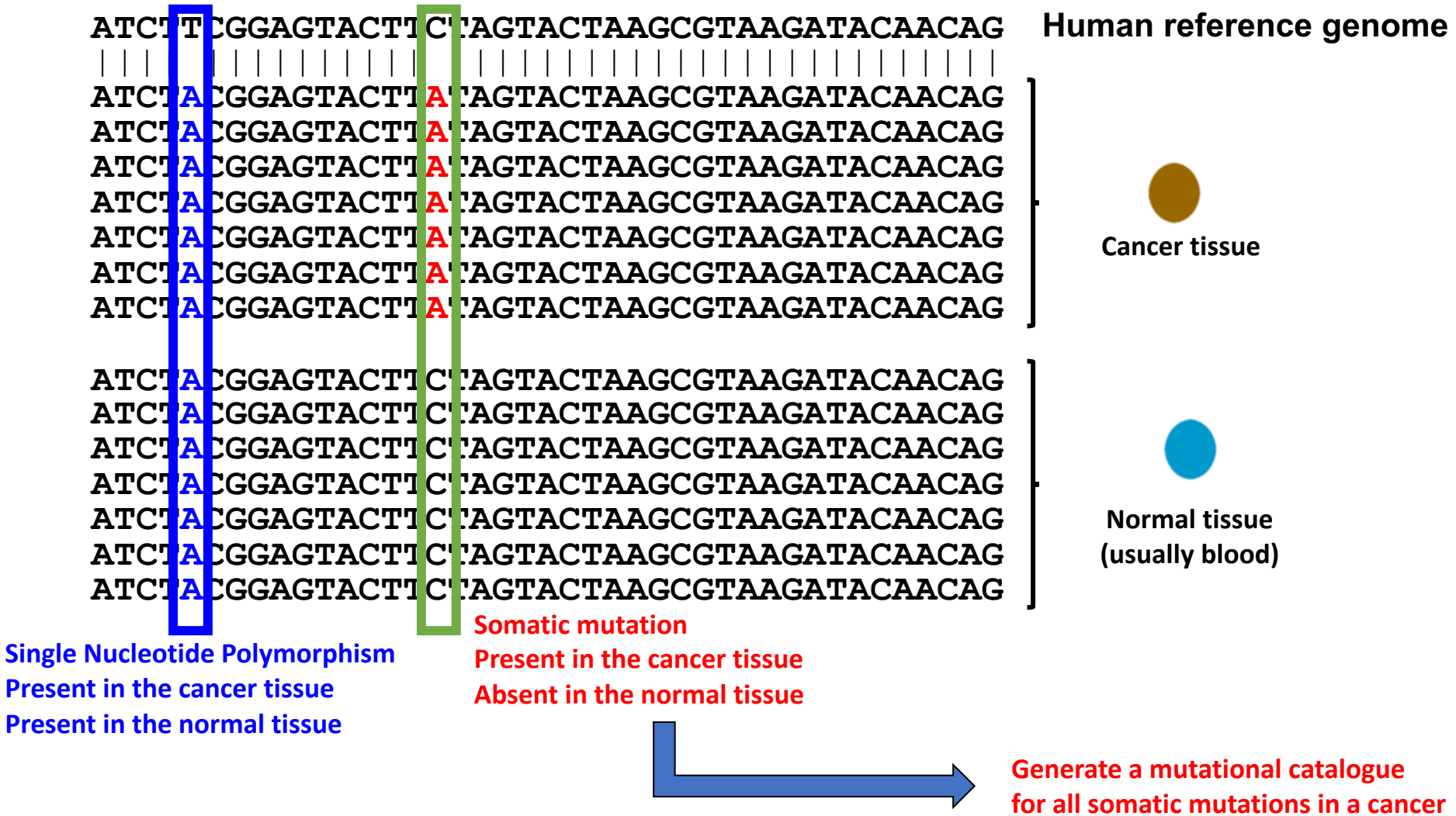
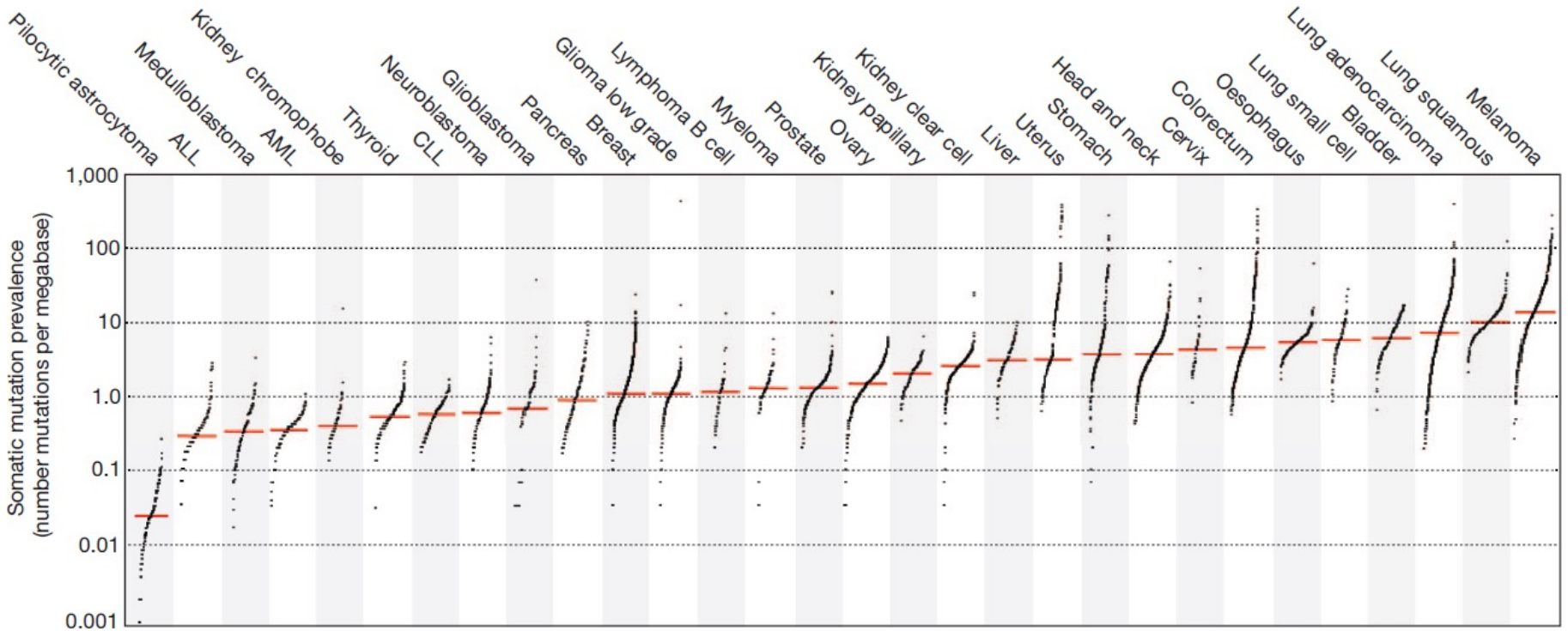


Somatic mutations in cancer

- The burden of somatic mutations is highly variable among different cancer types
- The most mutated cancer types (lung and skin cancers) are associated with well-known environmental mutagens (tobacco smoking and UV light exposure, respectively)



Statistical analysis to identify 1 to 10 driver mutations.

Alexandrov *et al.* 2013 Nature

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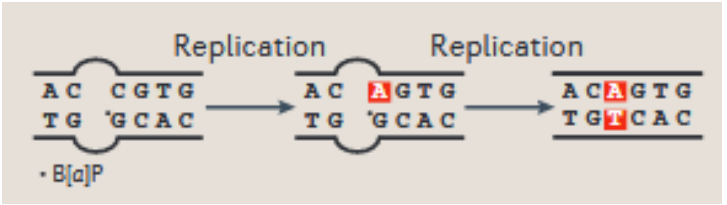
Mutational processes

Cancer genomes accumulate a large number of somatic mutations resulting from various endogenous and exogenous causes, including mutations triggered by carcinogenic exposures, normal cellular activities, and cancer-related aberrations of the DNA maintenance machinery.

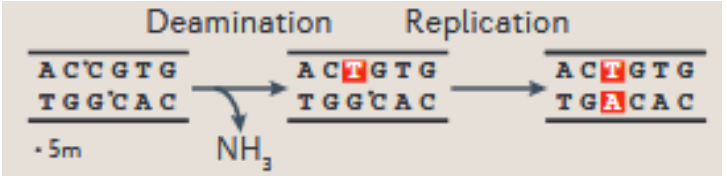
Environmental exposures

Tobacco smoking or chewing



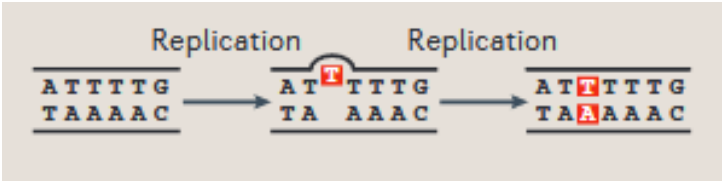
Normal cellular activities

Spontaneous deamination of methylated cytosines

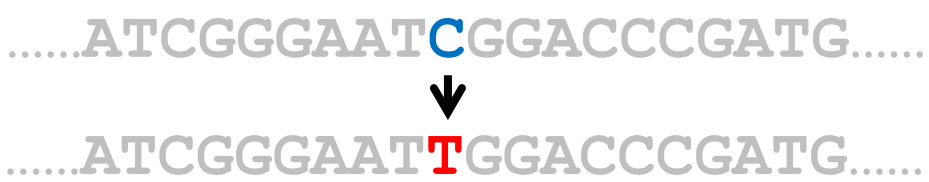


Failure in DNA replication or repair

Aberrant mismatch repair pathway



Classification of base substitution mutations



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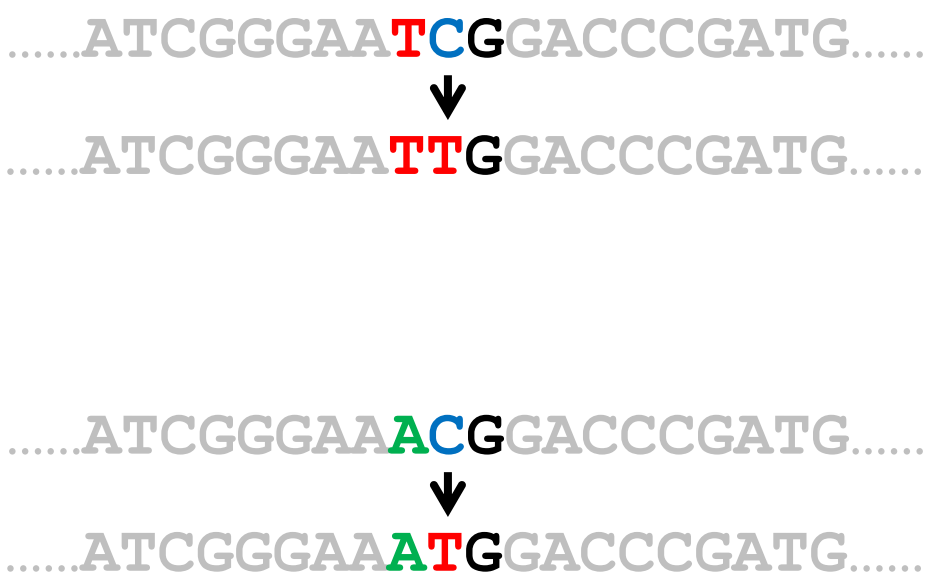

Classification of base substitution mutations

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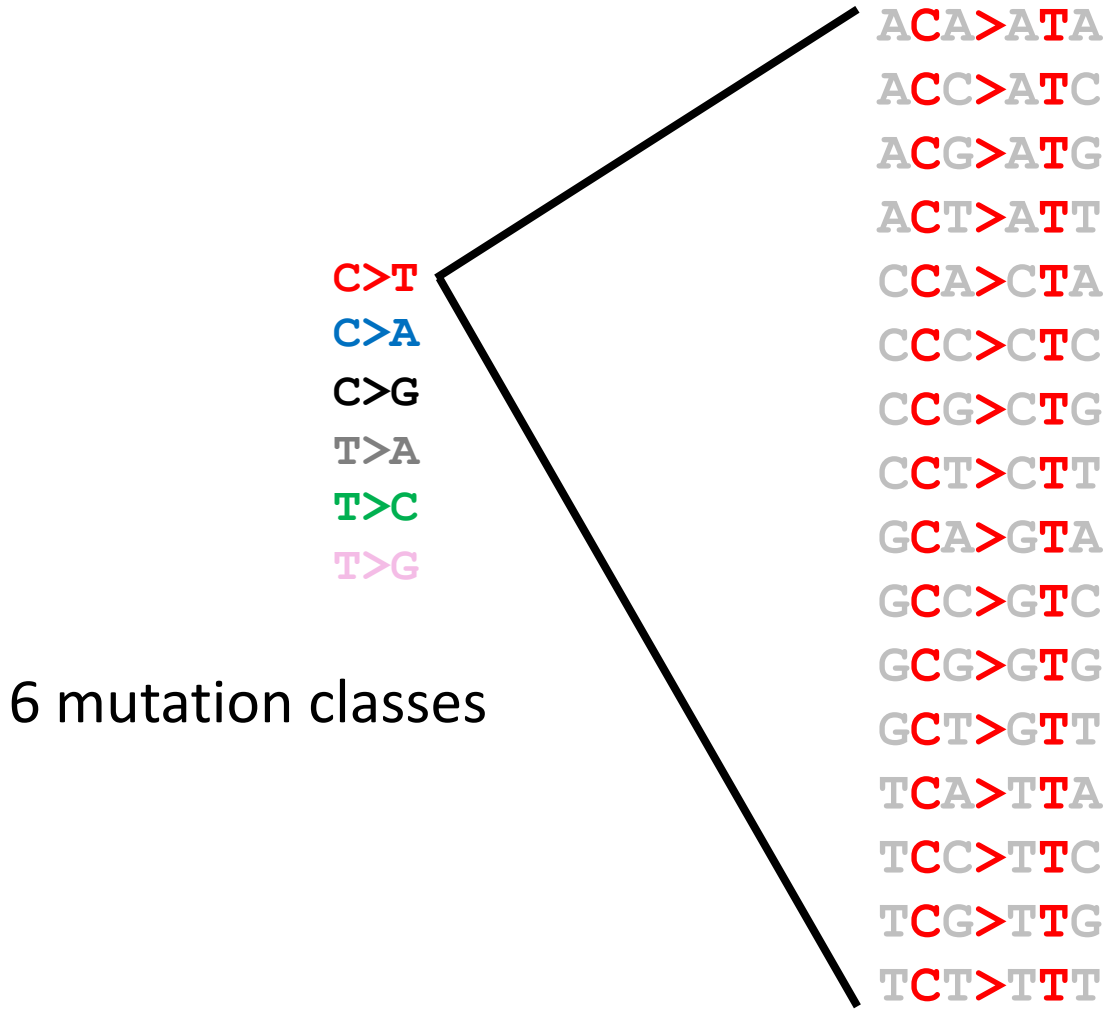
C>T
C>A
C>G
T>A
T>C
T>G

6 mutation classes

Classification of base substitution mutations



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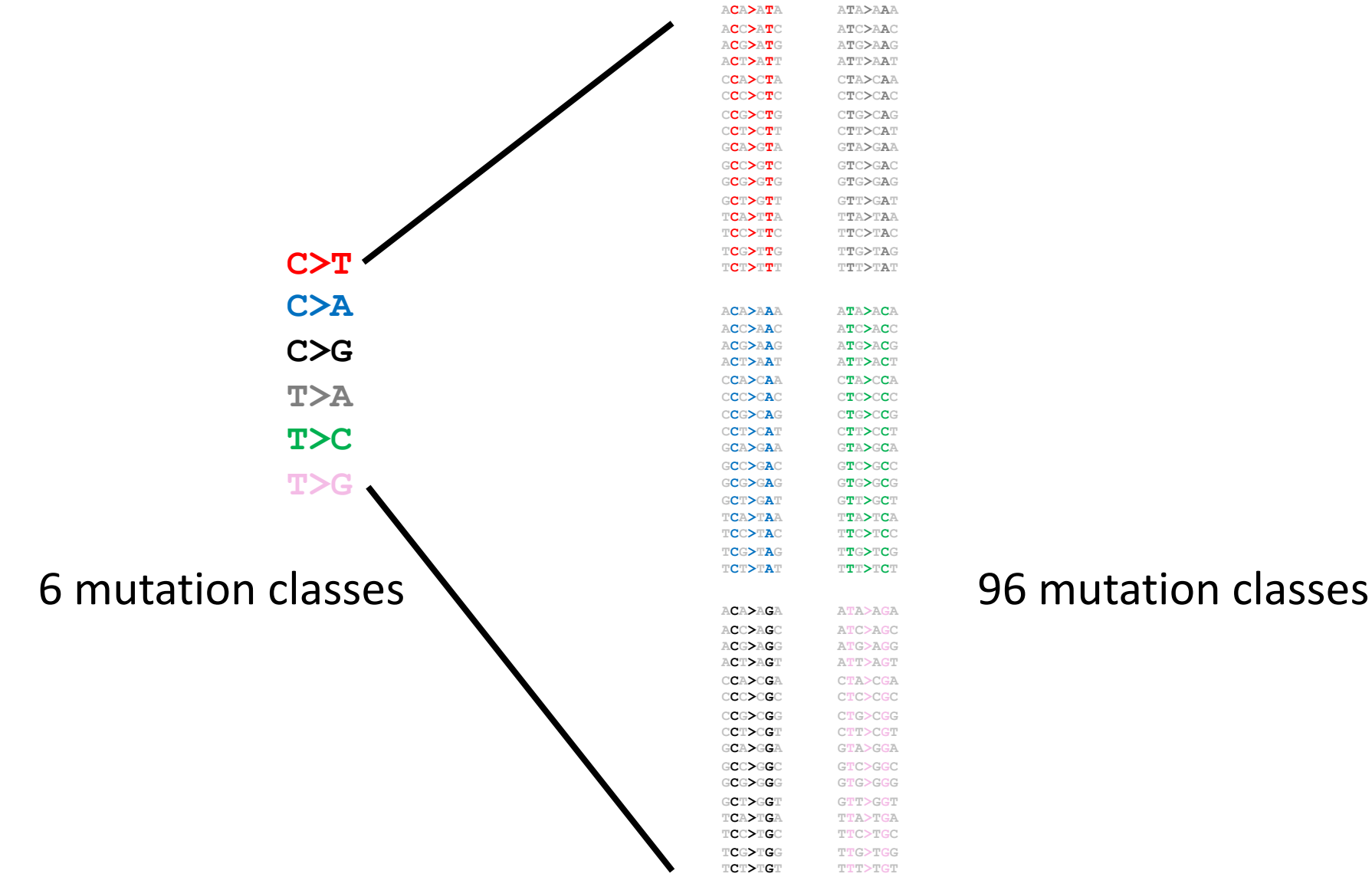

Patterns of mutations are defined by base substitutions and context

Six classes of single-base mutations

Reported by pyrimidine

Adding 5’ and 3’ adjacent bases

96 possibilities considering context