Cancer Evolution and Multistep Tumorigenesis

Cancer Biology I (PATH4500)

September 24th, 2025

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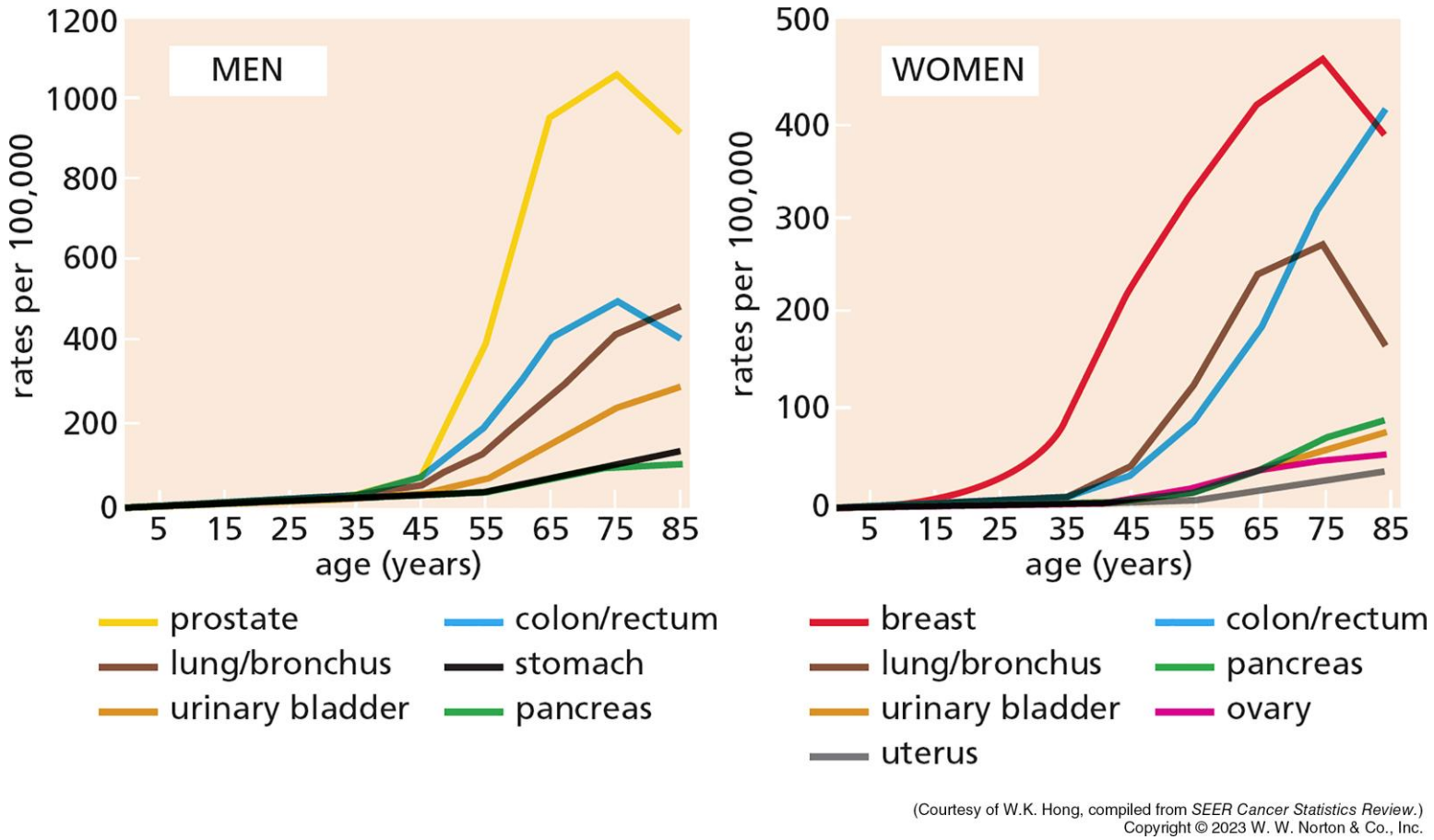
Cancer Evolution and Multistep Tumorigenesis

-KEY LEARNING OBJECTIVES-

- To describe the multi-step process of tumorigenesis.
- To recognize the contribution of cancer cell intrinsic mechanisms (genetic and epigenetic) and the influence of non-tumor mechanisms (e.g., tumor microenvironment, immune response).
- To examine the hallmarks of cancer.
- To identify different models of cancer evolution.

Most human cancers develop over many decades of time

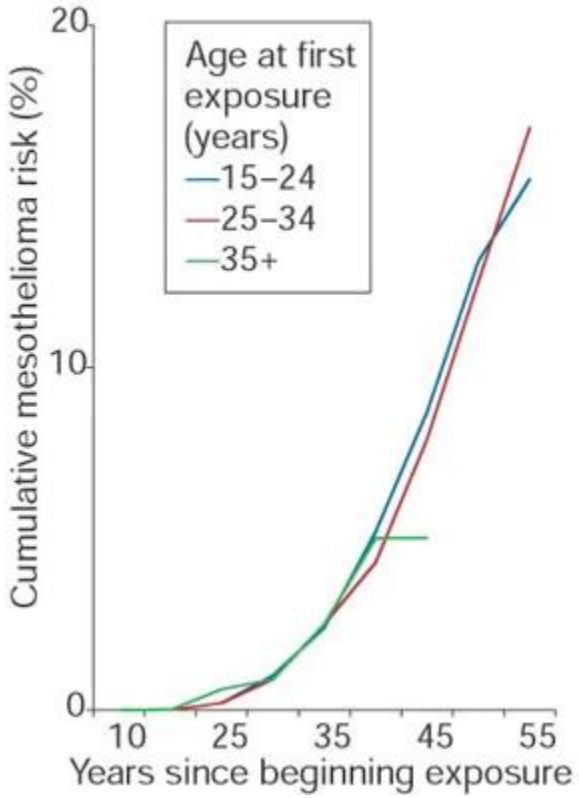
Age is a large factor in incidence of cancer



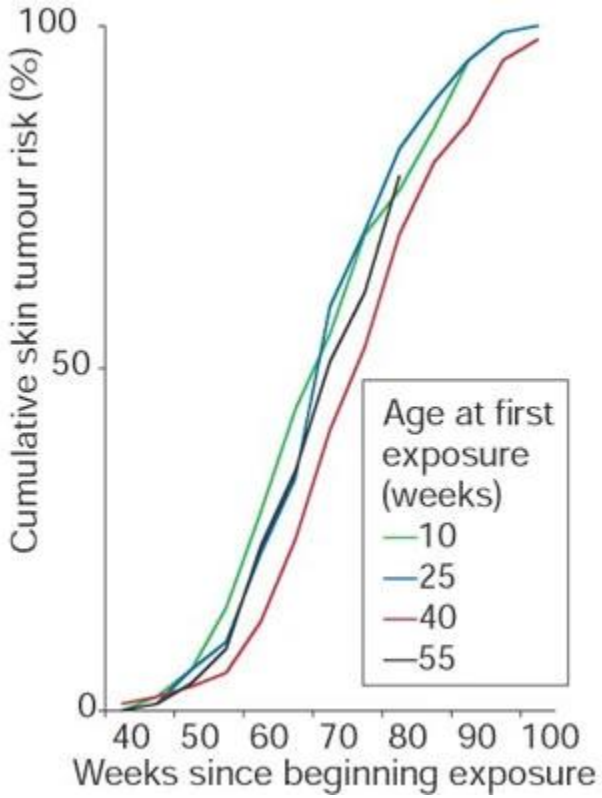
(Courtesy of W.K. Hong, compiled from *SEER Cancer Statistics Review*.)

Such dynamics imply a sequence of random independent events that occur at comparable frequencies over extended periods of time. The probability of these events to occur per unit of time may vary dramatically from one individual to another, being affected by inherited predisposition, diet, and lifestyle, among other variables.

Cancer incidence and duration of carcinogen exposure



Cumulative mesothelioma risk in USA workers exposed to asbestos.

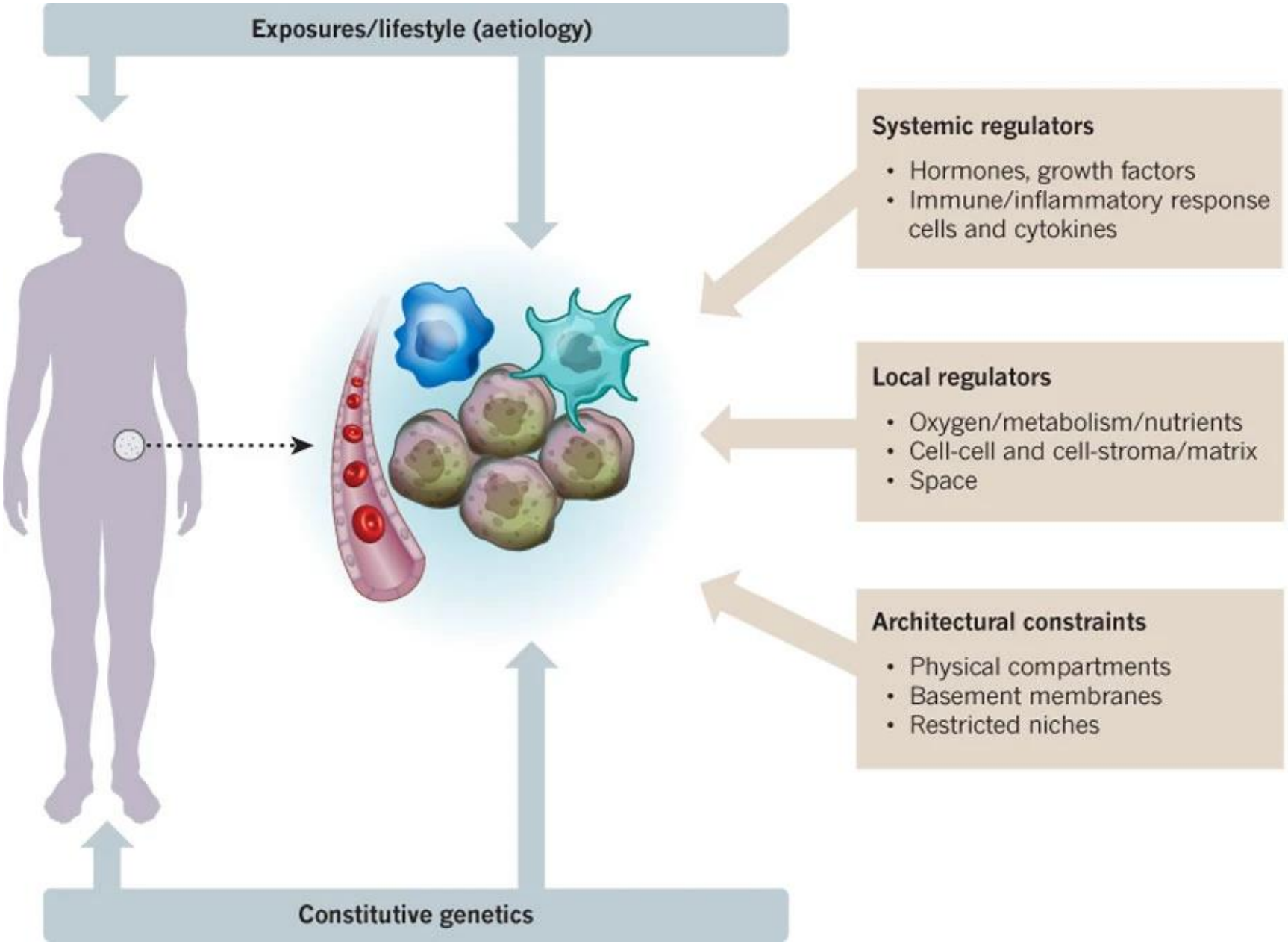


Cumulative skin tumor risk in mice treated with benzo(a)pyrene.

Malignant transformation correlates with the *duration of the exposure* rather than the age of the exposed individuals or the age when the exposure began.

Peto, Nature, 2001

Multiple components influence cancer evolution



Greaves & Maley, Nature, 2012

Cancer development is a multi-step process
-from adenoma to colon cancer-

Stage 0 (Carcinoma in Situ):
This is the earliest stage of cancer. Abnormal cells are present only in the innermost lining (mucosa) and have not spread.

Stage I:
The tumor has grown into the layer of tissue just below the inner lining (submucosa) or into the thick muscle layer (muscularis propria), but it has not spread to lymph nodes or distant organs.

Stage II:
The tumor has grown through the colon wall and possibly into nearby tissues or organs, but it has not spread to lymph nodes or distant sites.

Stage III:
The cancer has spread to one or more nearby lymph nodes, but there is no distant metastasis.

Stage IV:
The cancer has spread to distant organs, such as the liver or lungs.

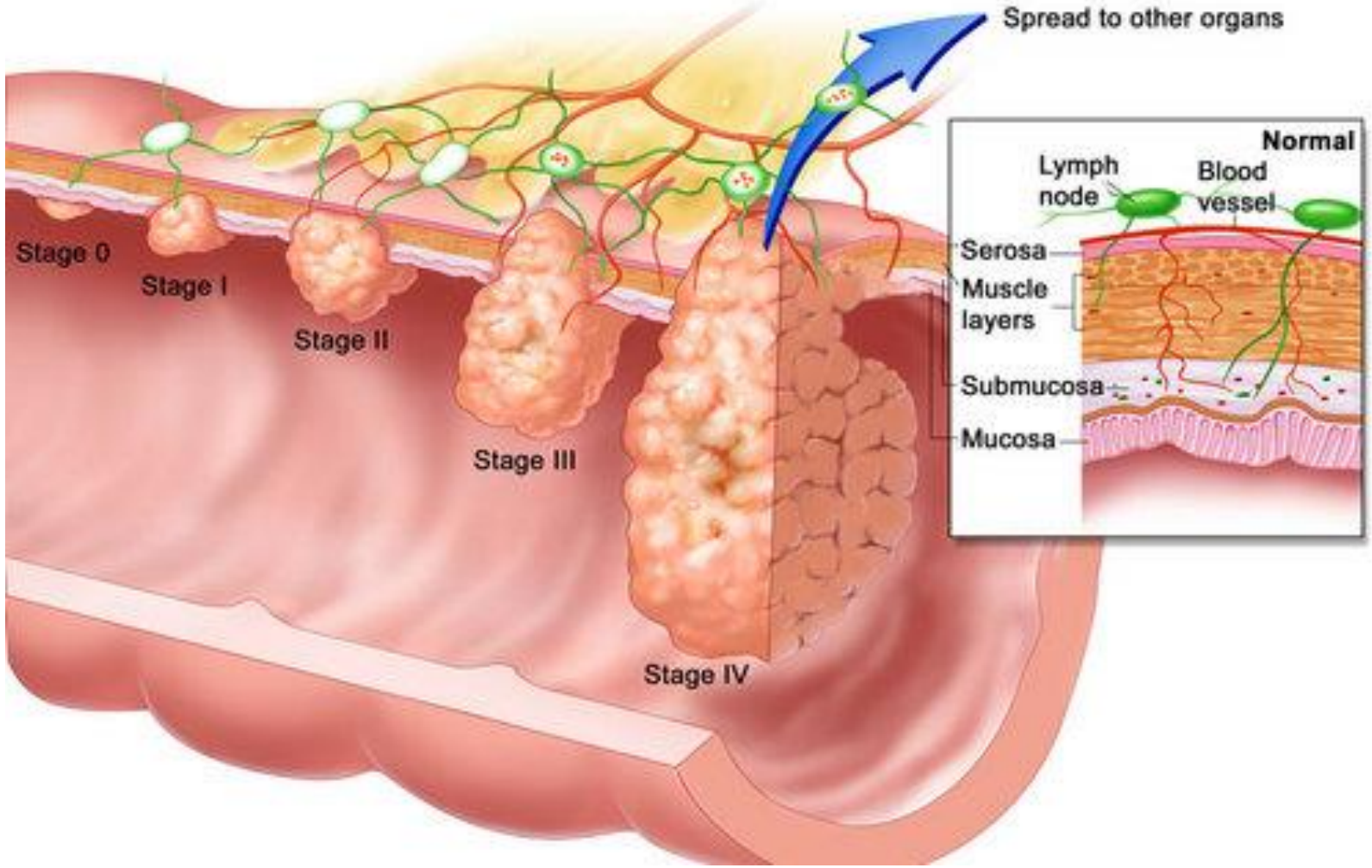
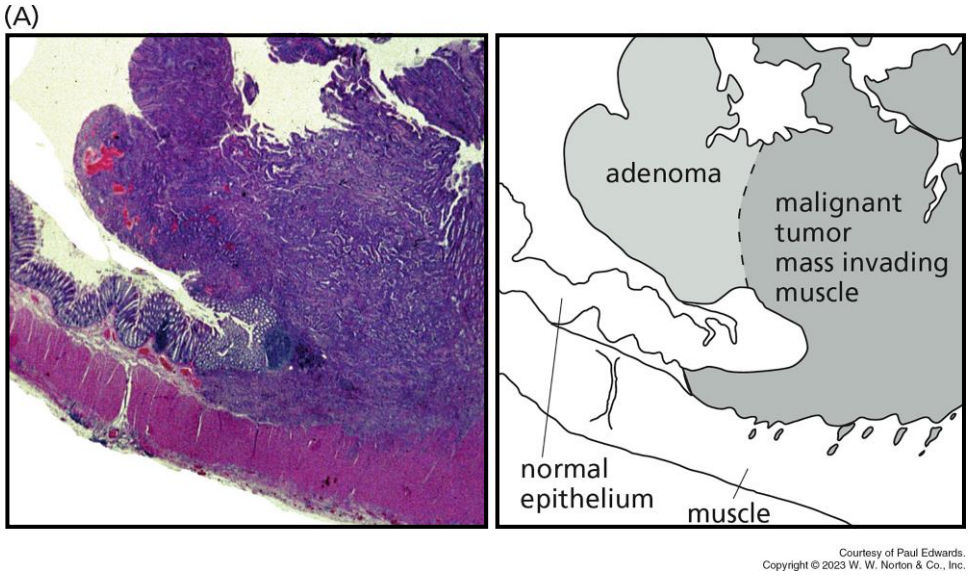
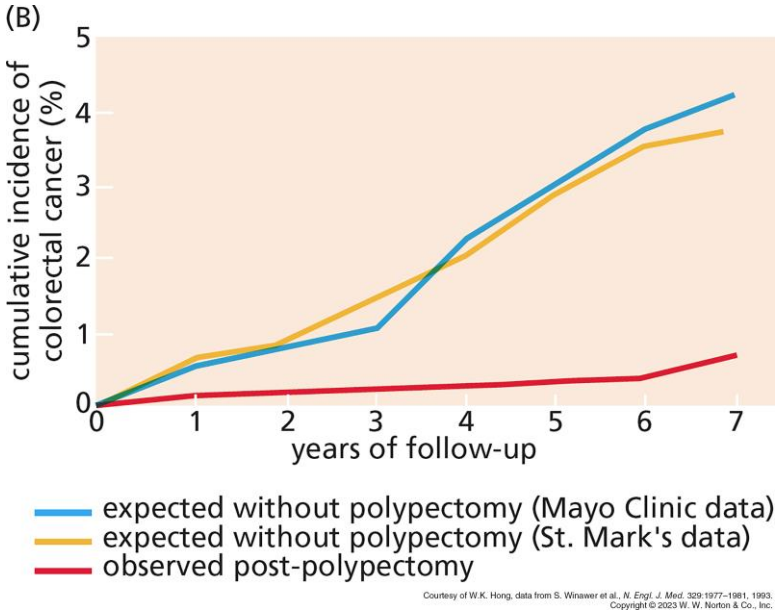


Image credit: Terese Winslow, The National Cancer Institute (2005)

Cancer development is a multi-step process -evidence for adenoma to carcinoma progression-



Occasionally, carcinomas are observed to be growing directly out of adenomas.

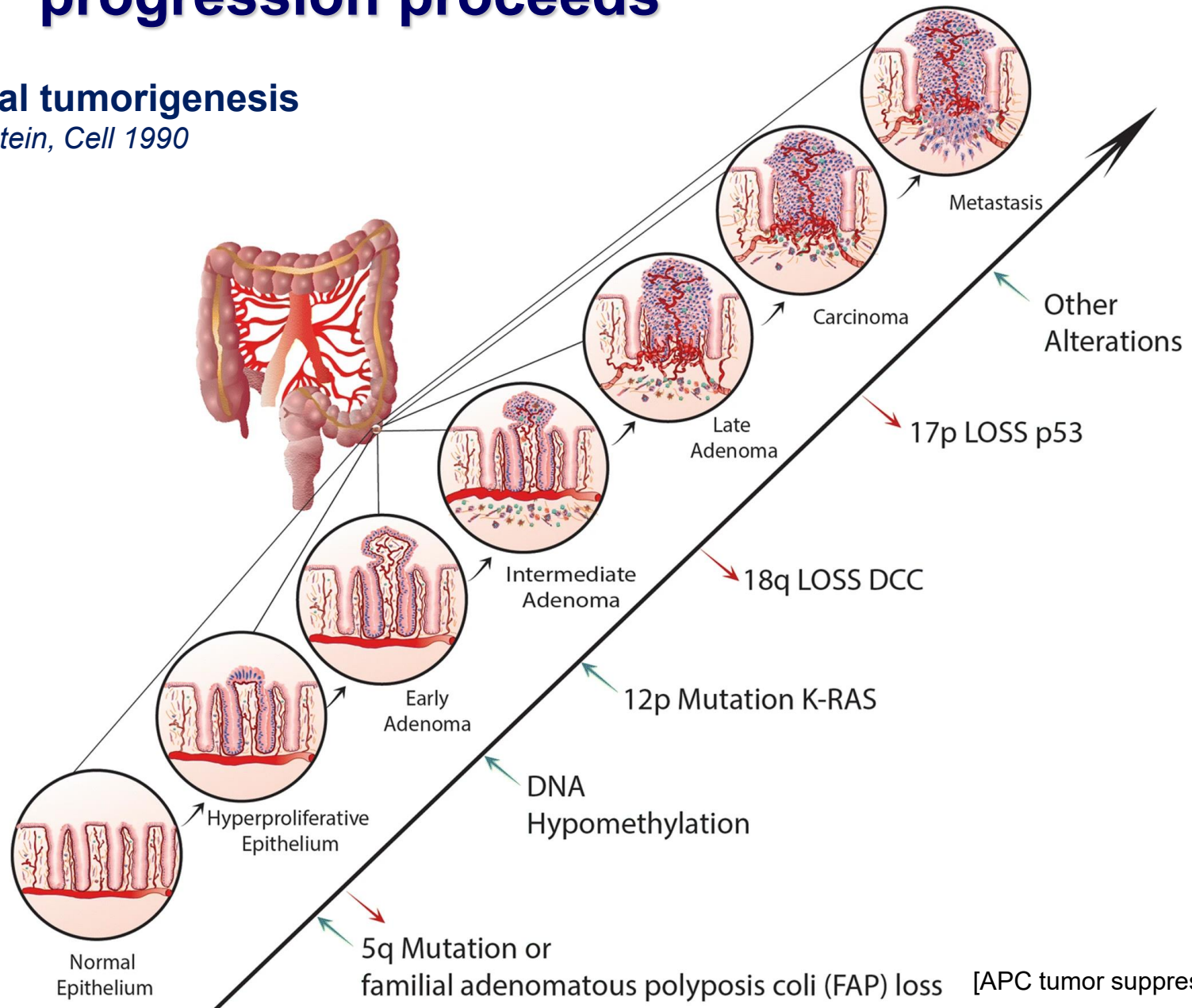


Polypectomy (surgical removal of polyps) reduces the risk of colorectal cancer.

Cells accumulate genetic and epigenetic alterations as tumor progression proceeds

A genetic model for colorectal tumorigenesis

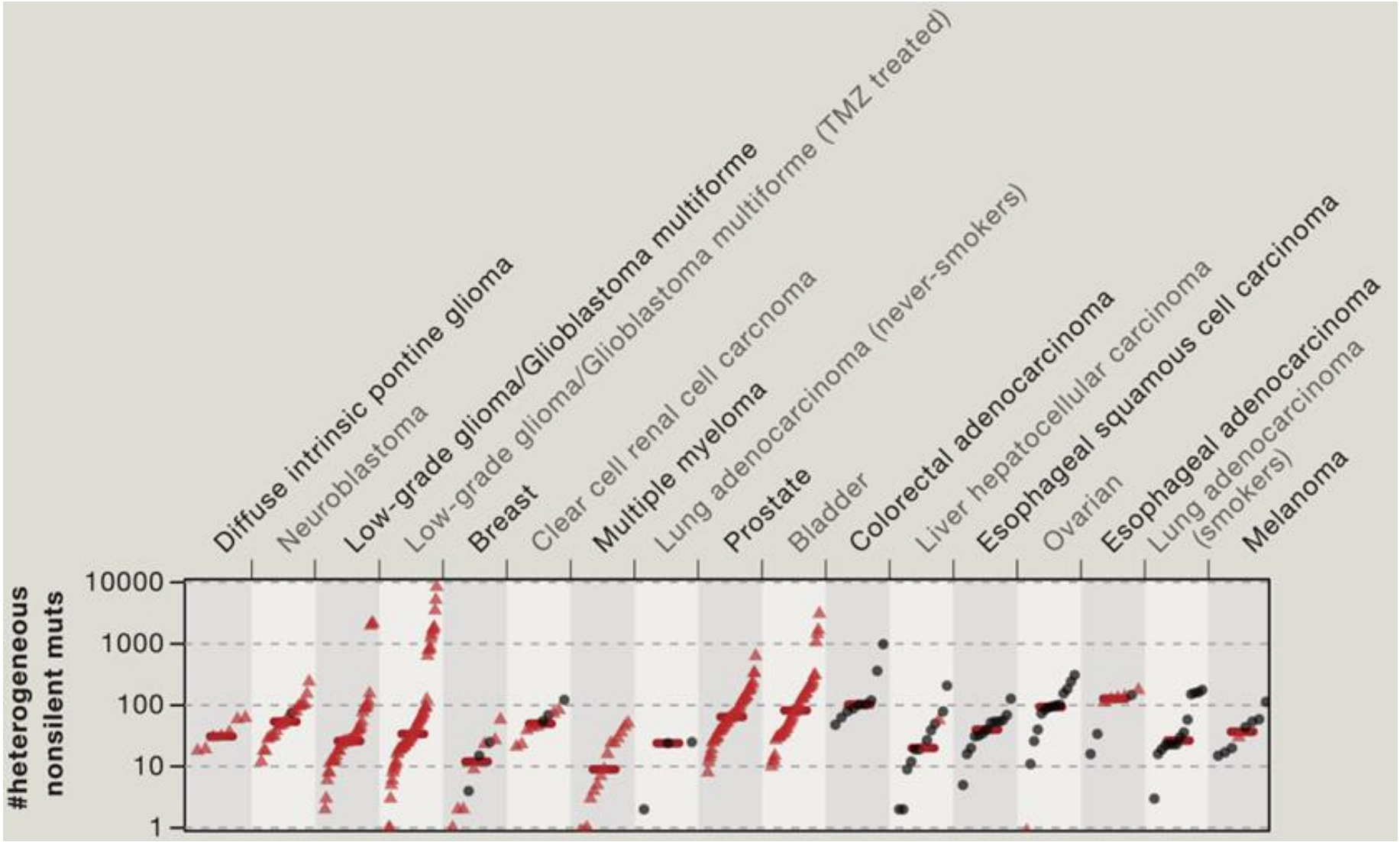
adapted from *Fearon & Vogelstein, Cell 1990*



[APC tumor suppressor gene]

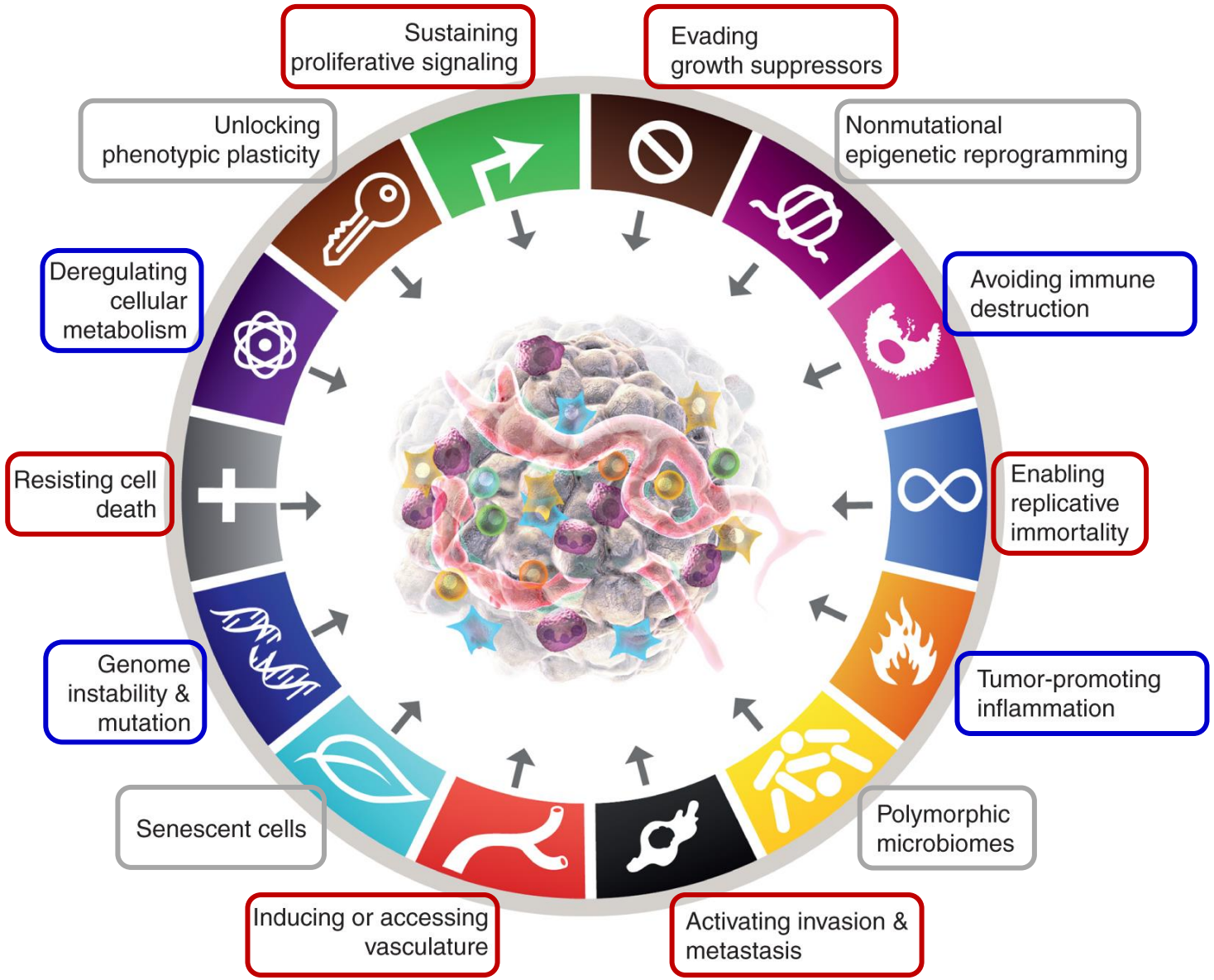
Menter et al., Current Gastroenterology Reports (2019)

Hundreds of non-silent mutations are detected in cancer cells



McGranahan & Swanton, Cell, 2017

Hallmarks of Cancer



The Hallmarks of cancer
Hanahan & Weinberg, Cell 2000

Hallmarks of cancer: next generation
Hanahan & Weinberg, Cell 2011

Hallmarks of cancer: new dimensions
Hanahan, Cancer Discovery 2022

Hanahan, Cancer Discov., 2022

Cancer Evolution

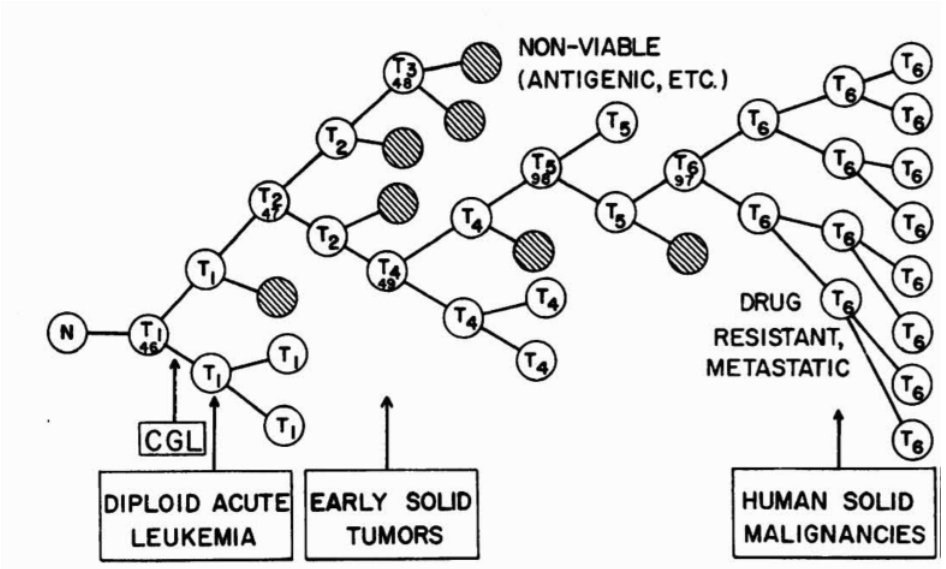
The Clonal Evolution of Tumor Cell Populations

Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression.

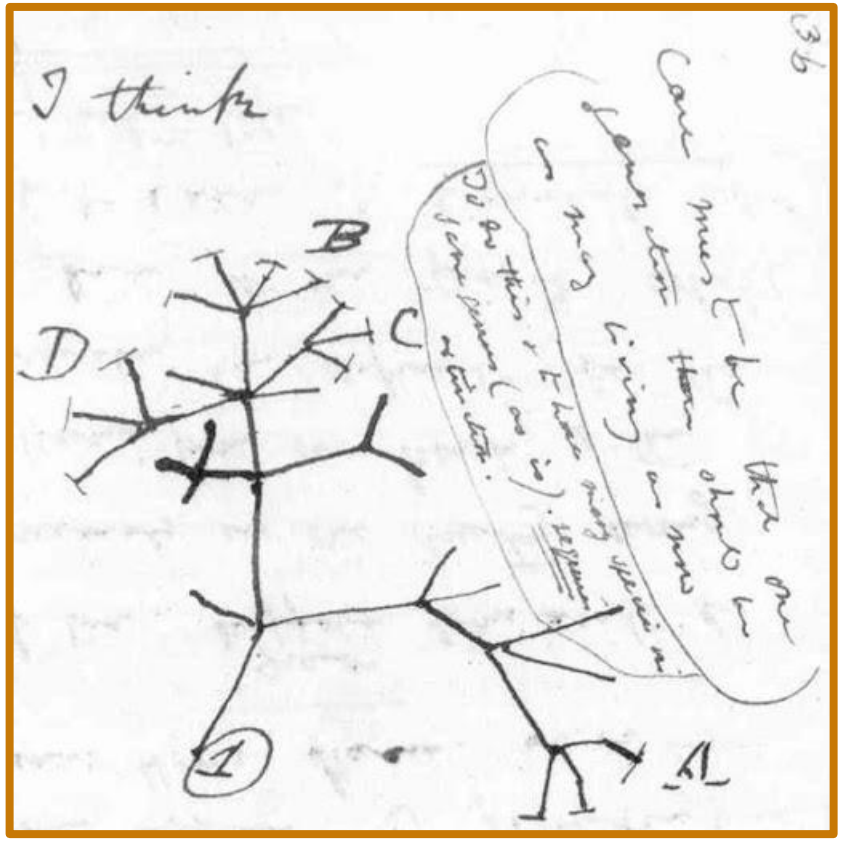
Peter C. Nowell

Science 1976

Model of clonal evolution in neoplasia

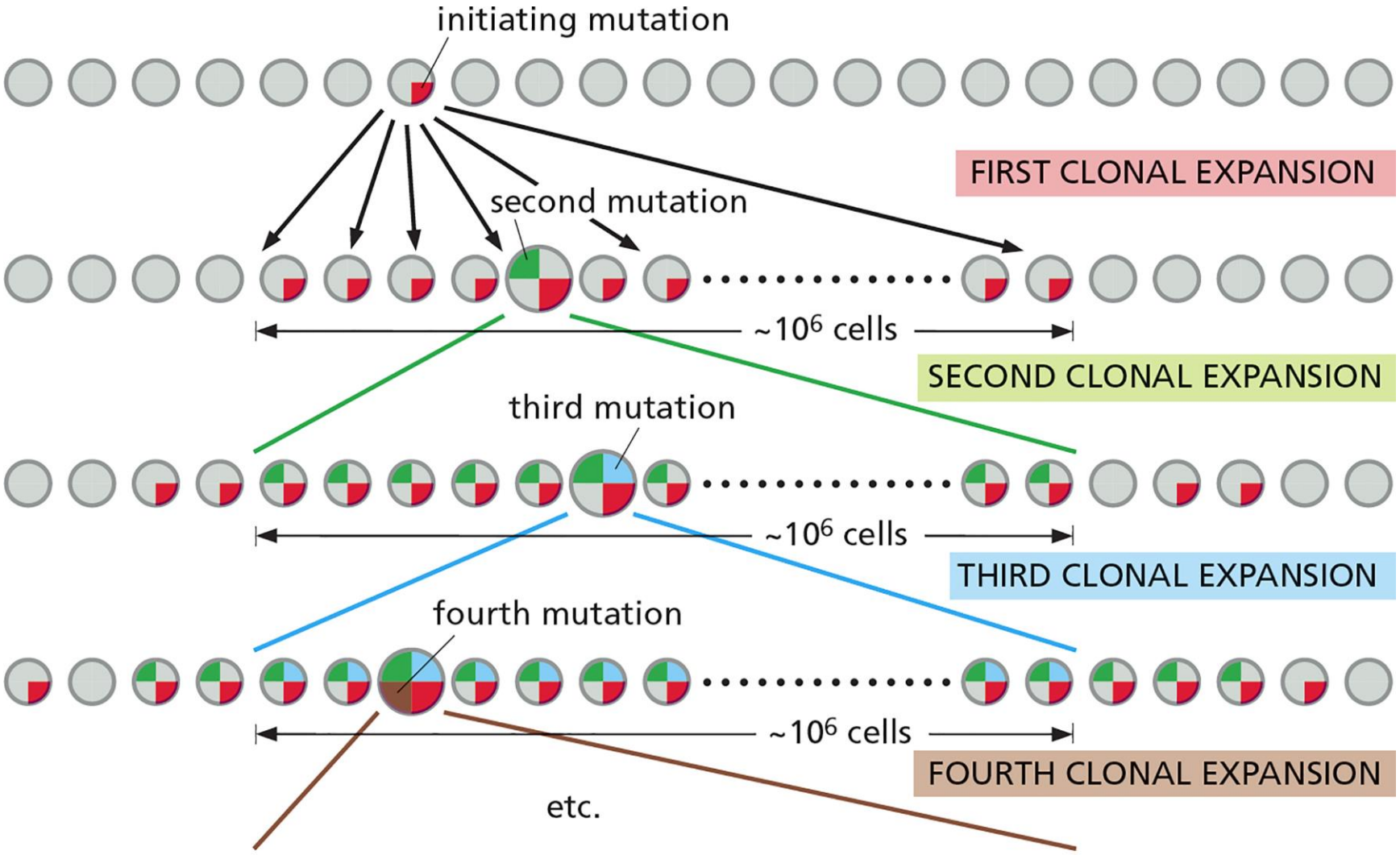


Branching evolutionary tree of speciation
(Charles Darwin,1837)

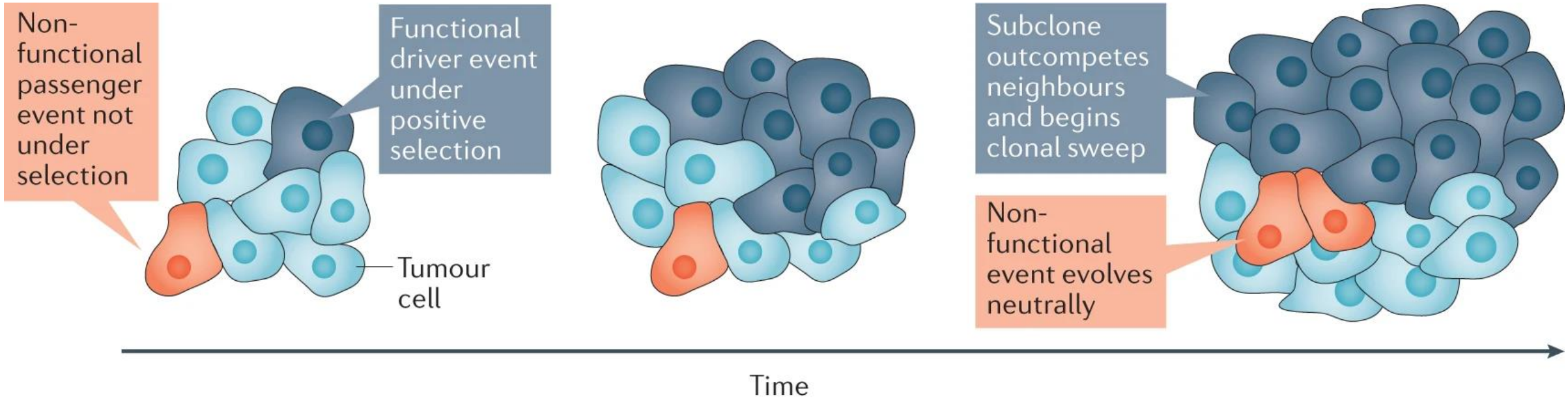


Cancer development follows the rules of Darwinian evolution

Random mutations create genetic and phenotypic variability in a cell population, and the forces of selection may favor the outgrowth of cells with increased fitness.



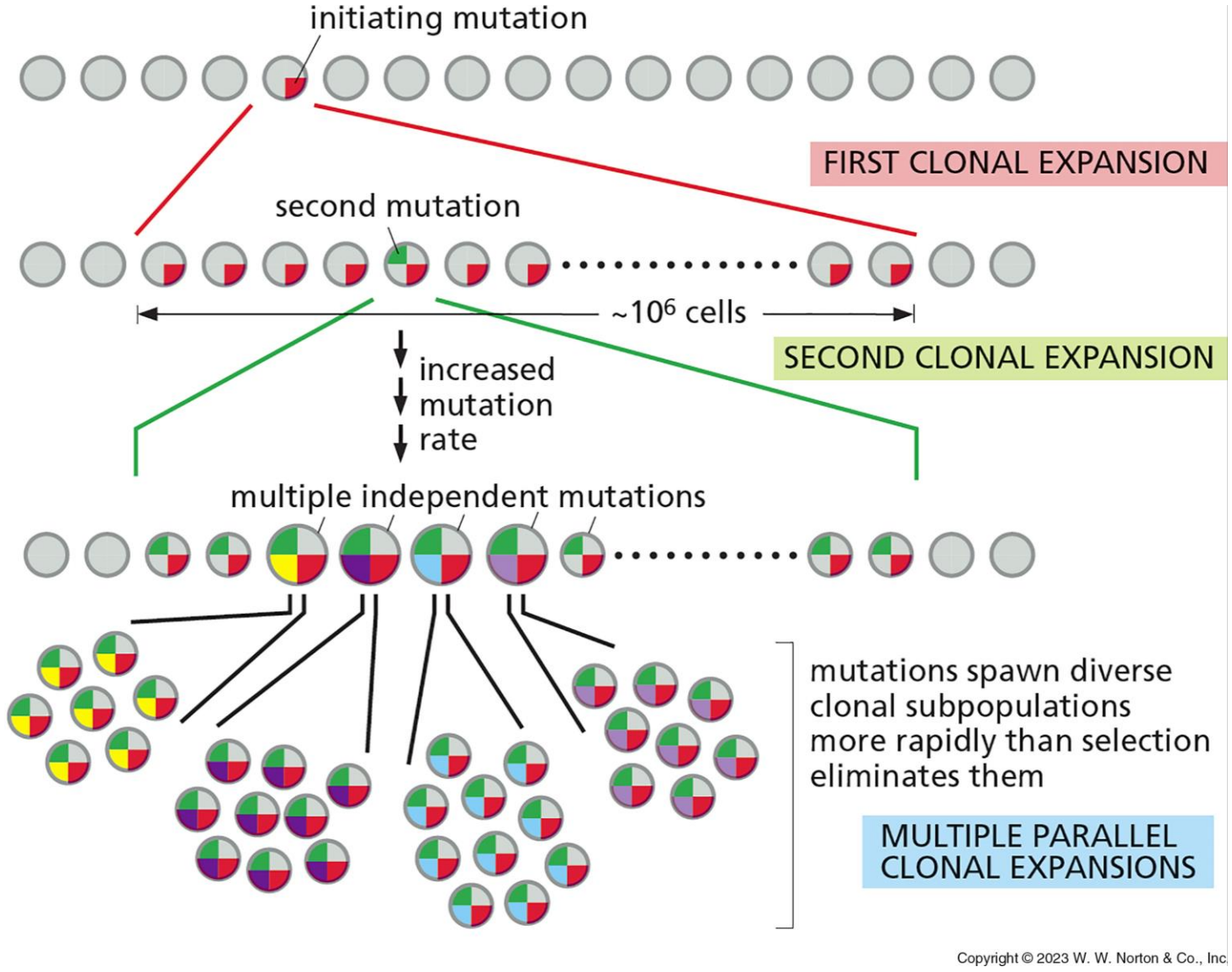
Functional and non-functional intra-tumor heterogeneity in tumor evolution



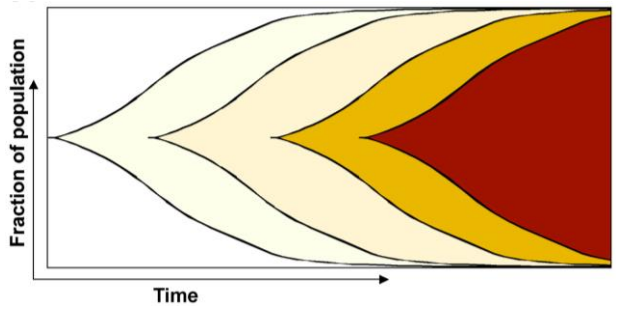
The increased rate of phenotypic variation in cancers compared with normal tissues means that new subclones arise and compete. A minority contain a driver event, such as a genetic mutation or copy number alteration, that grants a selective advantage. These subclones may grow at a faster rate than their neighbors and outcompete them in a ‘selective sweep’.

Black & McGranahan, Nature Reviews Cancer, 2021

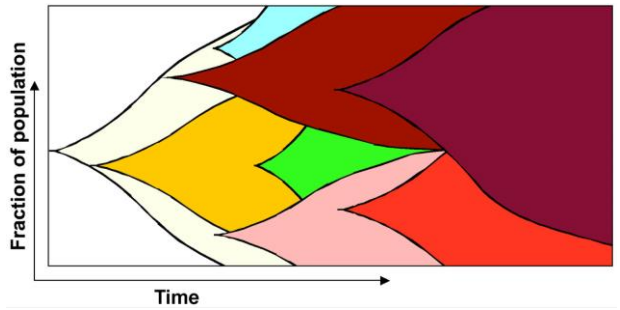
Clonal diversification within a tumor



Linear clonal succession

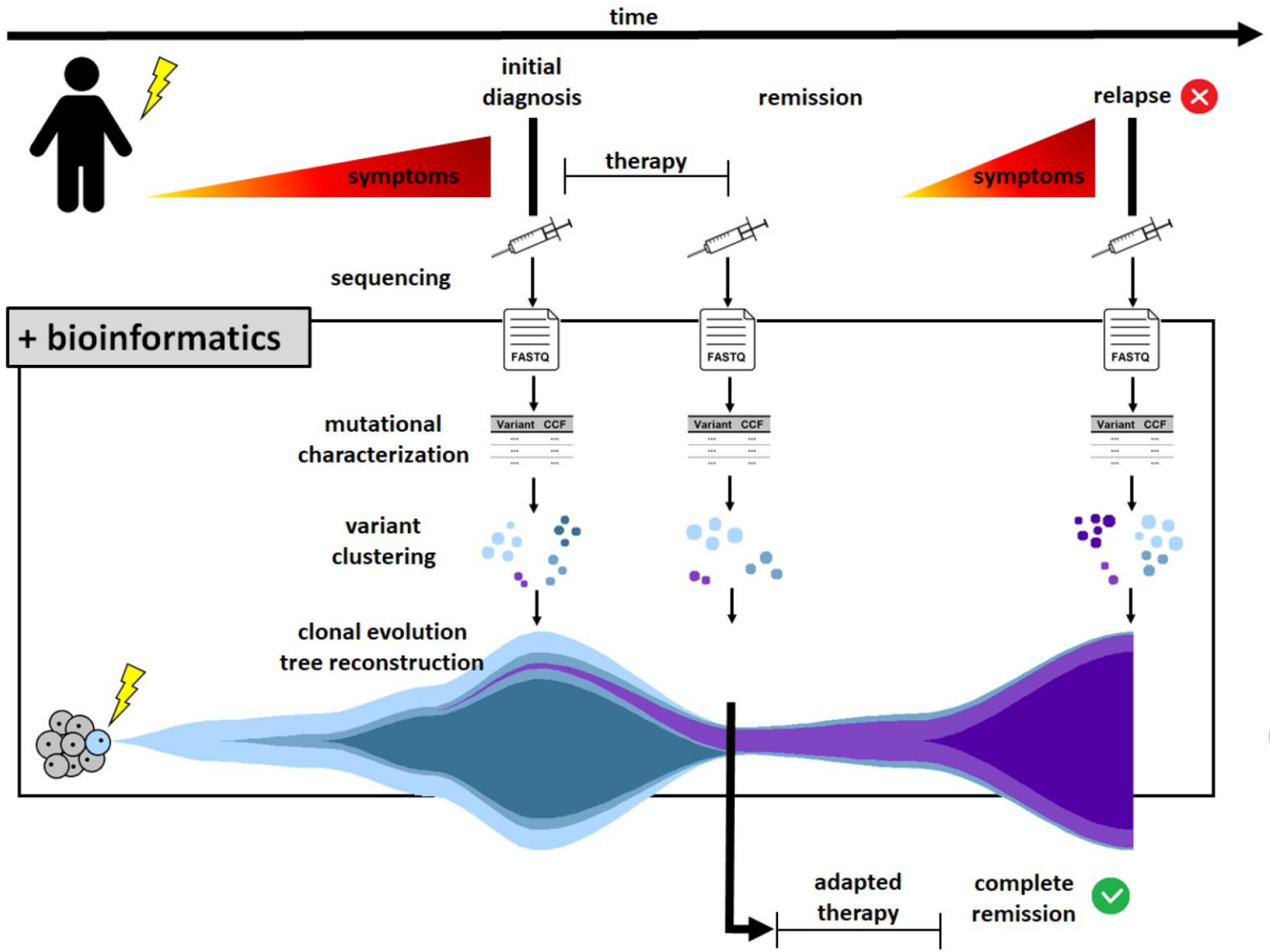


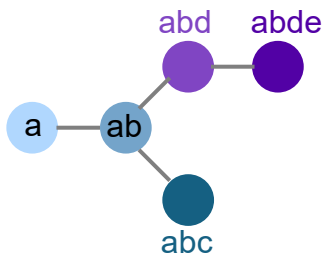
Dynamic clonal diversification



Marusyk and Polyak, Biochim. Biophys. Acta, 2010

Inferring tumor evolution and phylogenetic structure from genetic data





Sampling over time

Sequencing

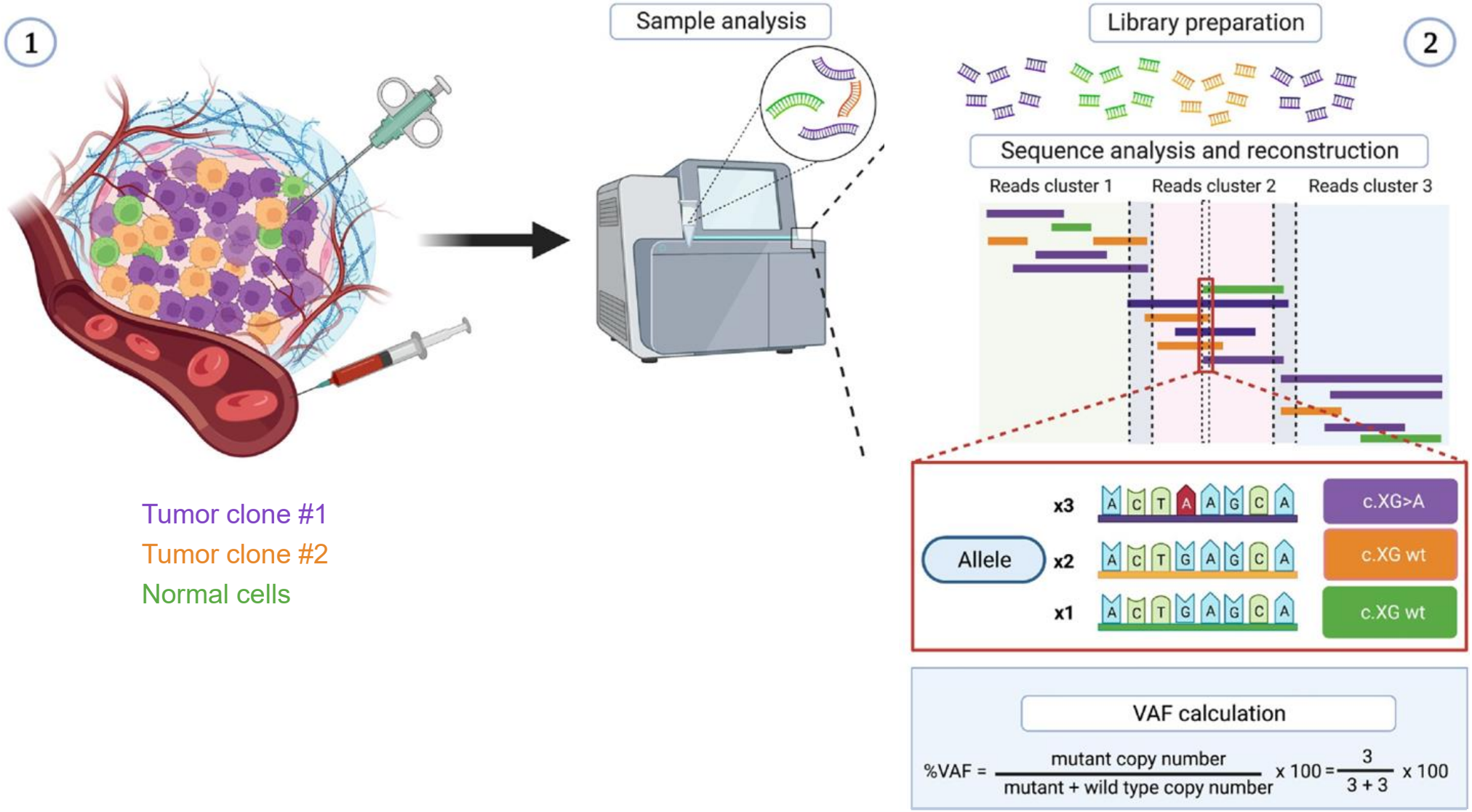
Assess Variant Allele Frequencies (VAFs)

Clonal evolution visualization

Sandmann et al., Int. J. Environ. Res. Public Health, 2023

Inferring Variant Allelic Frequencies (VAFs) of somatic mutations

Bulk sequencing



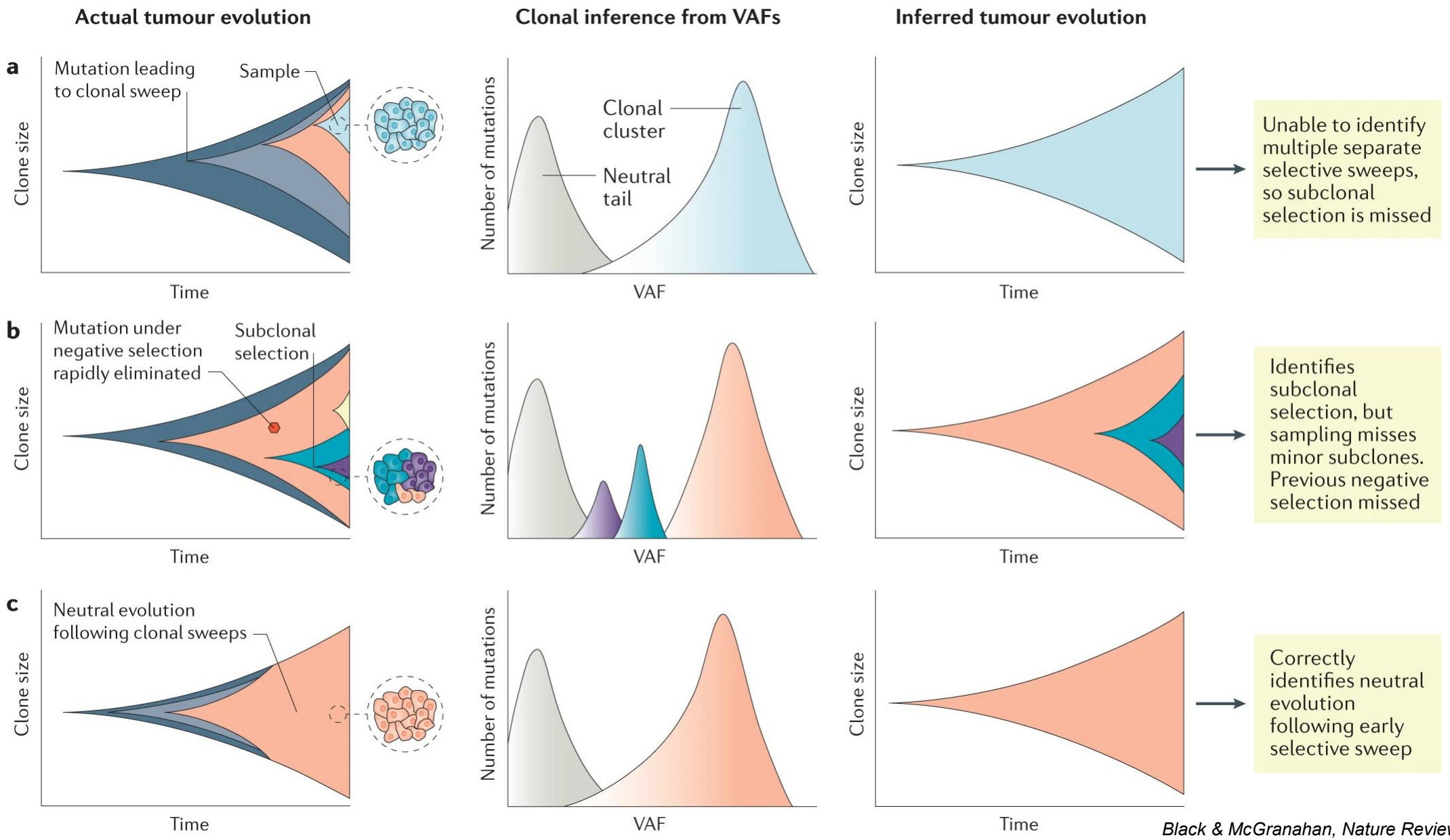
Tumor clone #1

Tumor clone #2

Normal cells

Boscolo-Bielo et al., Trends in Cancer, 2023

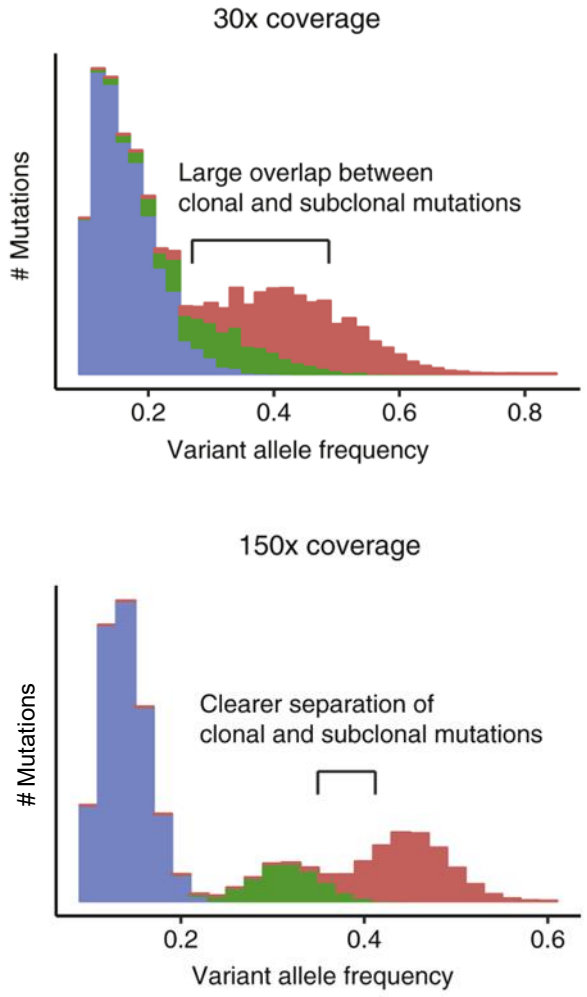
Inferring tumor evolution from VAFs of somatic mutations



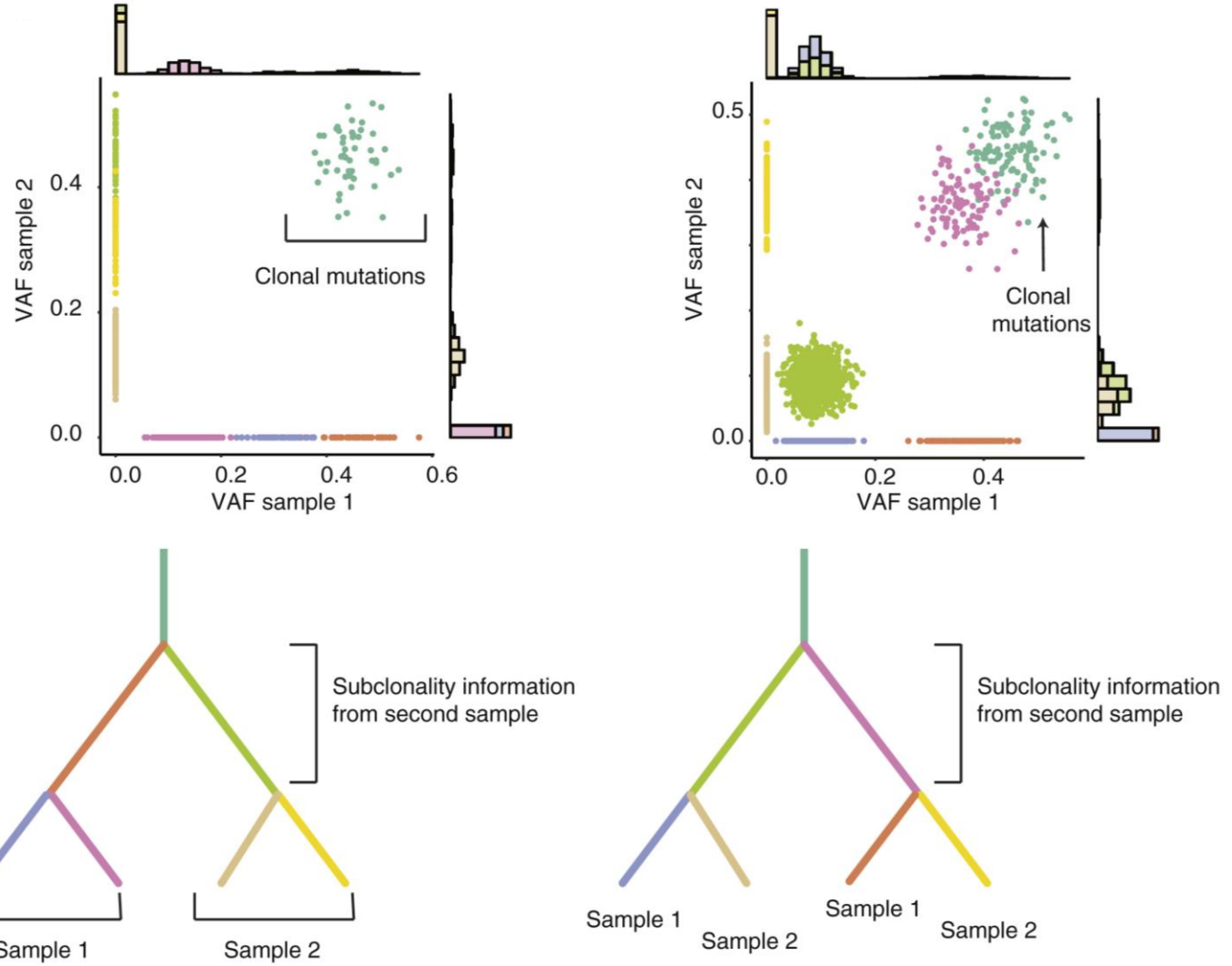
Black & McGranahan, Nature Reviews Cancer, 2021

Inferring tumor evolution and phylogenetic structure from VAFs

Subclonal resolution improves with higher sequencing depth

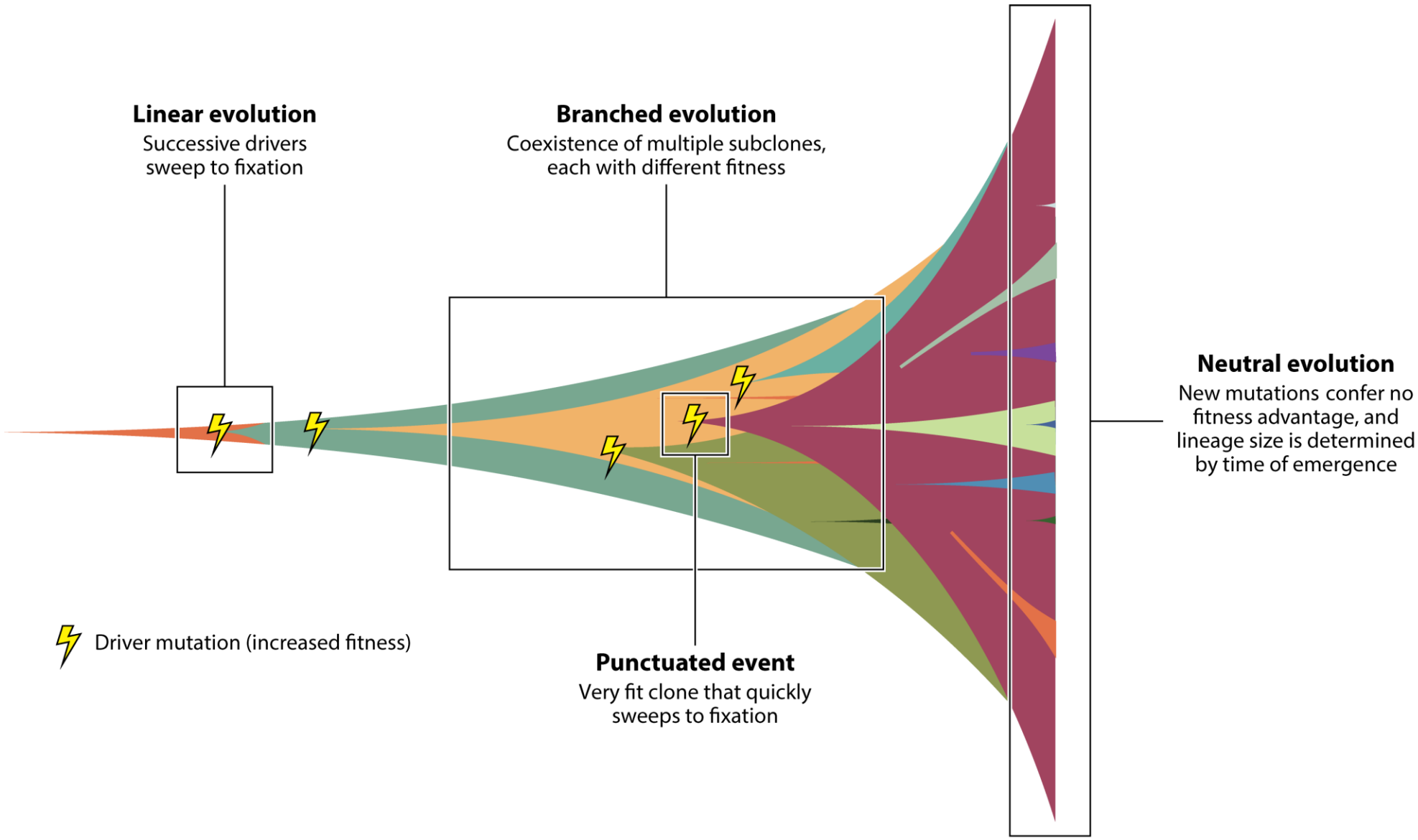


Analysis of multiple samples of the same tumor improves inference of phylogenetic structure



Korber & Hofer, Current Opinion in Systems Biology, 2019

Models of cancer evolution



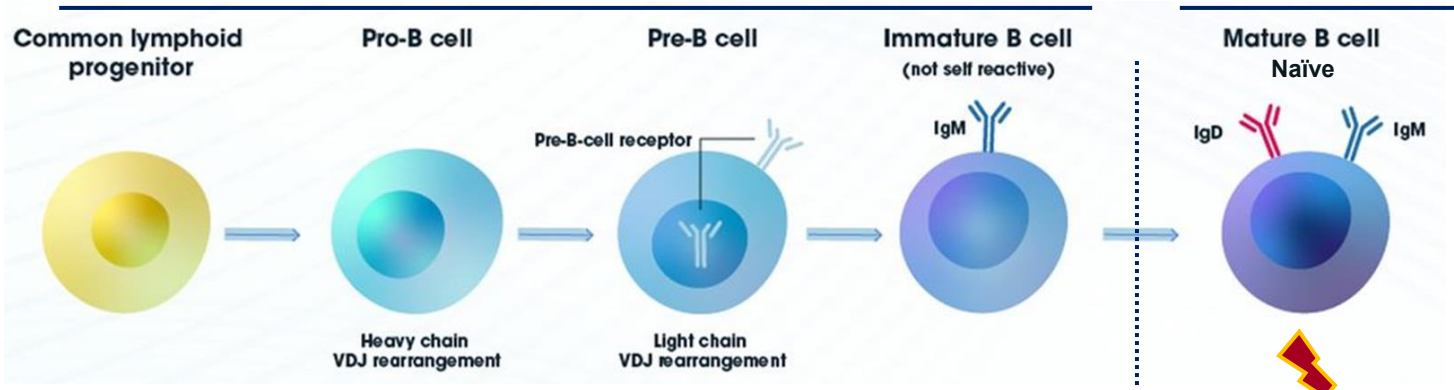
Williams MJ, et al. 2019.
Annu. Rev. Genom. Hum. Genet. 20:309–29

Examples of Cancer Evolution

Malignant transformation at different stages of B cell development

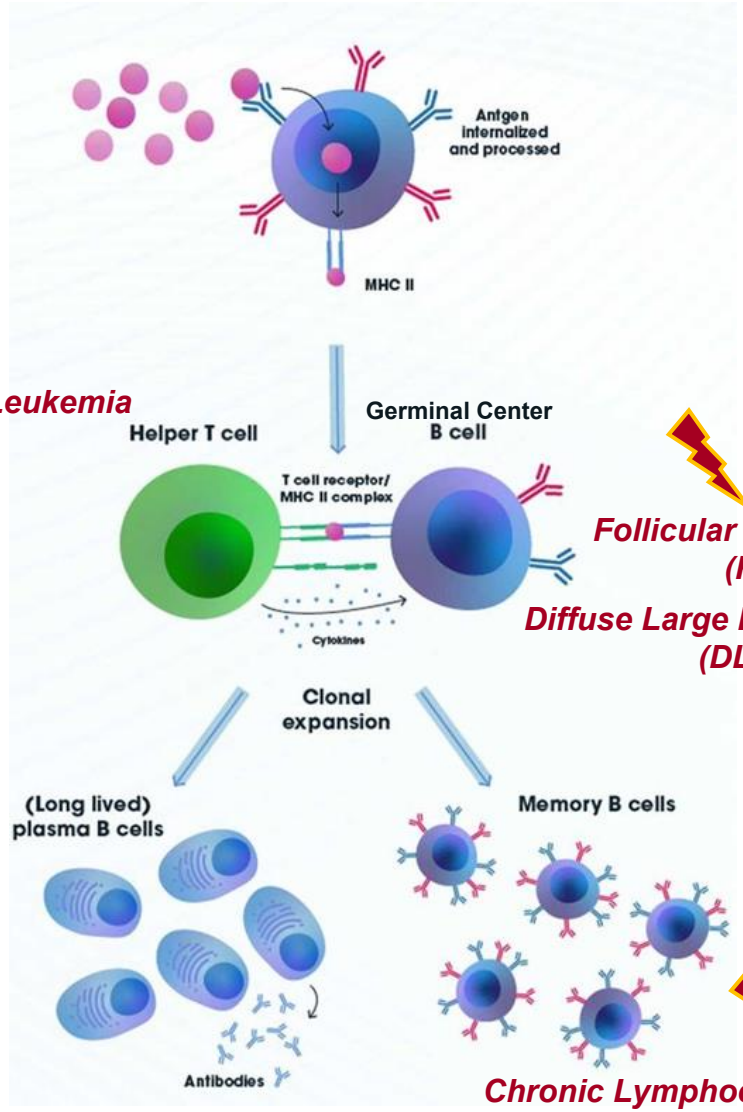
BONE MARROW

SECONDARY LYMPHOID ORGANS



Chronic Lymphocytic Leukemia (CLL)

Acute Lymphoblastic Leukemia (ALL)



Follicular Lymphoma (FL)

Diffuse Large B cell Lymphoma (DLBCL)

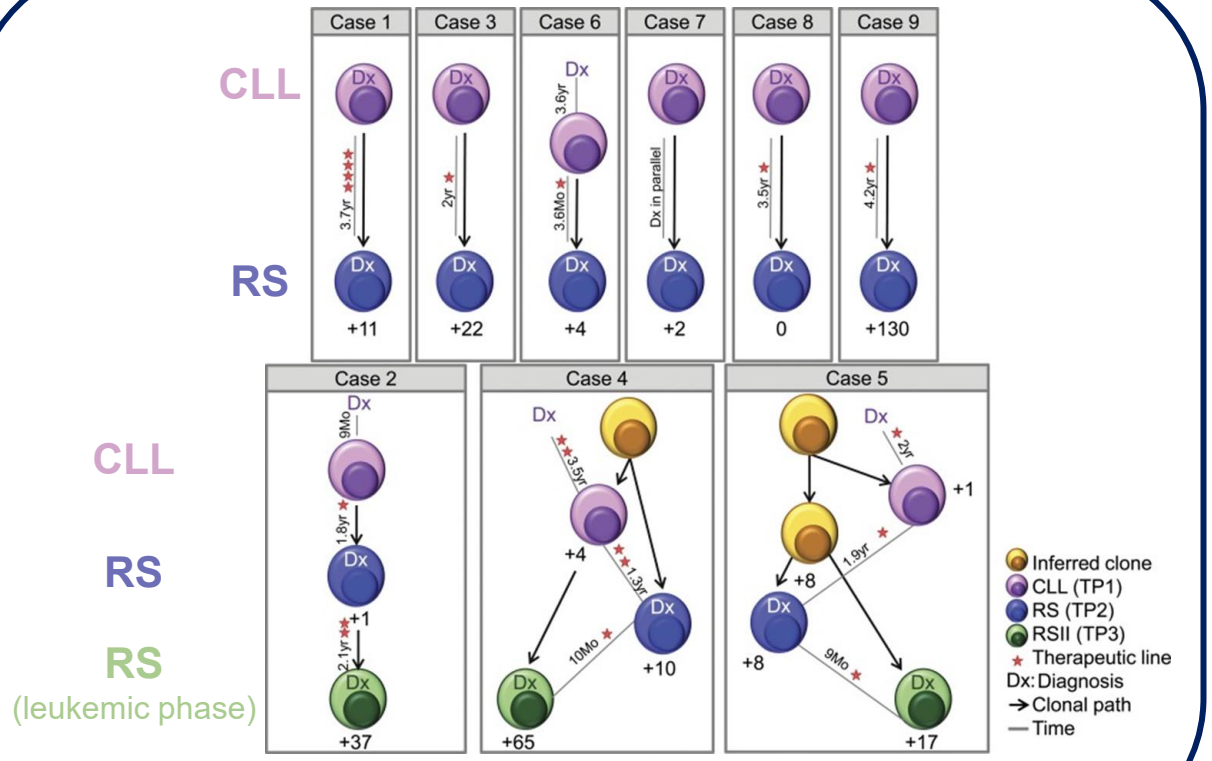
Chronic Lymphocytic Leukemia (CLL)

Adapted from: Harrison, Immunology and Microbiology, 2024

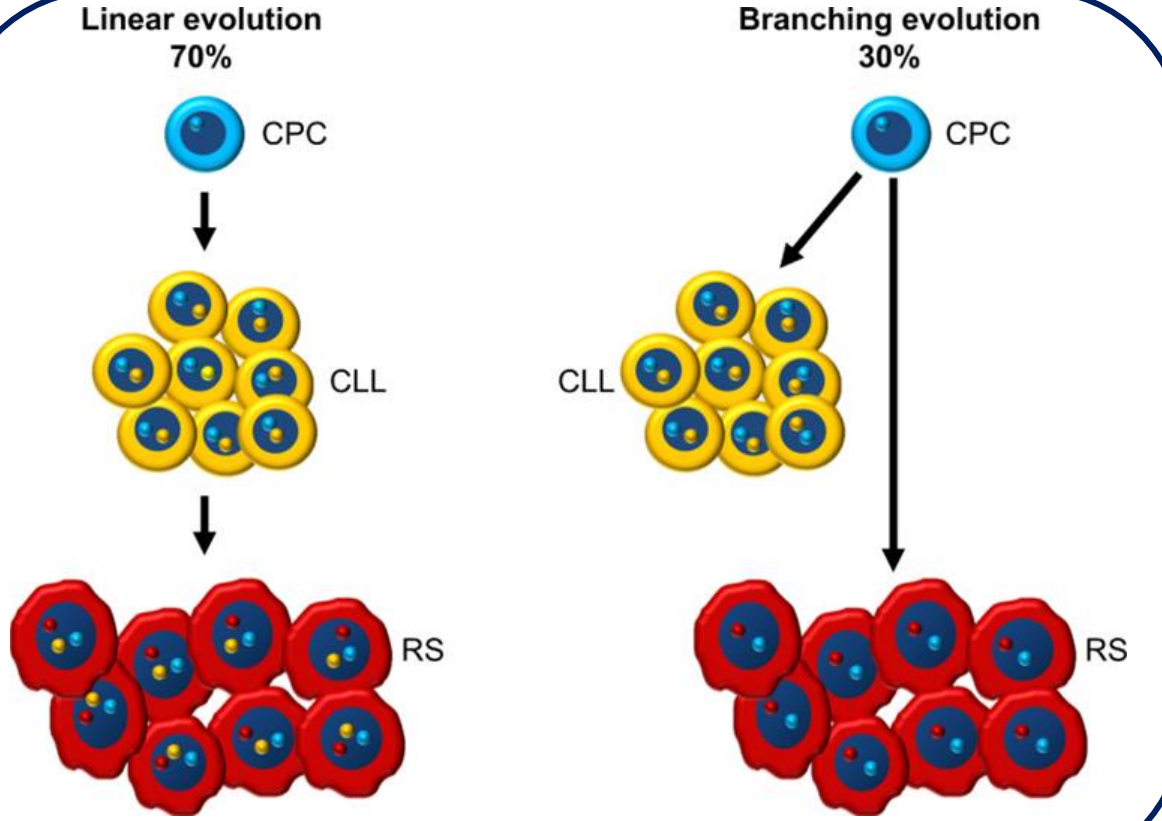
The CLL-RS transition occurs through a linear model in most cases

Chronic Lymphocytic Leukemia (CLL) ----------> *Richter's Syndrome (RS)* ----> *Richter's Syndrome (RS leukemic phase)*

DIAGNOSIS (Time-point 1) | **DIAGNOSIS** (Time-point 2) | **MONITORING** (Time-point 3)



Fabbri et al., JEM, 2013

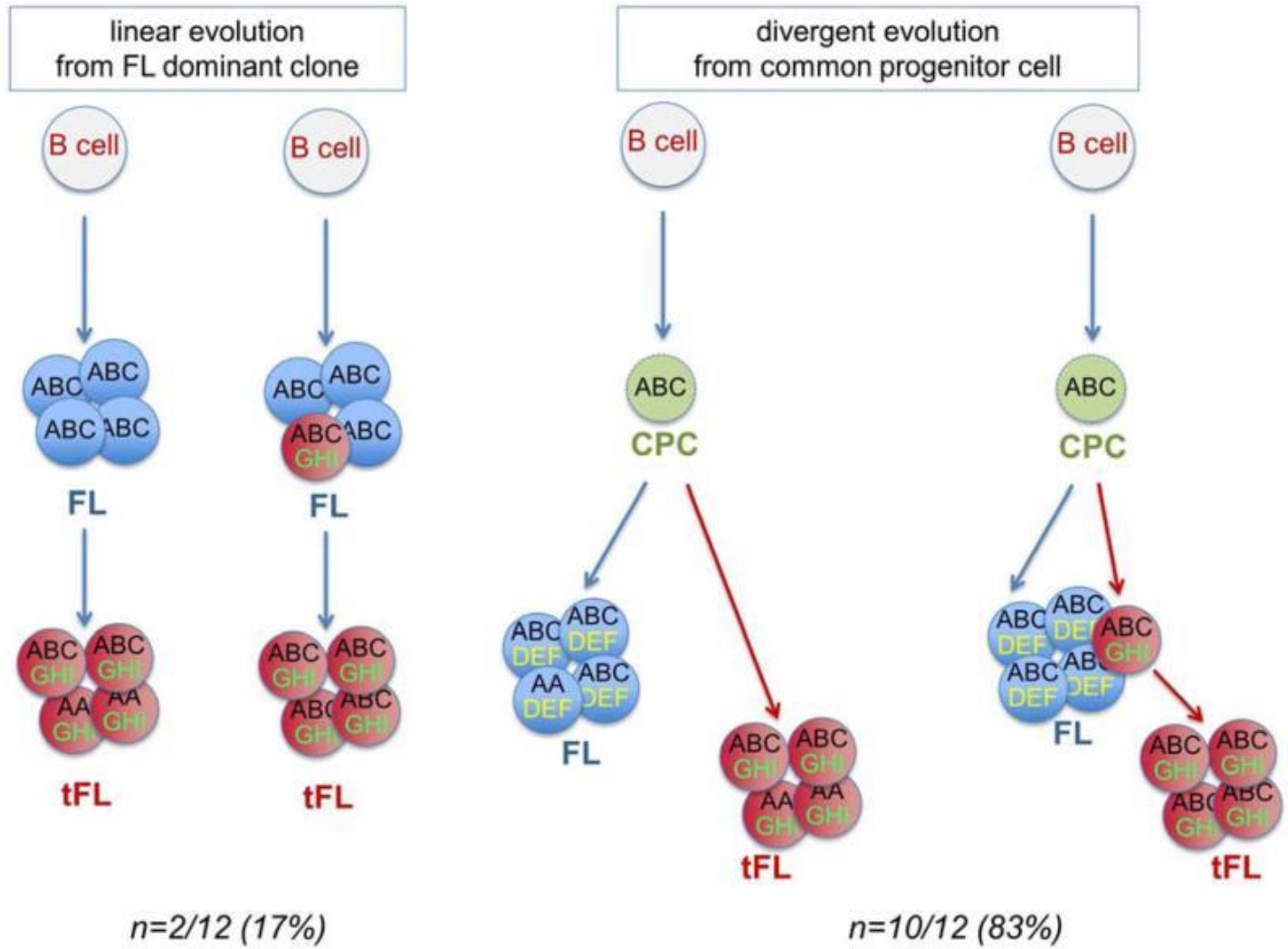


Rossi & Gaidano, Seminars in Oncology, 2016

FL transformation occurs through a branched model in most cases

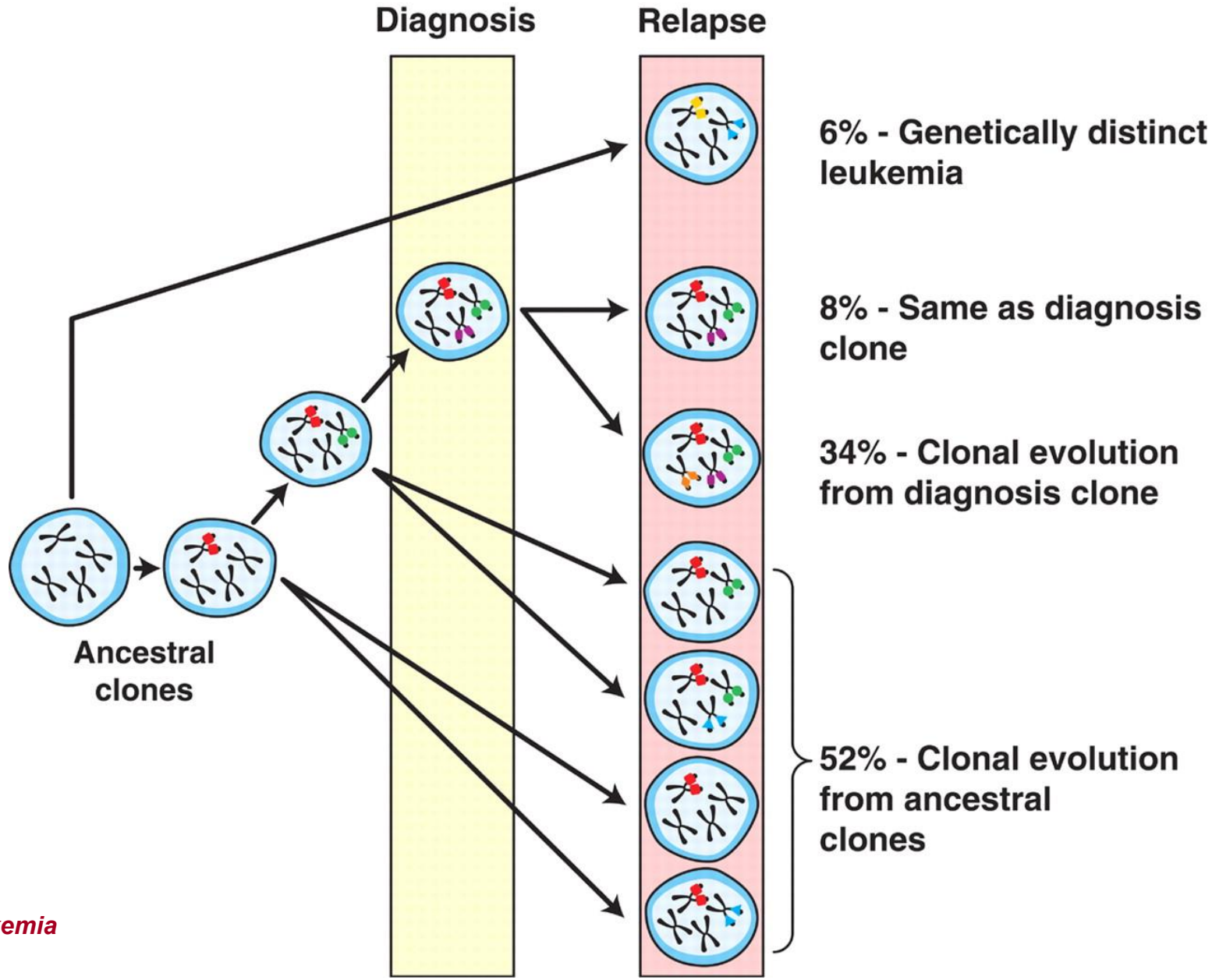
Follicular Lymphoma (FL)

Transformed Follicular Lymphoma (tFL)



Pasqualucci et al., Cell Rep 2014

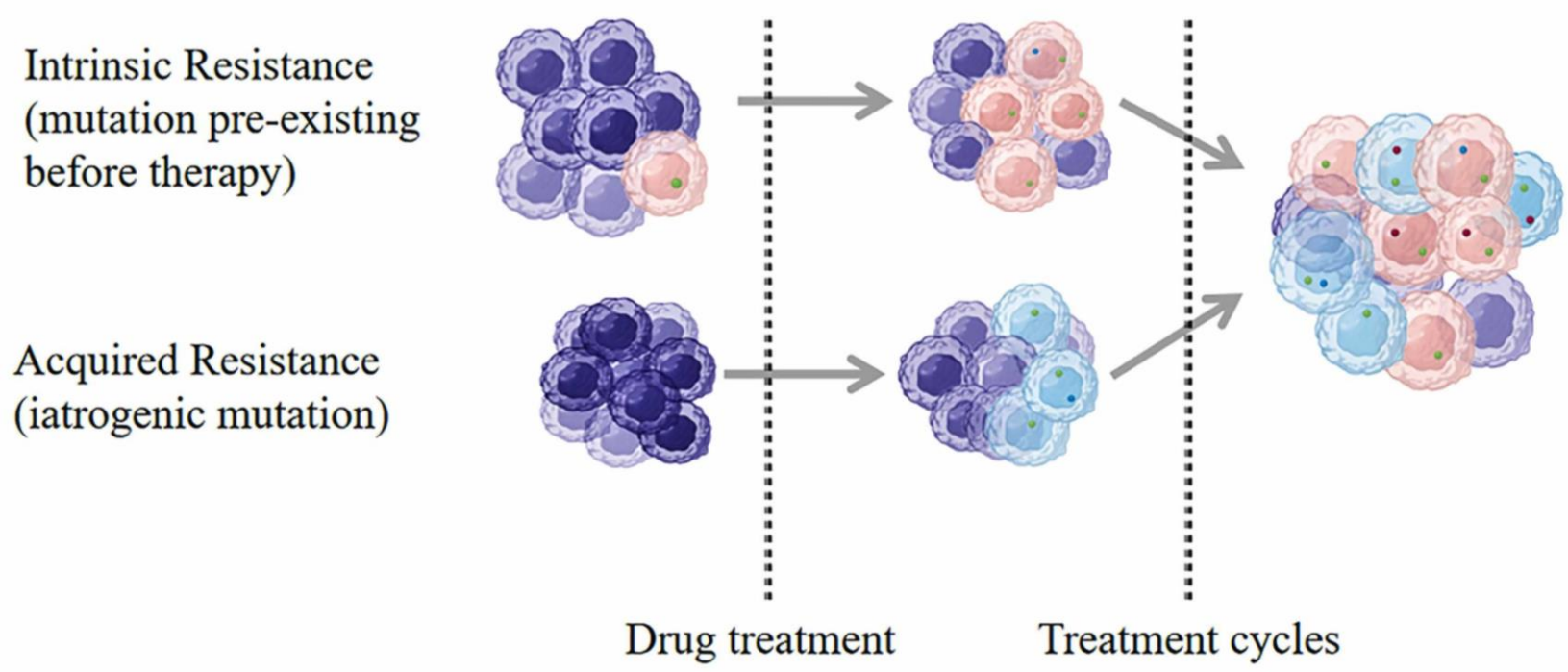
Clonal evolution and relapse in leukemia



Acute Lymphoblastic Leukemia (ALL)

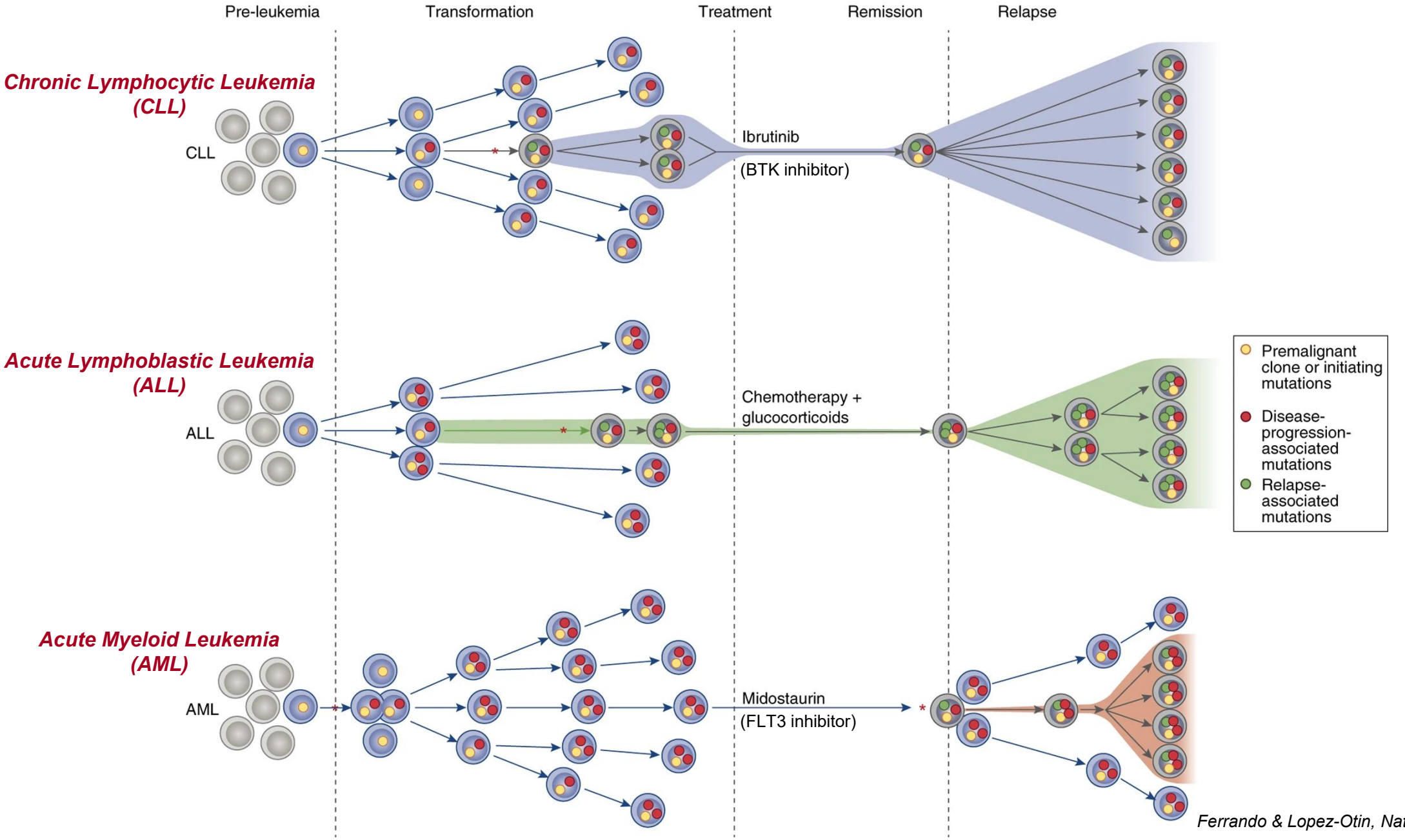
Mullighan et al., Science, 2008

Clonal diversification and development of therapy resistance



Anupriya S et al., Mutation Research Review, 2022

Clonal evolution and development of therapy resistance in leukemia



Ferrando & Lopez-Otin, Nature Medicine, 2017

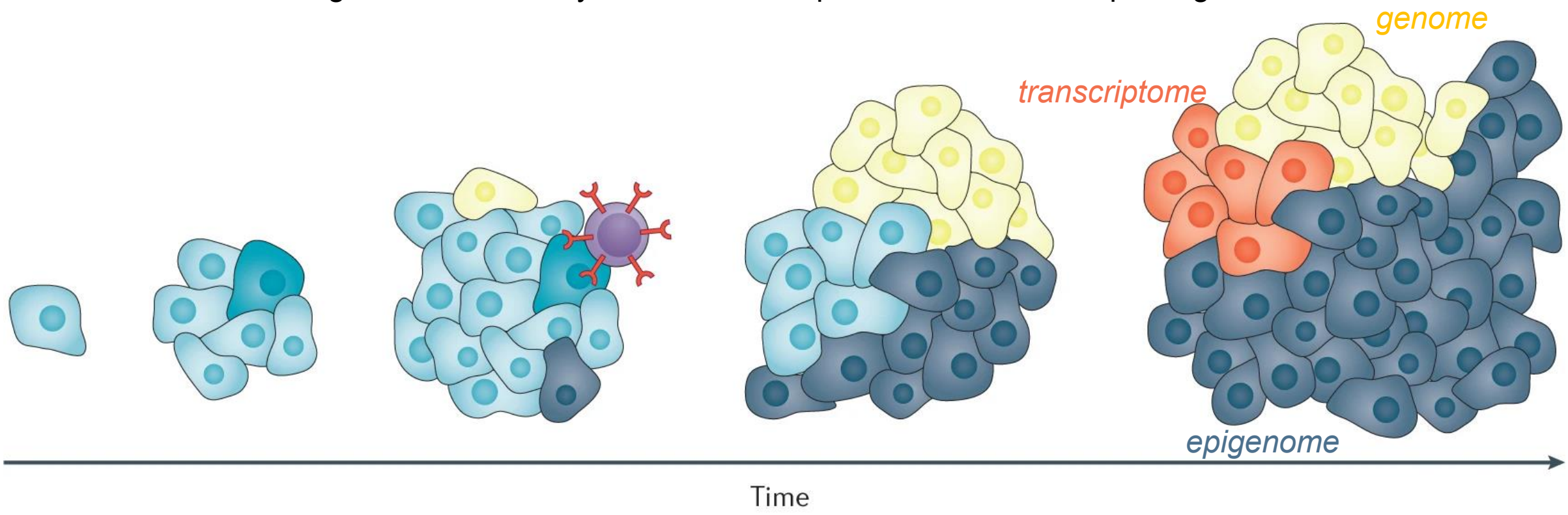
Inferring tumor evolution from genetic data -challenges-

?

Tumor evolution inference beyond the genomic approach

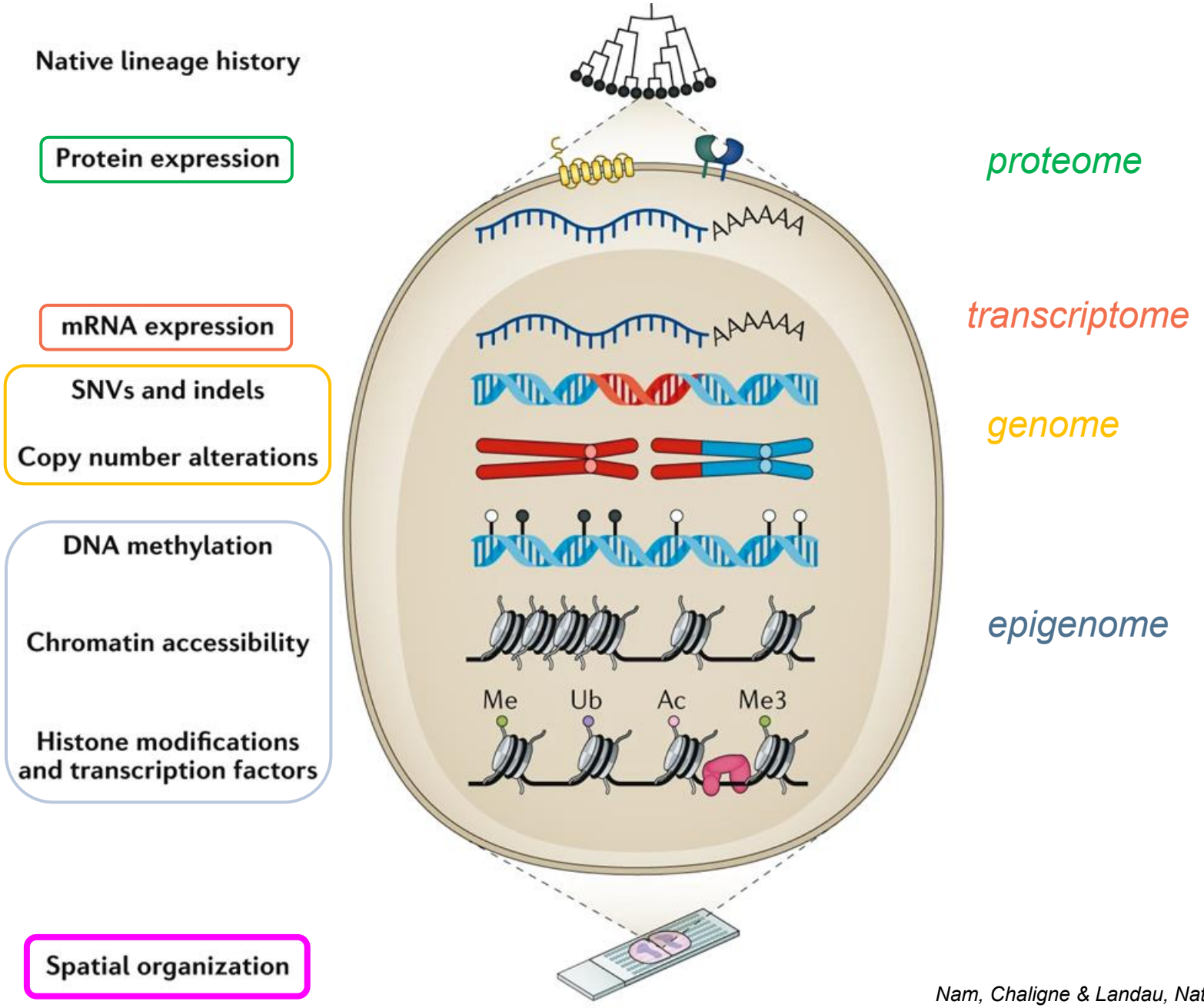
Genetic alterations are instrumental toward malignant transformation.

However, the genetic lens is only one face of the prism of forces underpinning tumor evolution.



Black & McGranahan, Nature Reviews Cancer, 2021

Toward tumor evolution inference using single-cell omics data



Nam, Chaligne & Landau, Nature Reviews Genetics, 2020

Cancer Evolution and Multistep Tumorigenesis

-CONCLUSIONS-

- Tumorigenesis: a multi-step process relying on the acquisition of alterations (genetic and epigenetic) which affect multiple distinct regulatory circuits within cells and systems and function in a complementary fashion to create the neoplastic phenotype.

- The neoplastic phenotype can be achieved trough multiple means and distinct alterations, however several hallmarks are shared across tumors, including: 1) ability to proliferate indefinitely; 2) reduced susceptibility to cell death; 3) acquisition of invasiveness and metastatic ability; 4) promoting angiogenesis; 5) ability to evade the immune system.

- Multi-step tumor progression can be depicted as a form of Darwinian evolution occurring within tissues. However, the contribution of epigenetic mechanisms and the rapid acquisition of genetic changes require to modify the linear Darwinian evolution model to incorporate complex branched evolution.

Suggested Readings

Clonal evolution in cancer.
Greaves M, **Maley CC.** Nature. 2012 Jan 18;481(7381):306-13. doi: 10.1038/nature10762.PMID: 22258609

Genetic and non-genetic clonal diversity in cancer evolution.
Black JRM, **McGranahan N.** Nat Rev Cancer. 2021 Jun;21(6):379-392. doi: 10.1038/s41568-021-00336-2. Epub 2021 Mar 16.PMID: 33727690