

BIMM 143

Cancer Genomics & Immunoinformatics

Lecture 18

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UC San Diego

<http://thegrantlab.org/bimm143>

Today's Menu

Cancer Genomics

Brief review of cancer fundamentals,
What is cancer and what causes it?

Mining Cancer Genomic Data

Hands-on analysis to identify genomic changes in different cancers and identify new targets for therapy

Cancer Immunotherapy

Hands-on analysis to design personalized cancer vaccines and harness the patient's own immune system to fight cancer

What is Cancer?

“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

Source: <https://www.cancer.gov>

NIH-NCI

Cancer is a disease of the Genome

- Caused by changes to genes that control the way our cells function, especially how they **grow and divide**.
- A major challenge in treating cancer is that every tumor is different: Each person's cancer has a unique combination of genetic changes (both “driver” & “passenger”).
- As the cancer continues to grow, additional changes will occur.



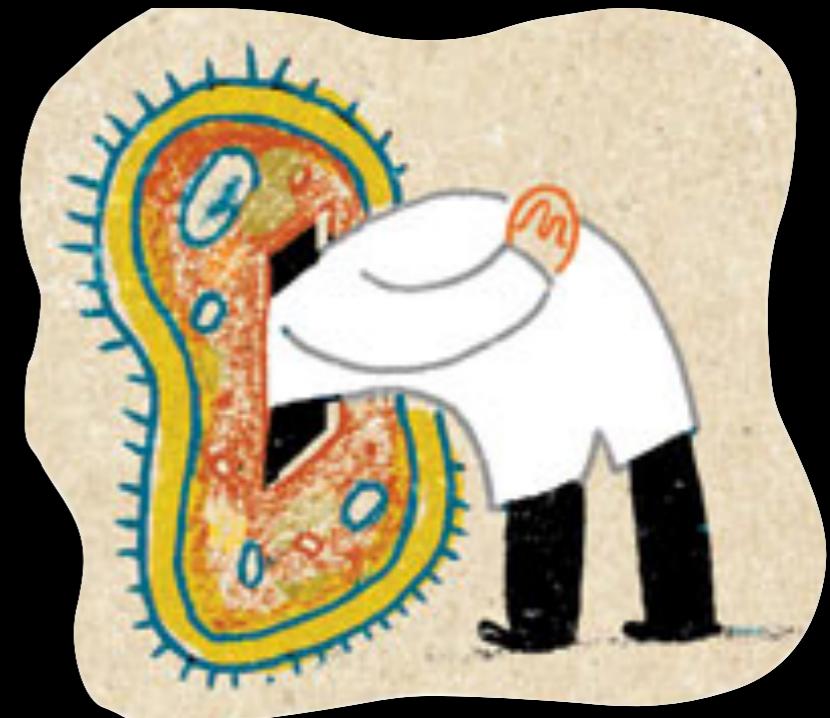
Healthy 46 chromosomes



Example cancer 59 chromosomes

Goals of Cancer Genome Research

- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



Finding Cancer Drivers



Motivation for adopting a genomics approach...

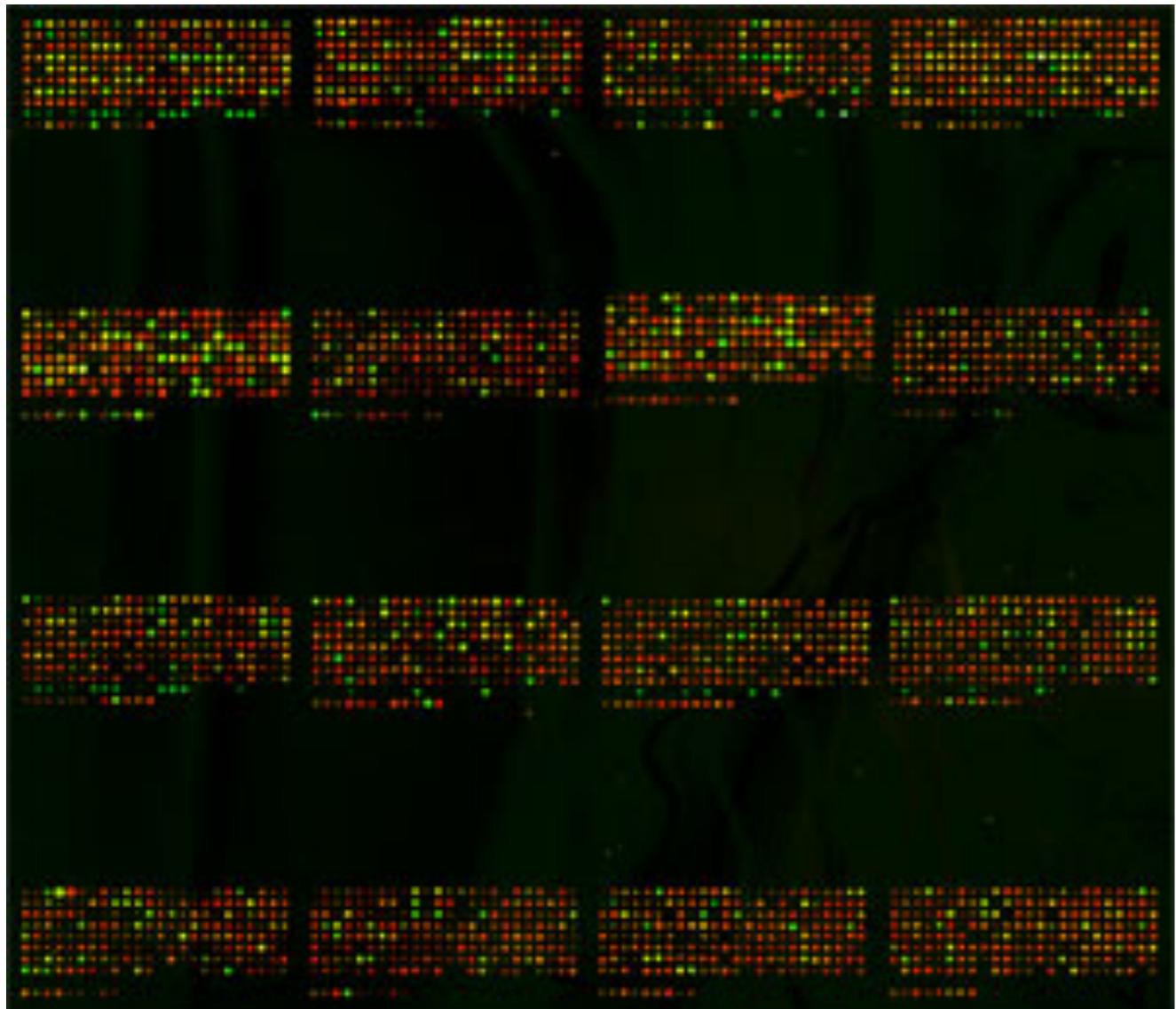
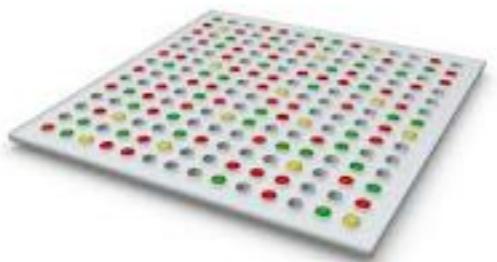
- Cancer is caused by mutations to specific genes
- Knowing which genes and proteins enables the development of **targeted treatments**
- 1st major Goal:
Define ALL cancer genes!

A G C T → A G A T



Use A Cancer Genomics Approach

Arrays

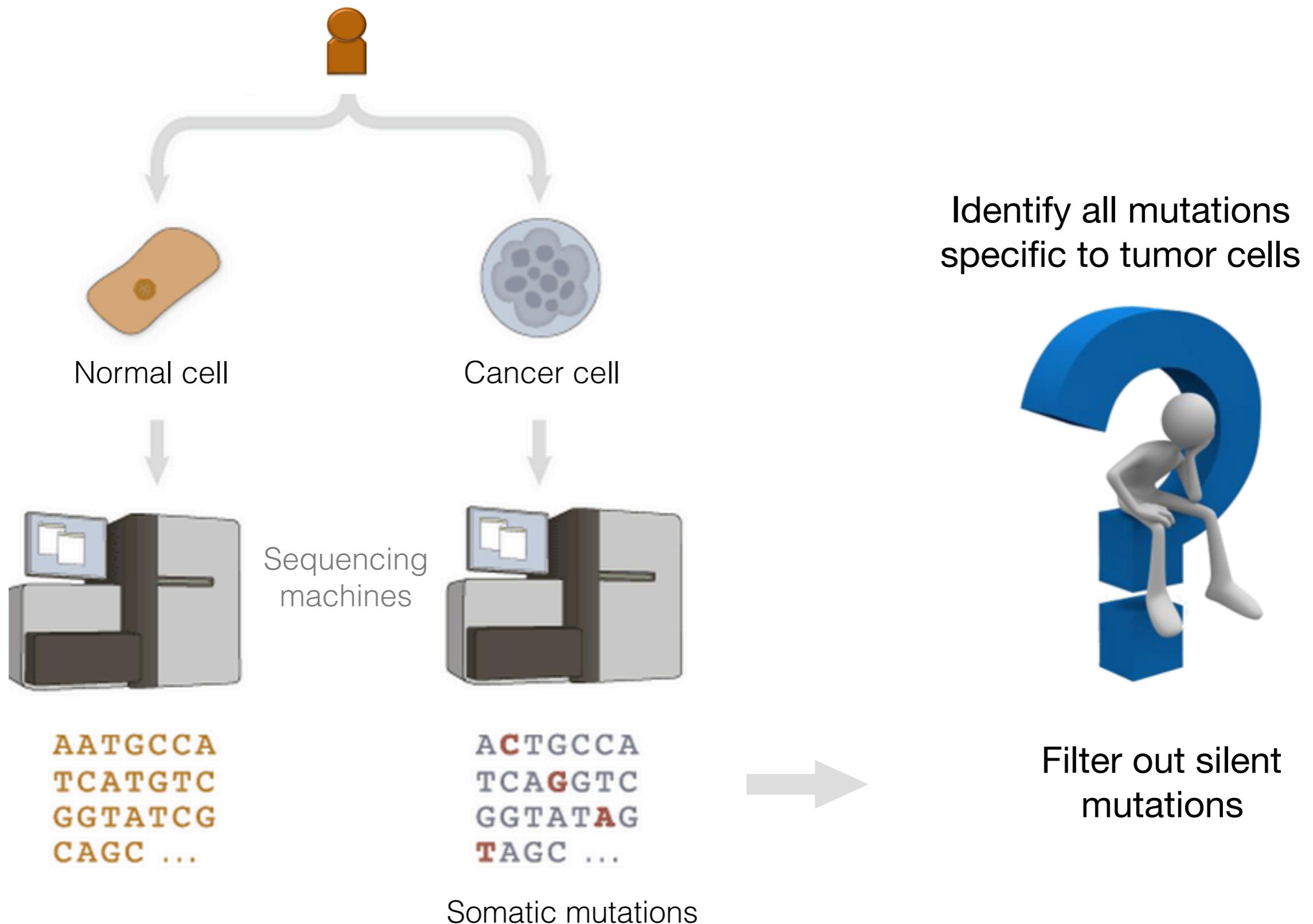


Parallel Sequencing

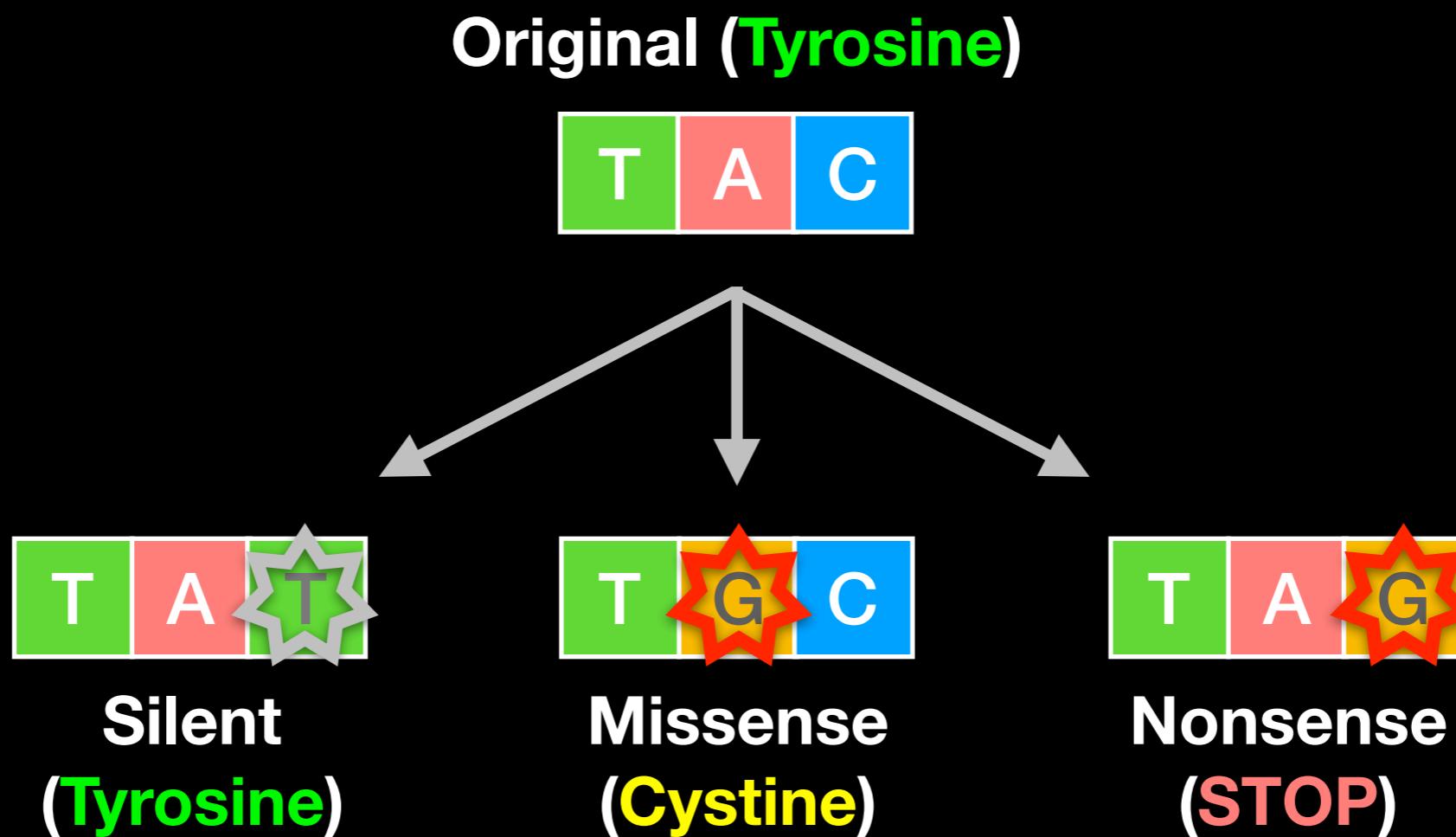


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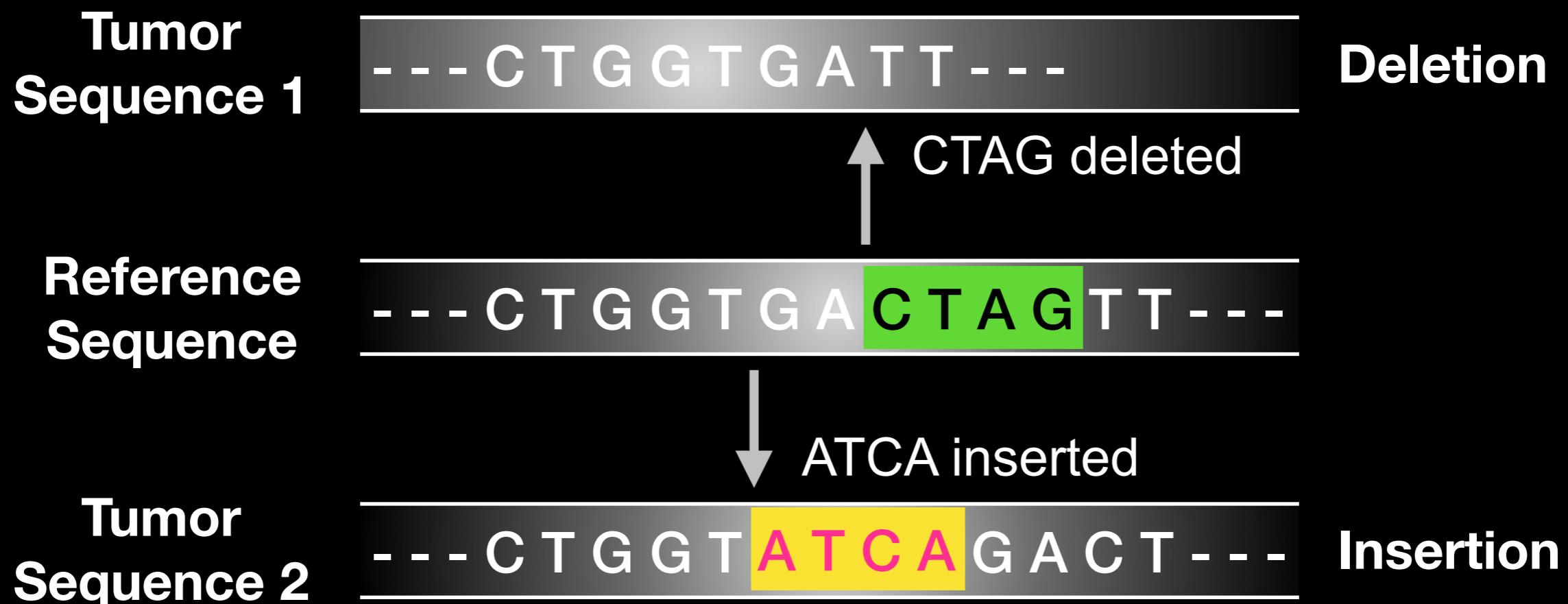
Finding Cancer Associated Mutations



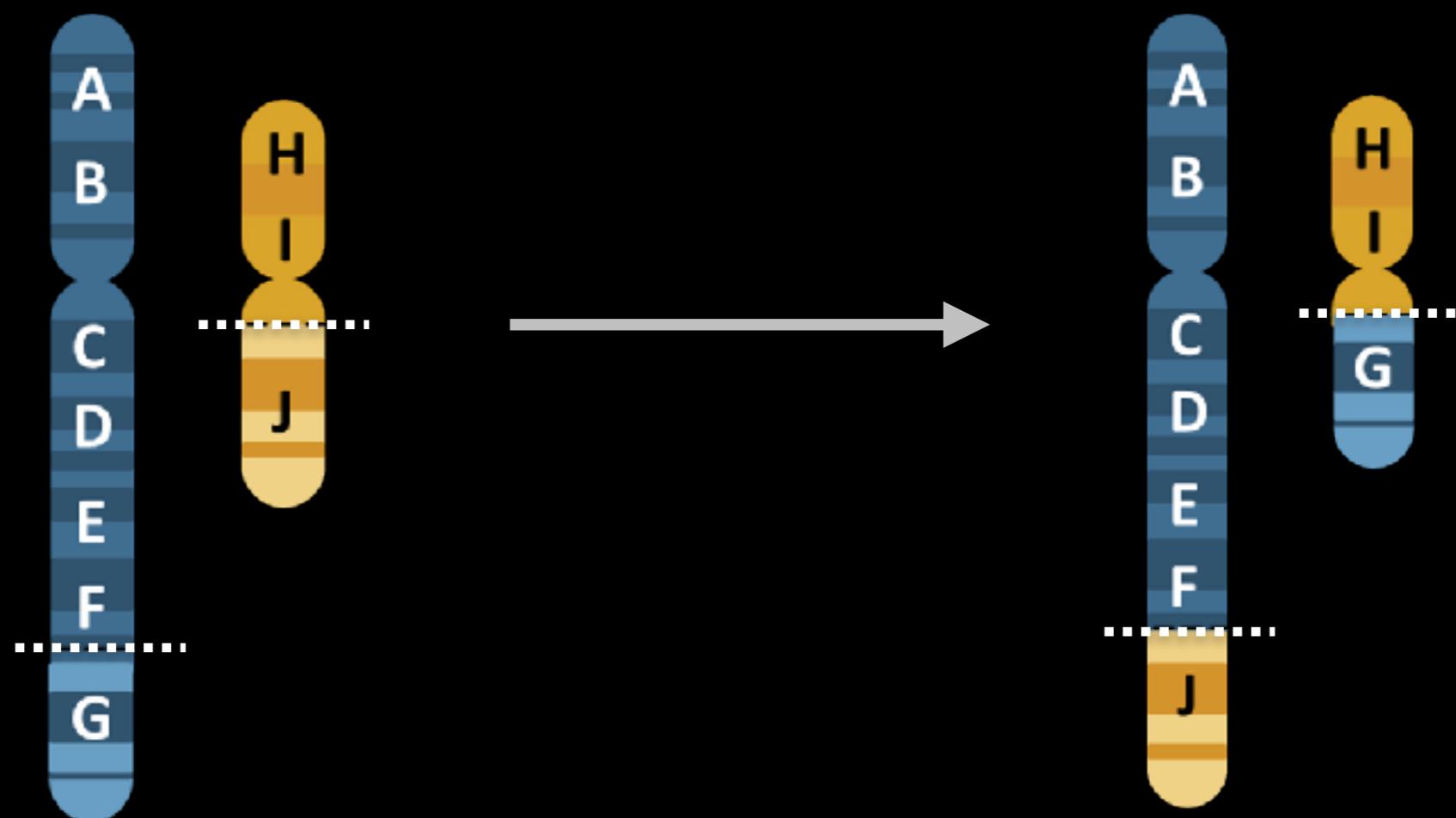
Mutations detected: Point mutations



Mutations detected: Indels



Mutations detected: Translocations



What can go wrong in cancer genomes?

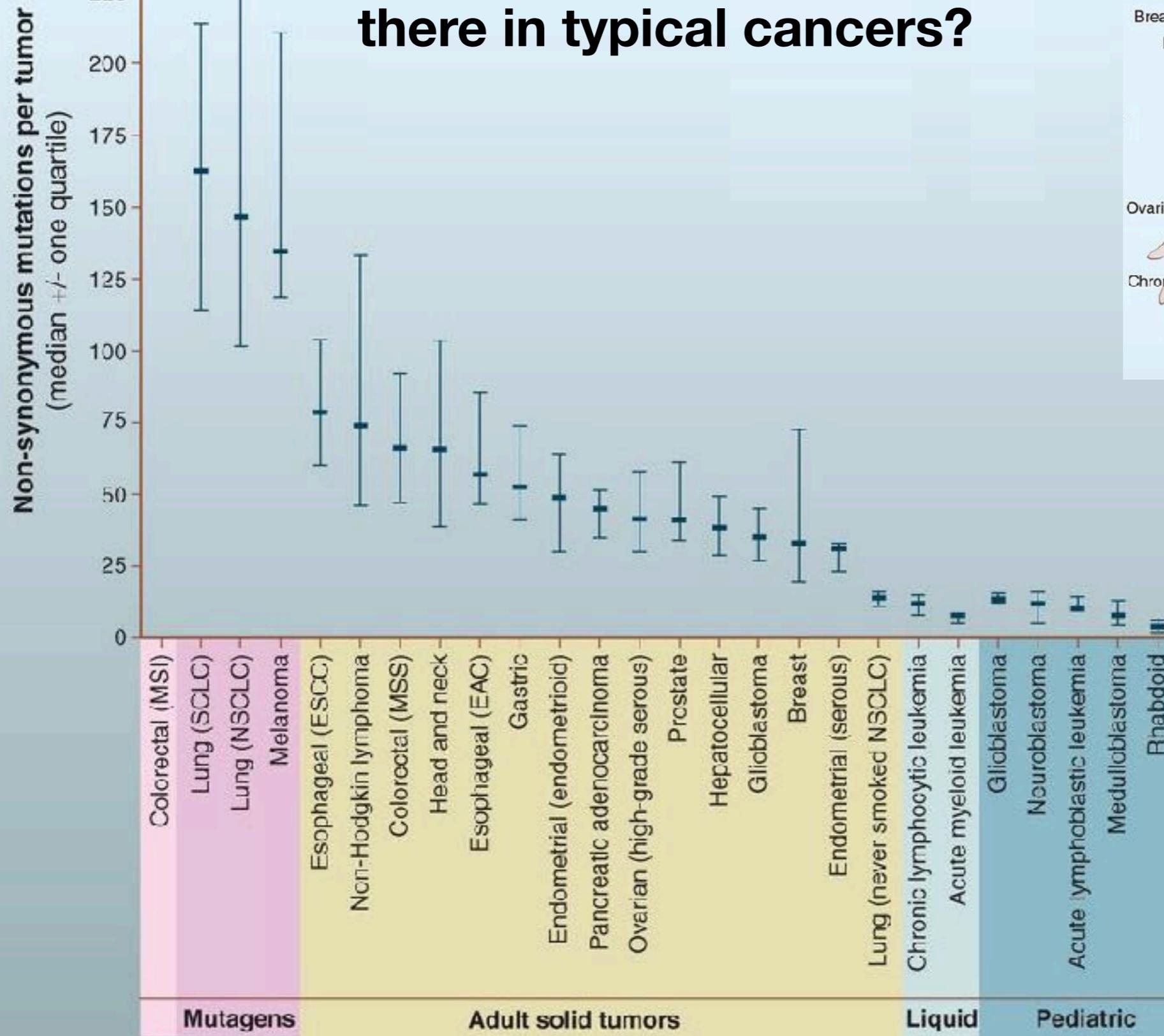
| Type of change | Some common technology to study changes |
|-----------------------------|---|
| DNA mutations | WGS, WXS |
| DNA structural variations | WGS |
| Copy number variation (CNV) | CGH array, SNP array, WGS |
| DNA methylation | Methylation array, RRBS, WGBS |
| mRNA expression changes | mRNA expression array, RNA-seq |
| miRNA expression changes | miRNA expression array, miRNA-seq |
| <i>Protein expression</i> | Protein arrays, mass spectrometry |

WGS = whole genome sequencing, WXS = whole exome sequencing

RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

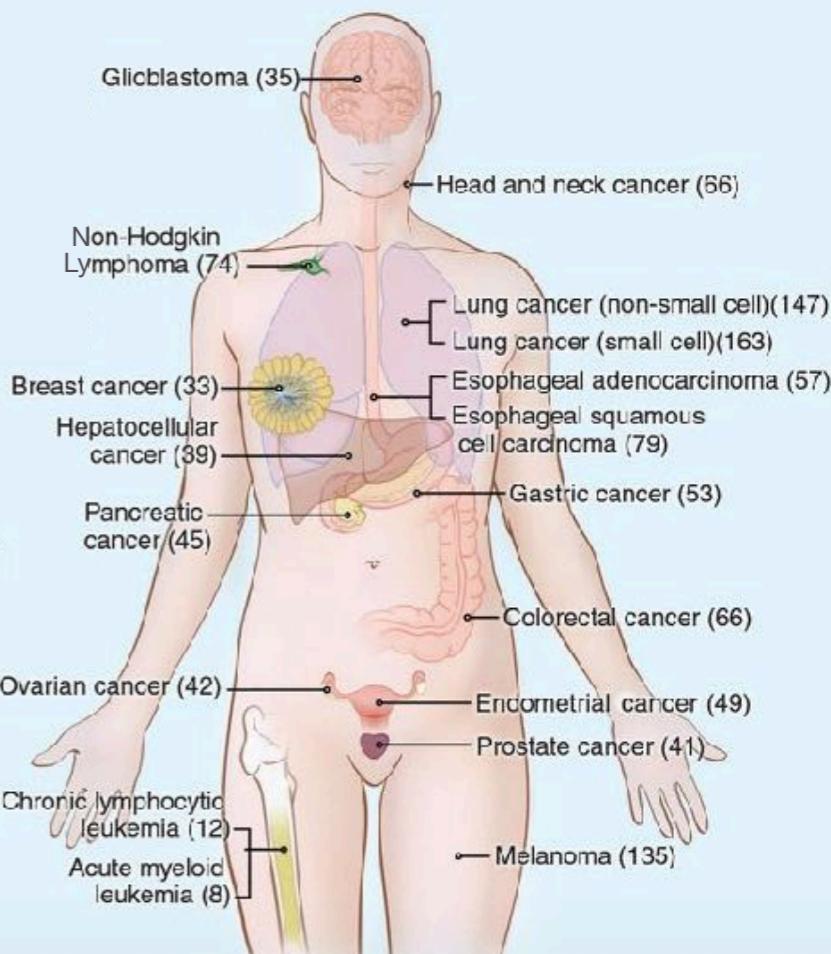
B

1500
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225
200
175
150
125
100
75
50
25
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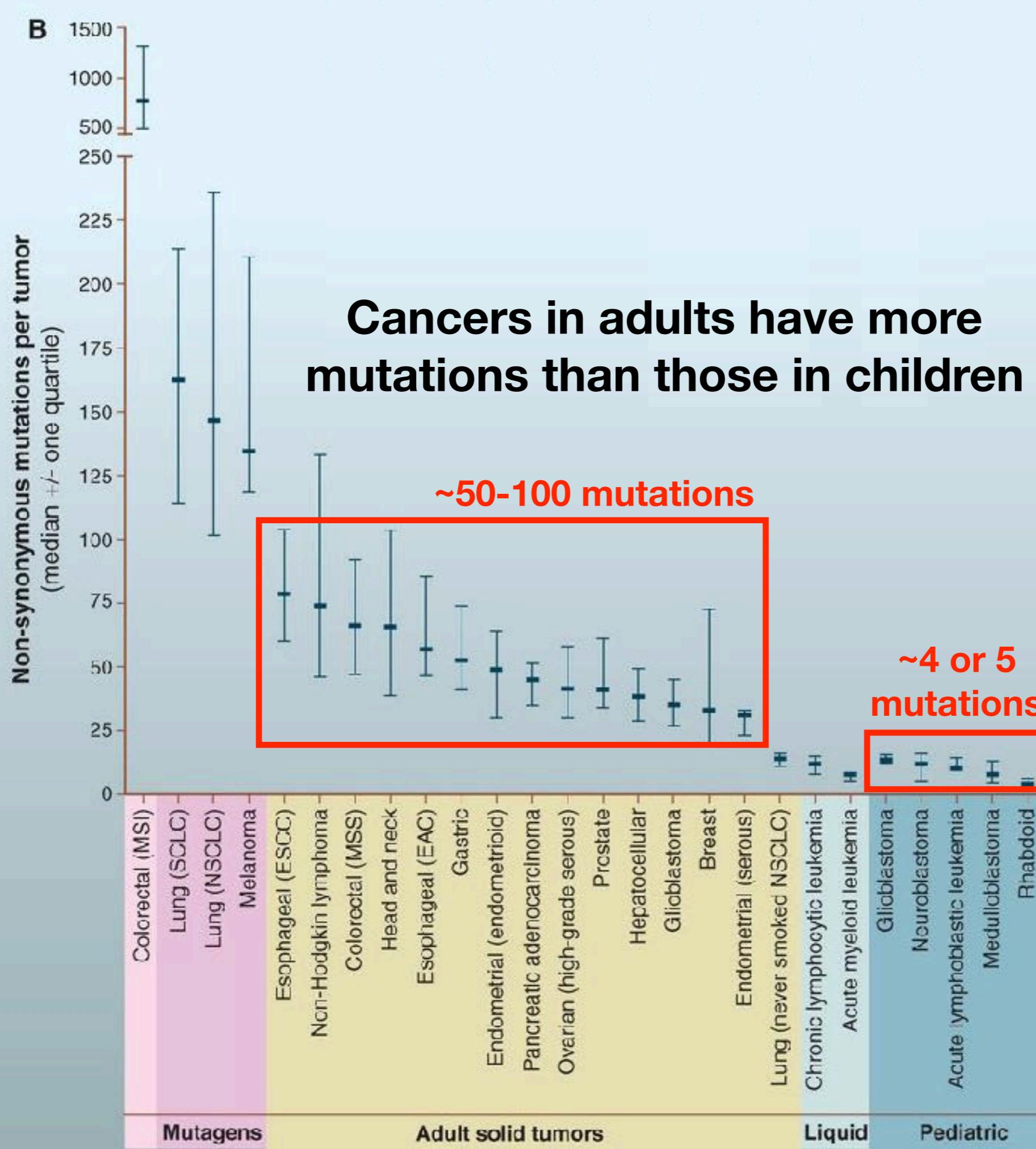
Genomics allows us to
answer the question:

How many mutations are
there in typical cancers?

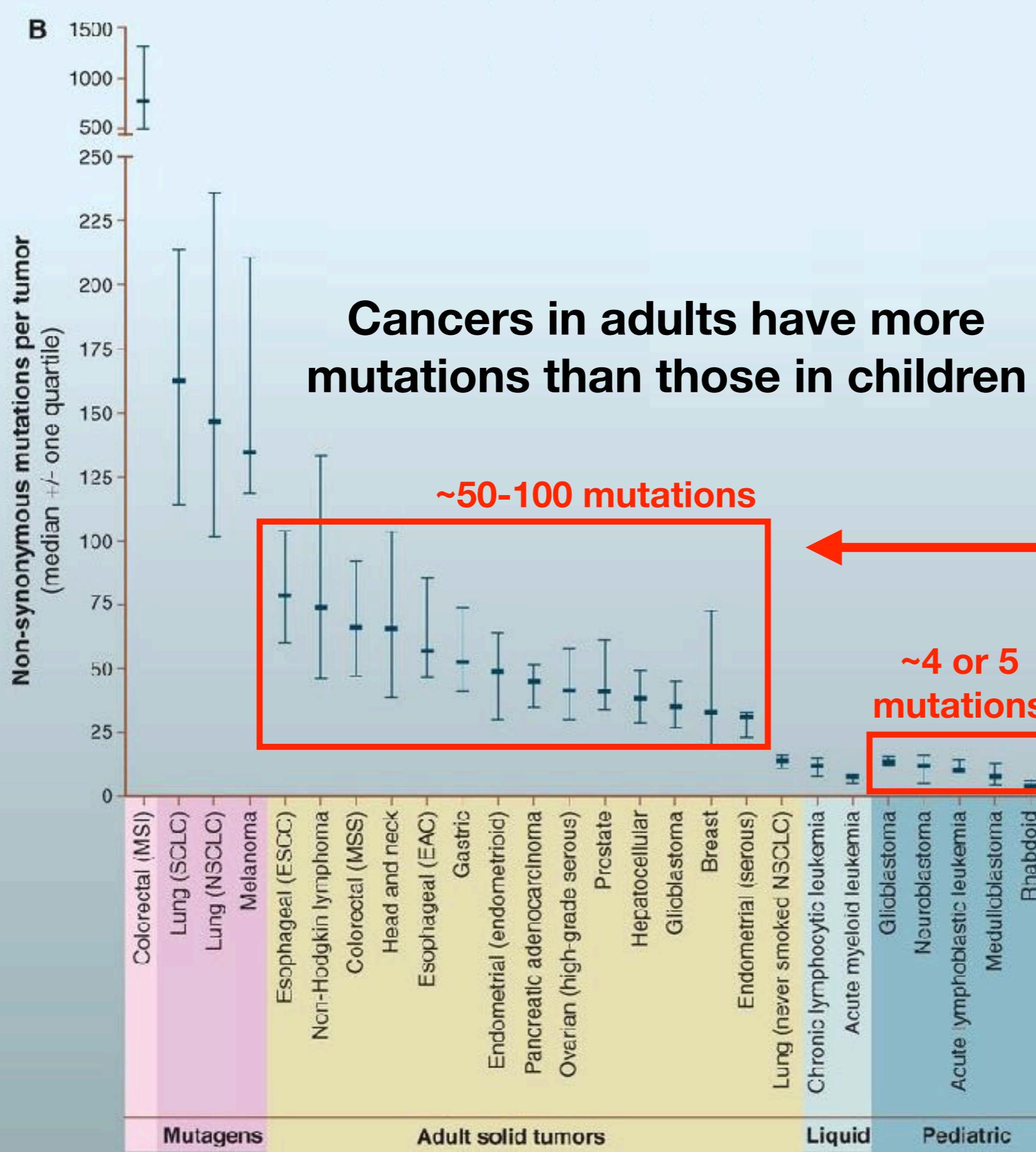


Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al.
Science (2013)

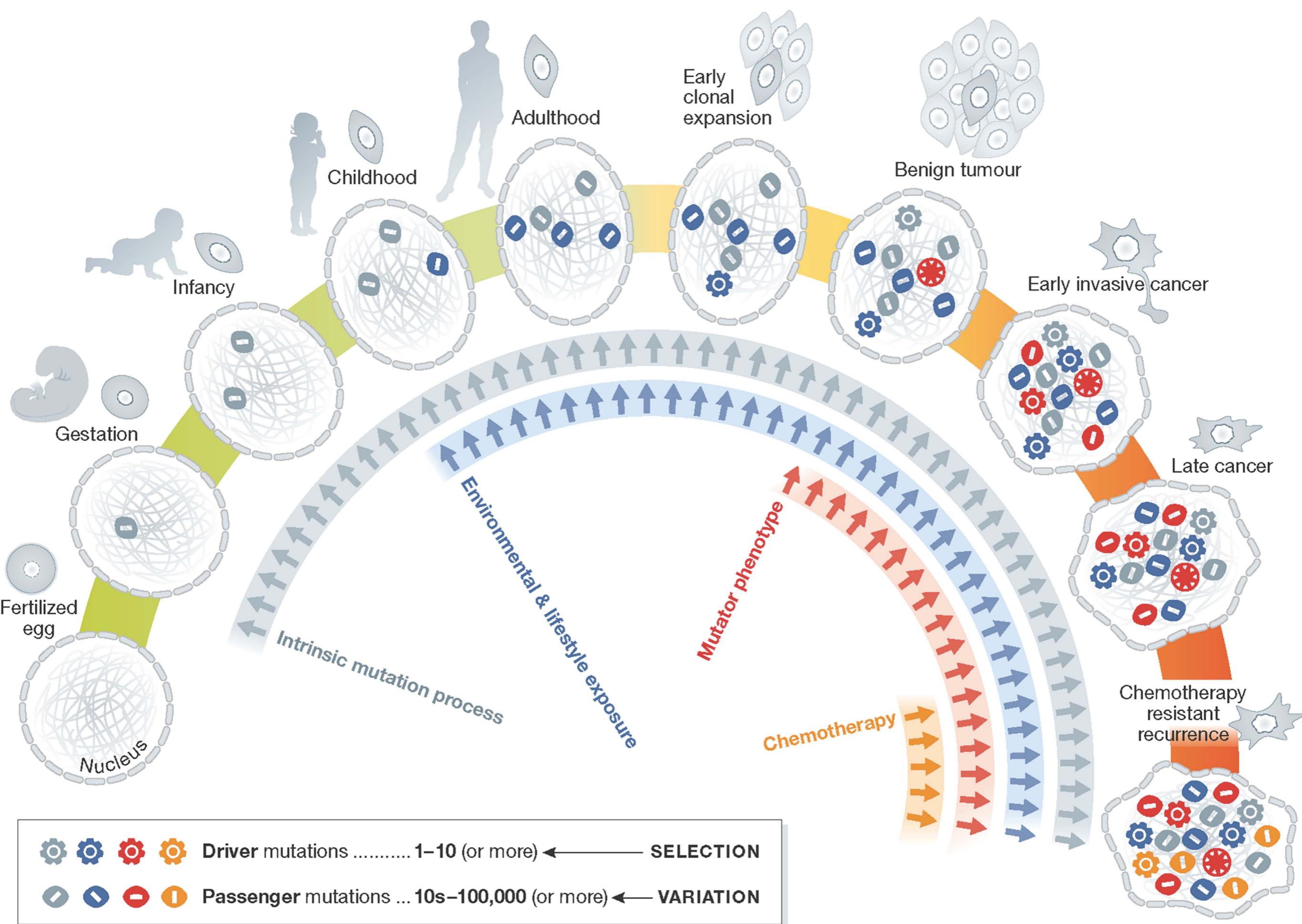


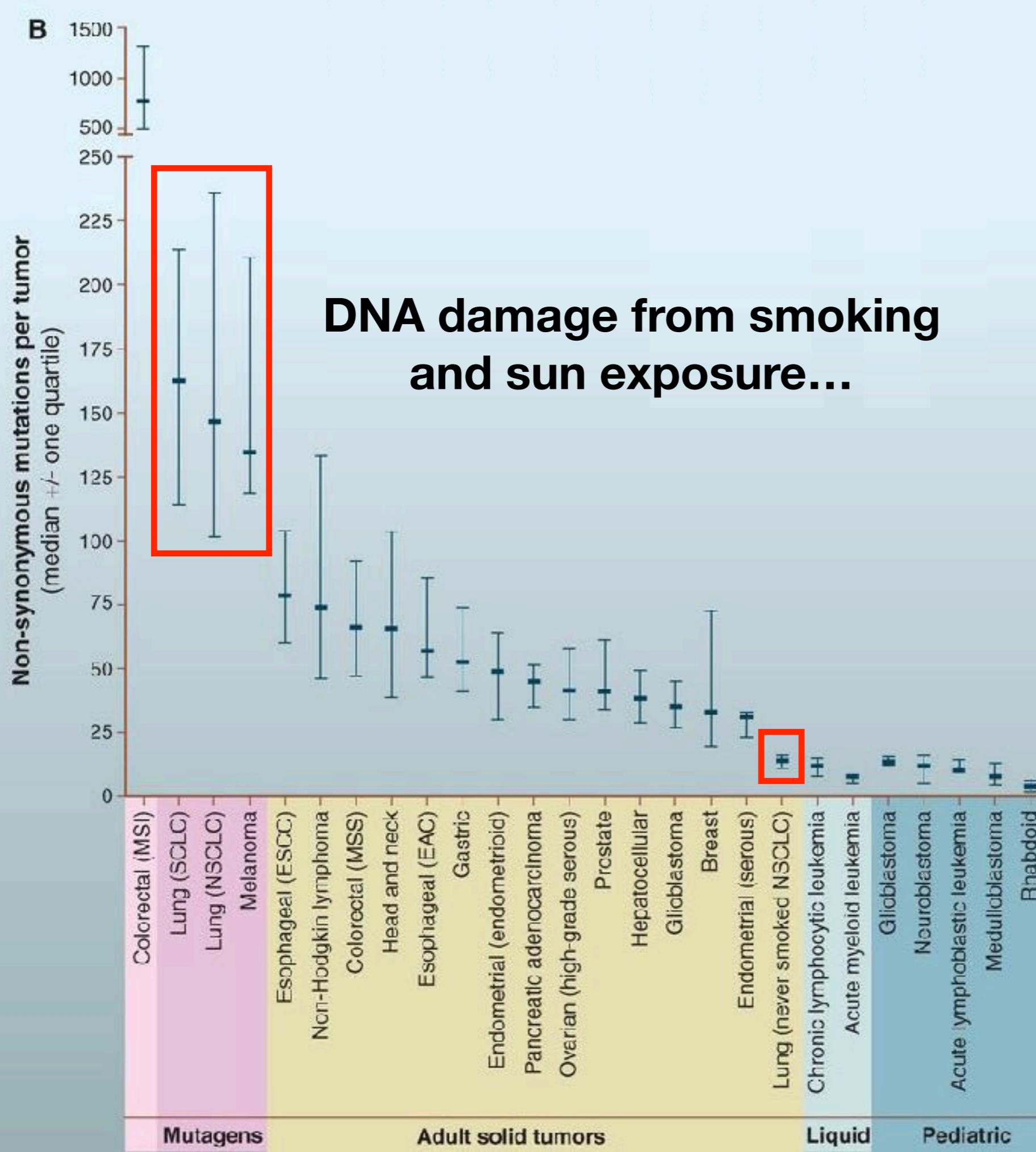
Vogelstein et al.
Science (2013)



Vogelstein et al.
Science (2013)

Most of these mutations are likely “passenger” mutations

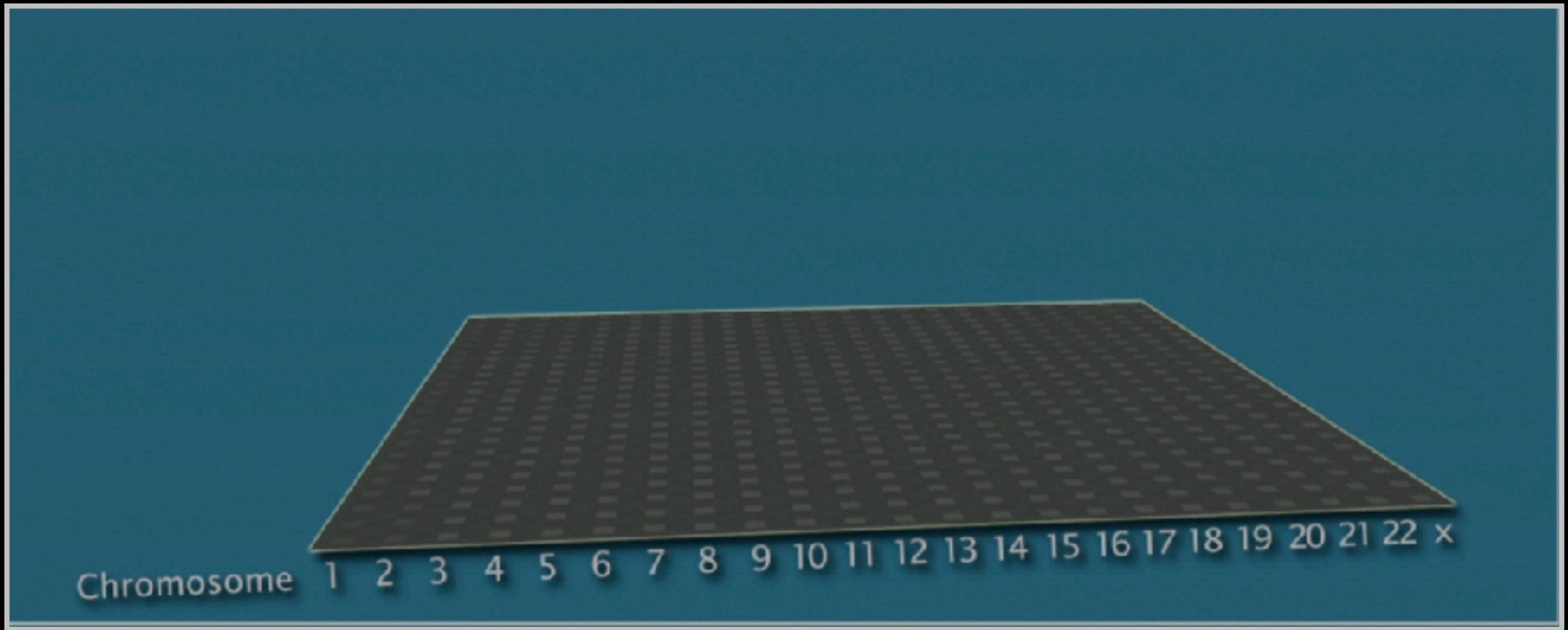




DNA damage from smoking and sun exposure...

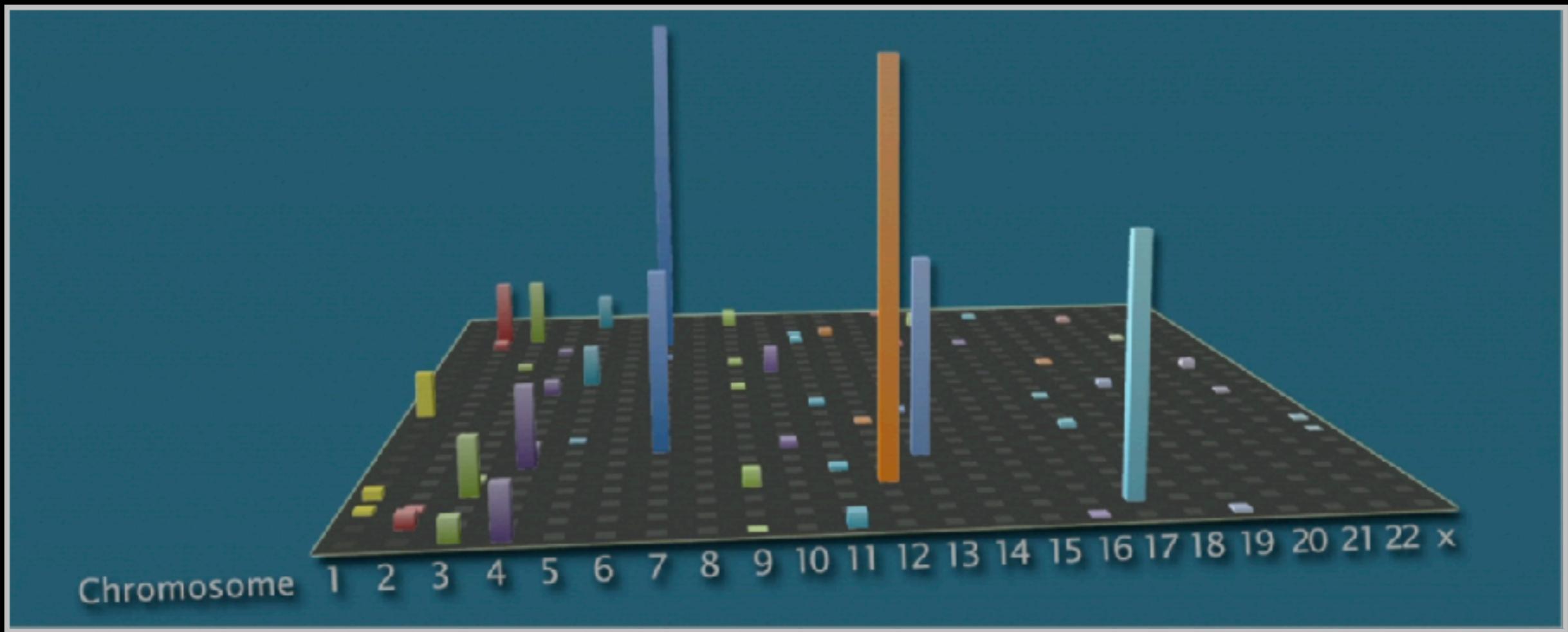
Vogelstein et al.
Science (2013)

Genomic approaches can identify the genes most commonly mutated in cancer



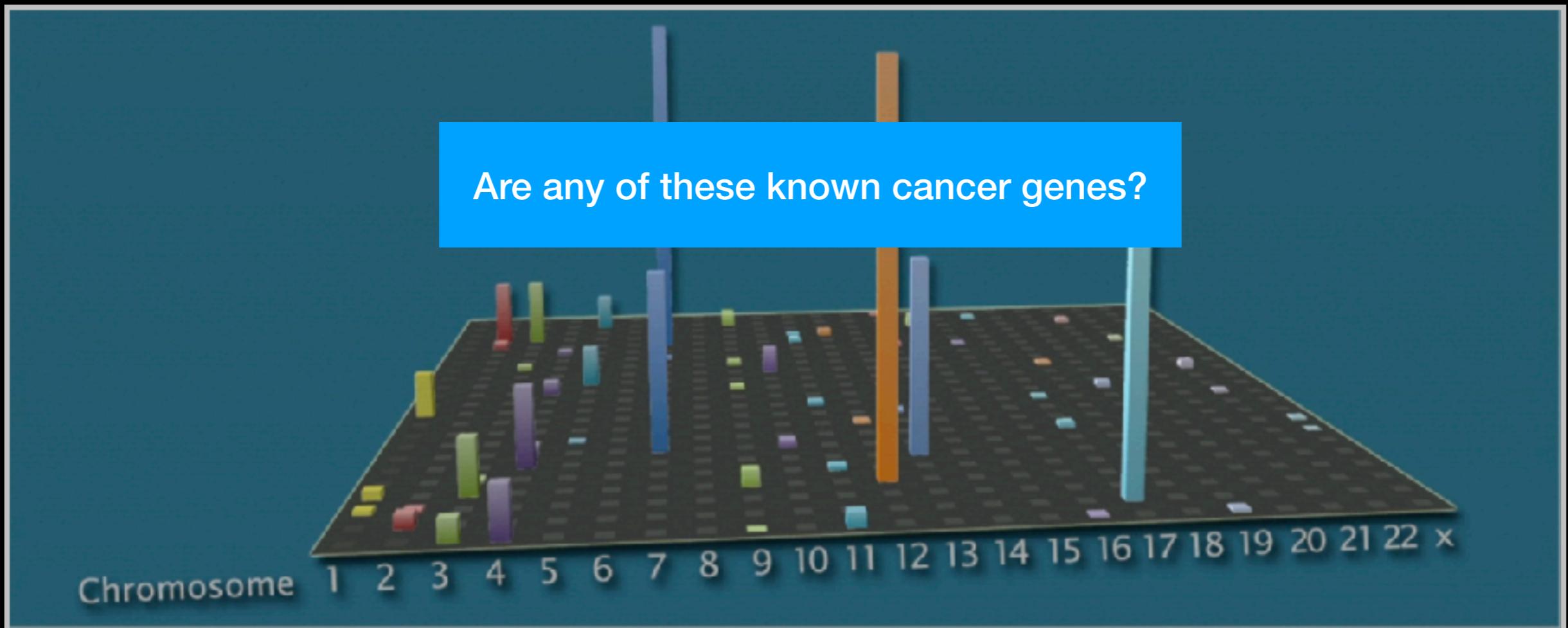
Arrange all genes in a matrix, ordered by chromosomes

Identifying genes most commonly mutated in cancer



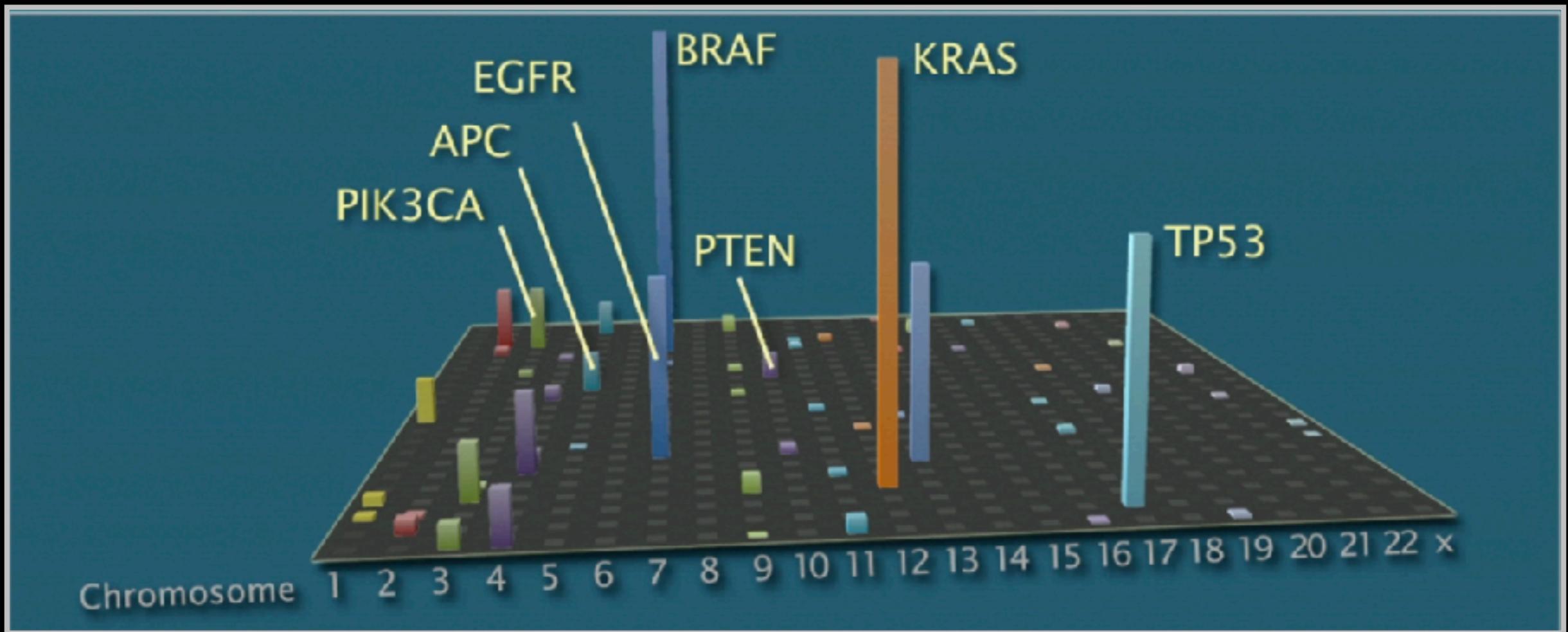
Add all data together to see which genes are most often mutated

Identifying genes most commonly mutated in cancer



Add all data together to see which genes are most often mutated

Identifying genes most commonly mutated in cancer



Many are famous proto-oncogenes, many others are new cancer genes!

Three Main Types of Cancer Genes:

- **Oncogenes**, such as **Ras**, normally function to accelerate cell division and growth. They can be mutated to act like stuck gas pedals.
- **Tumor suppressor genes**, such as **p53** normal act like breaks. Mutations can cause these breaks to fail.
- **DNA repair genes**, such as **BRCA1 & 2**, normally function to fix minor damage to DNA when it replicates. When these genes are mutated, DNA damage can accumulate and lead to cancer.

Functions of the 140 cancer genes

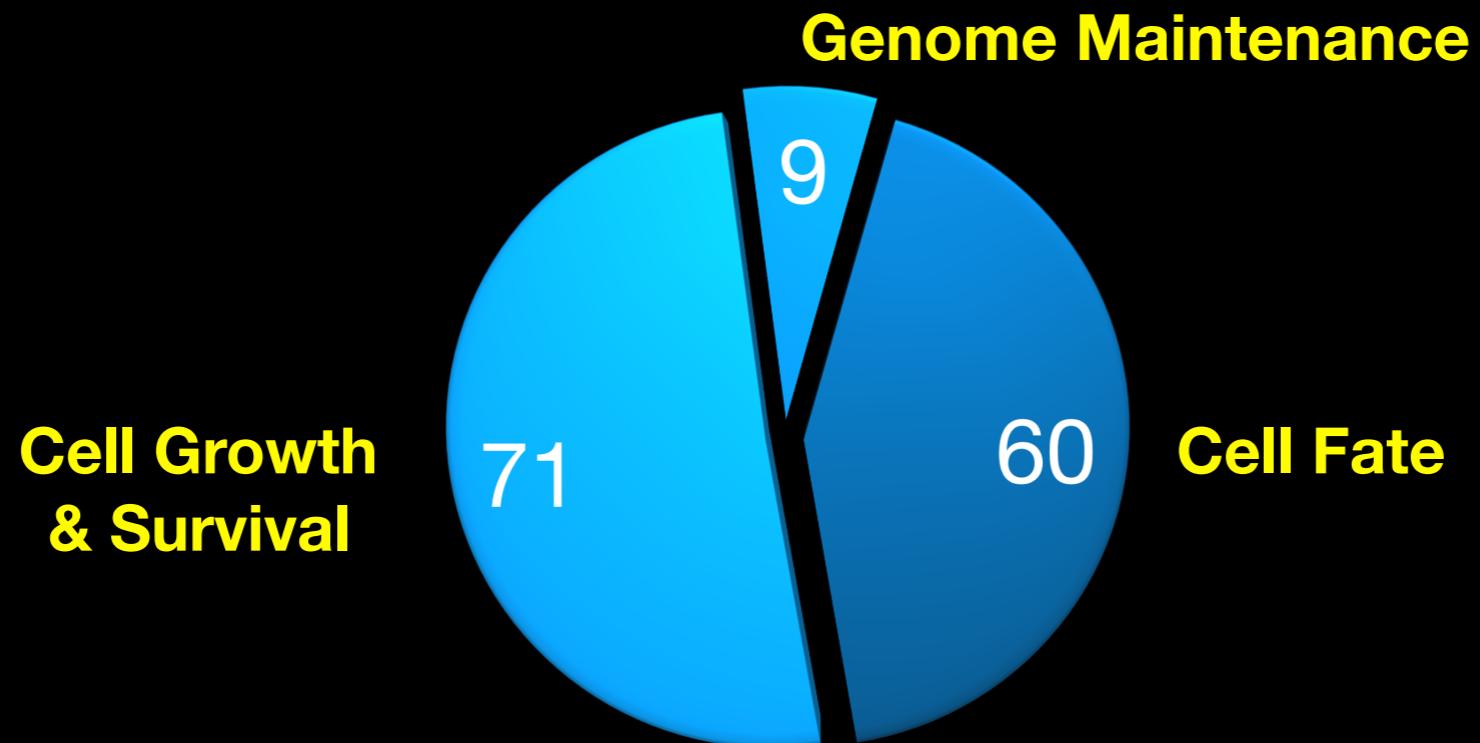
Current genomics approaches have identified ~140 cancer genes. Of which there are:

- ~60 **Oncogenes** (normally stimulate growth)
- ~80 **Suppressor genes** (normally inhibit growth)

Functions of the 140 cancer genes

Current genomics approaches have identified ~140 cancer genes. Of which there are:

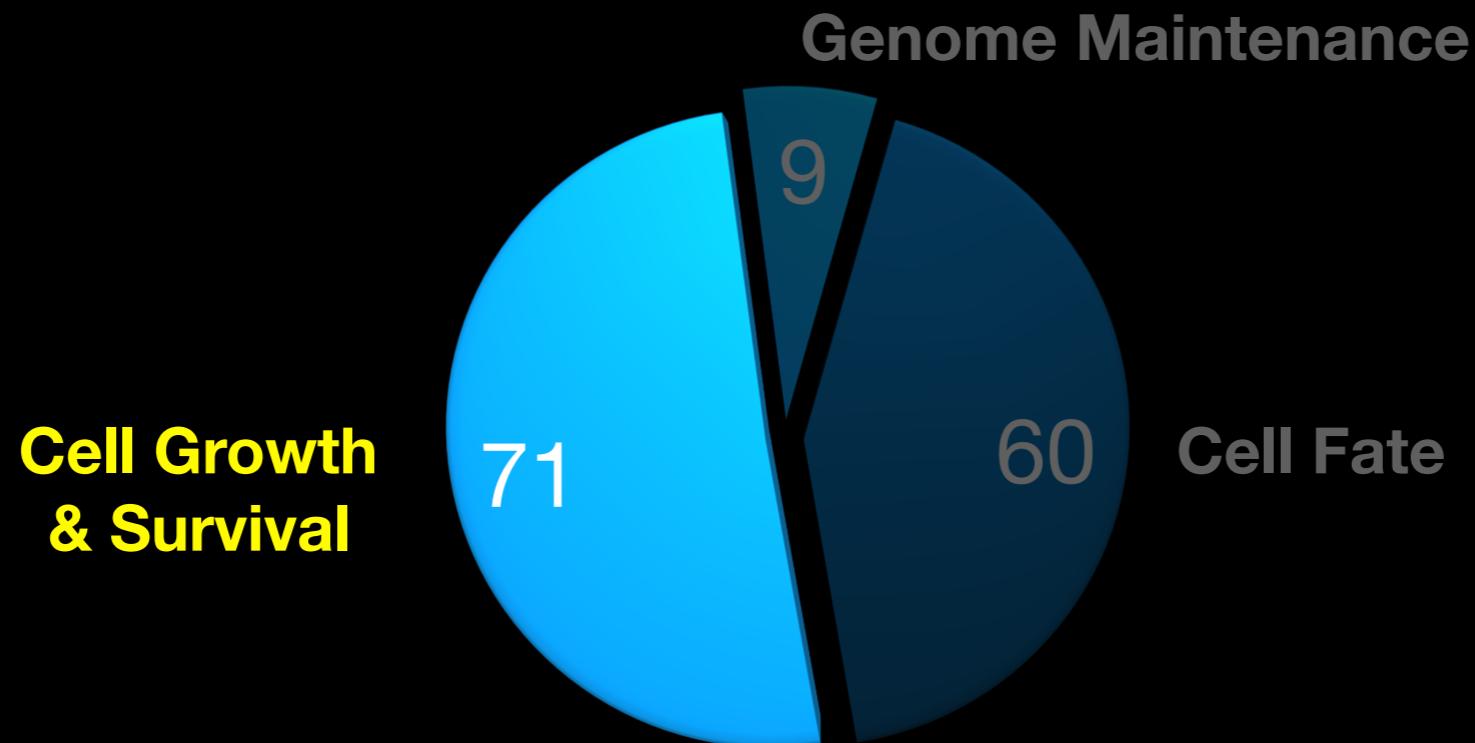
Three main categories



Functions of the 140 cancer genes

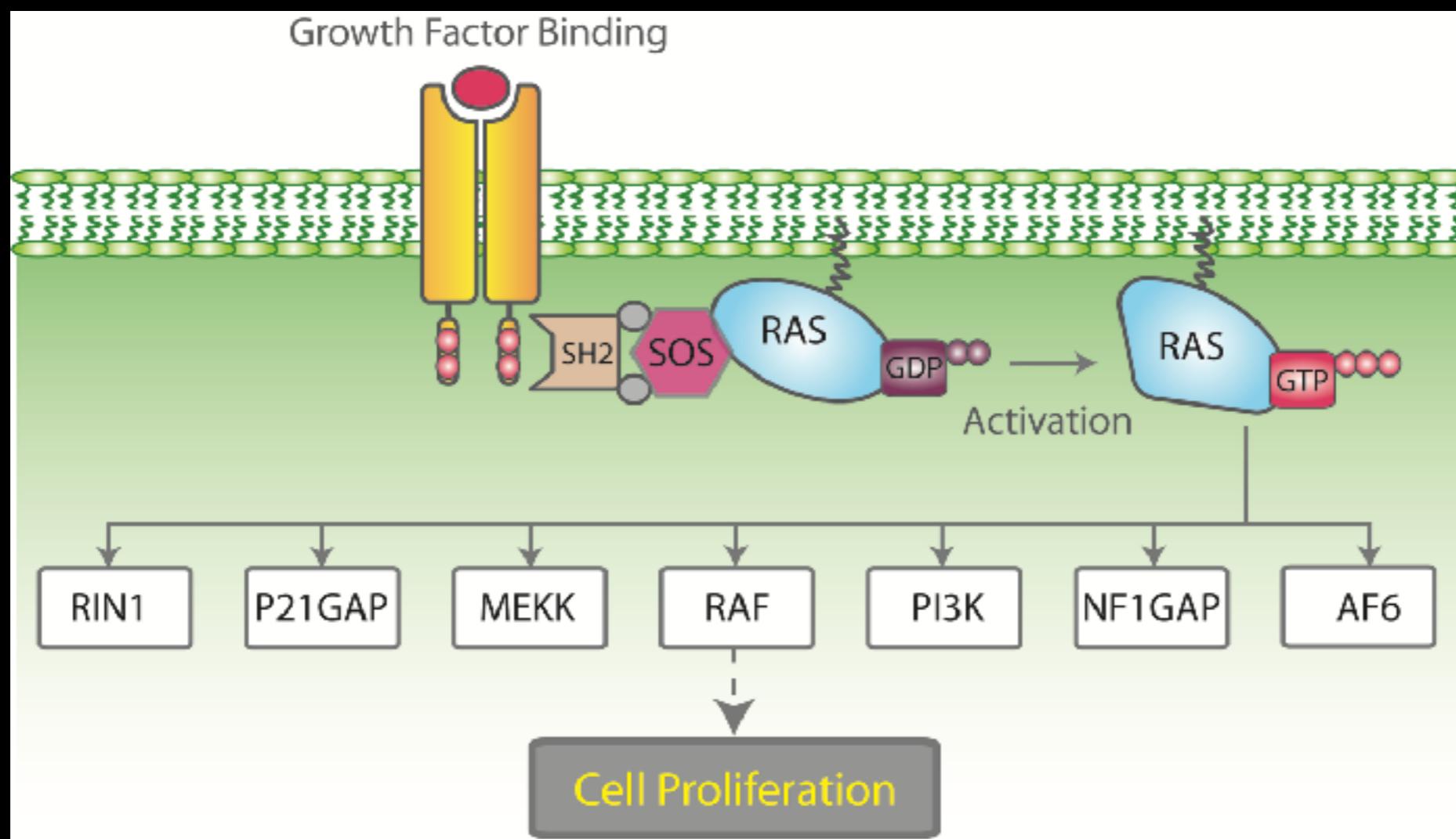
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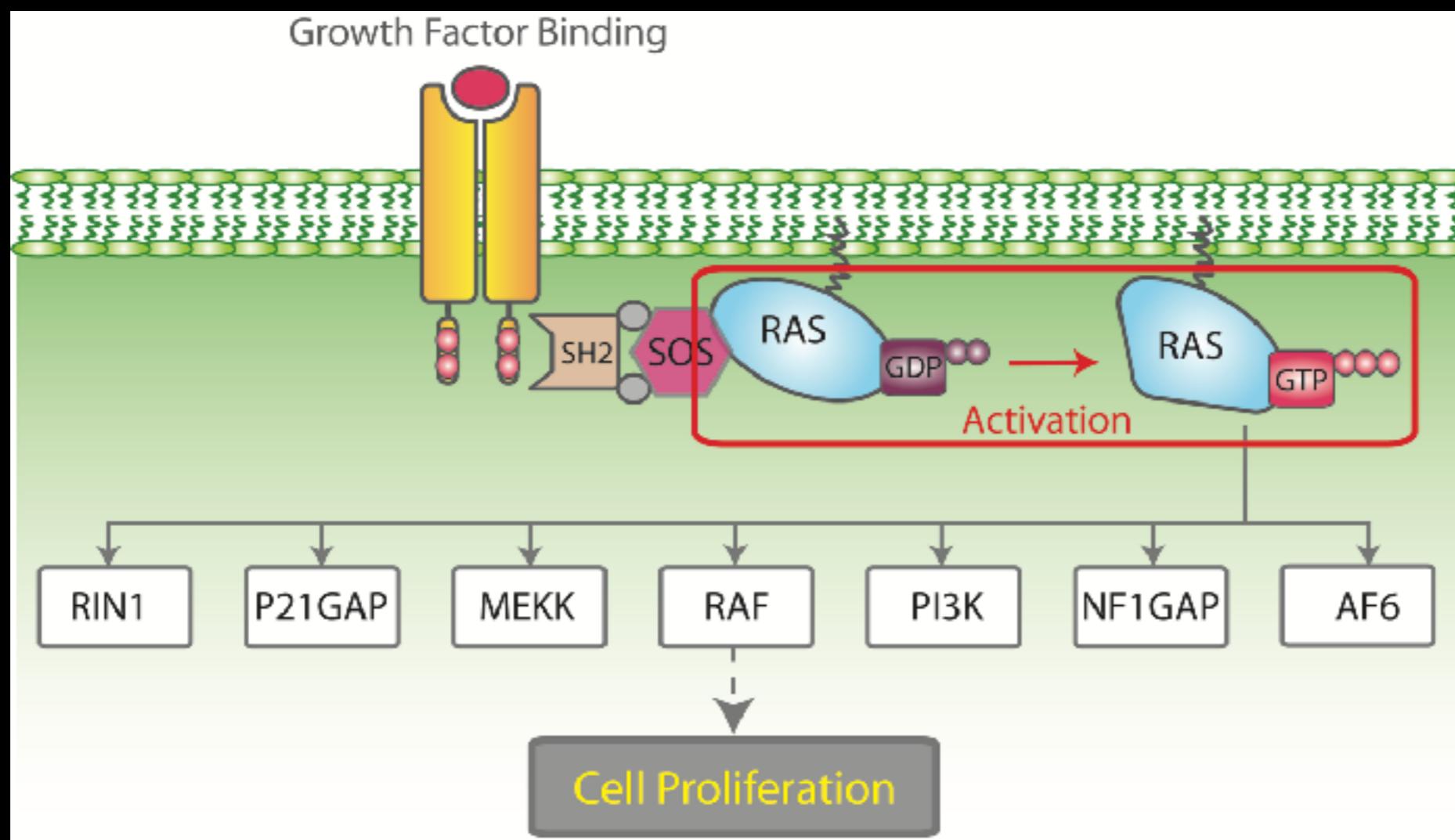
Cell growth and survival genes

Many participate in signaling pathways that promote cell proliferation
(E.G. EGFR, Ras, BRAF, MEK etc.)

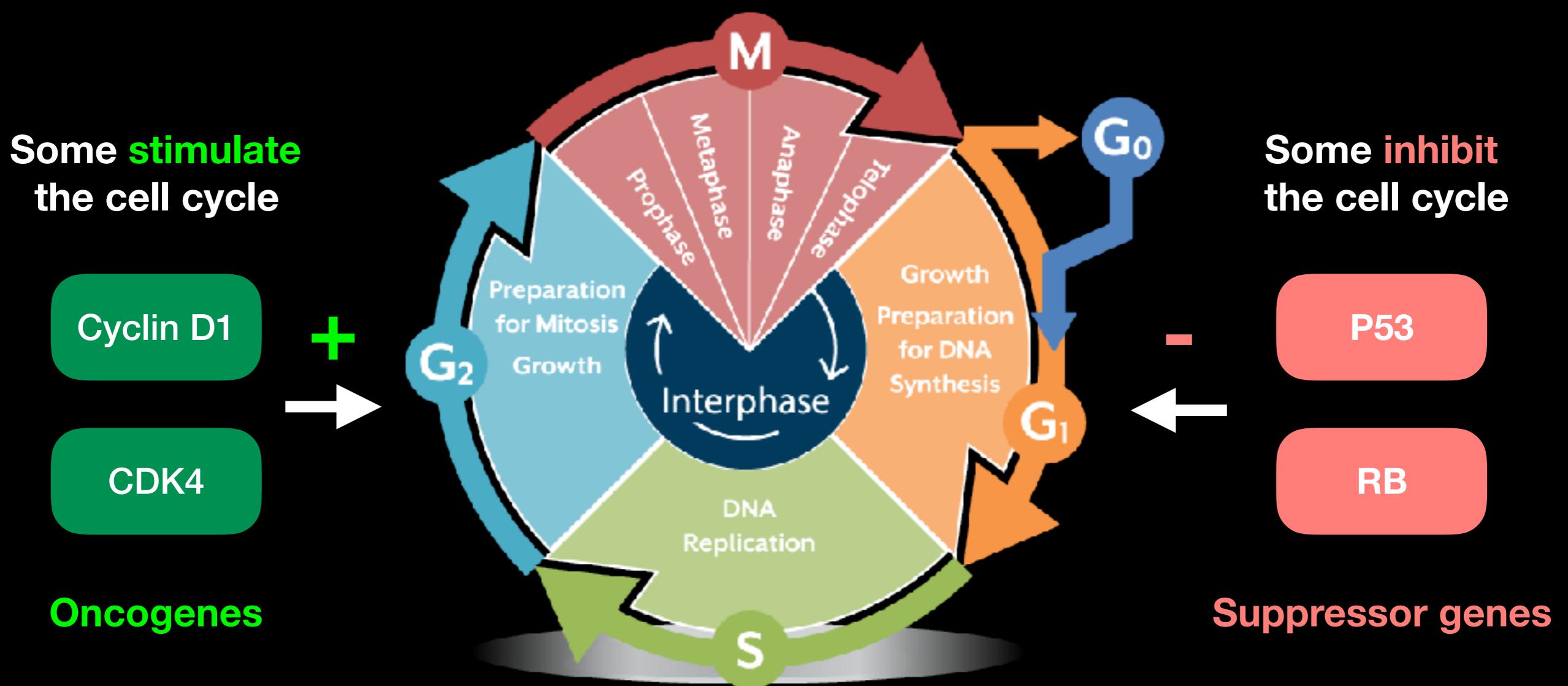


Cell growth and survival genes

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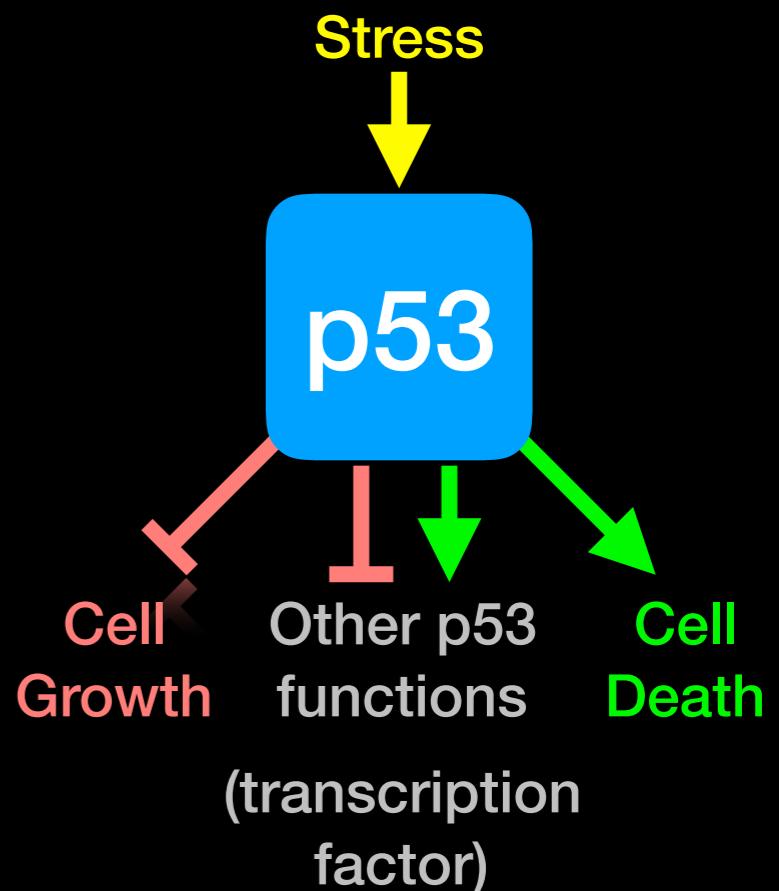
Regulators of Cell Cycle and Cell Death



p53 Regulates Cell Division

Probably the most famous cancer gene that is mutated in about half of all tumors. Often called the '*guardian of the genome*'

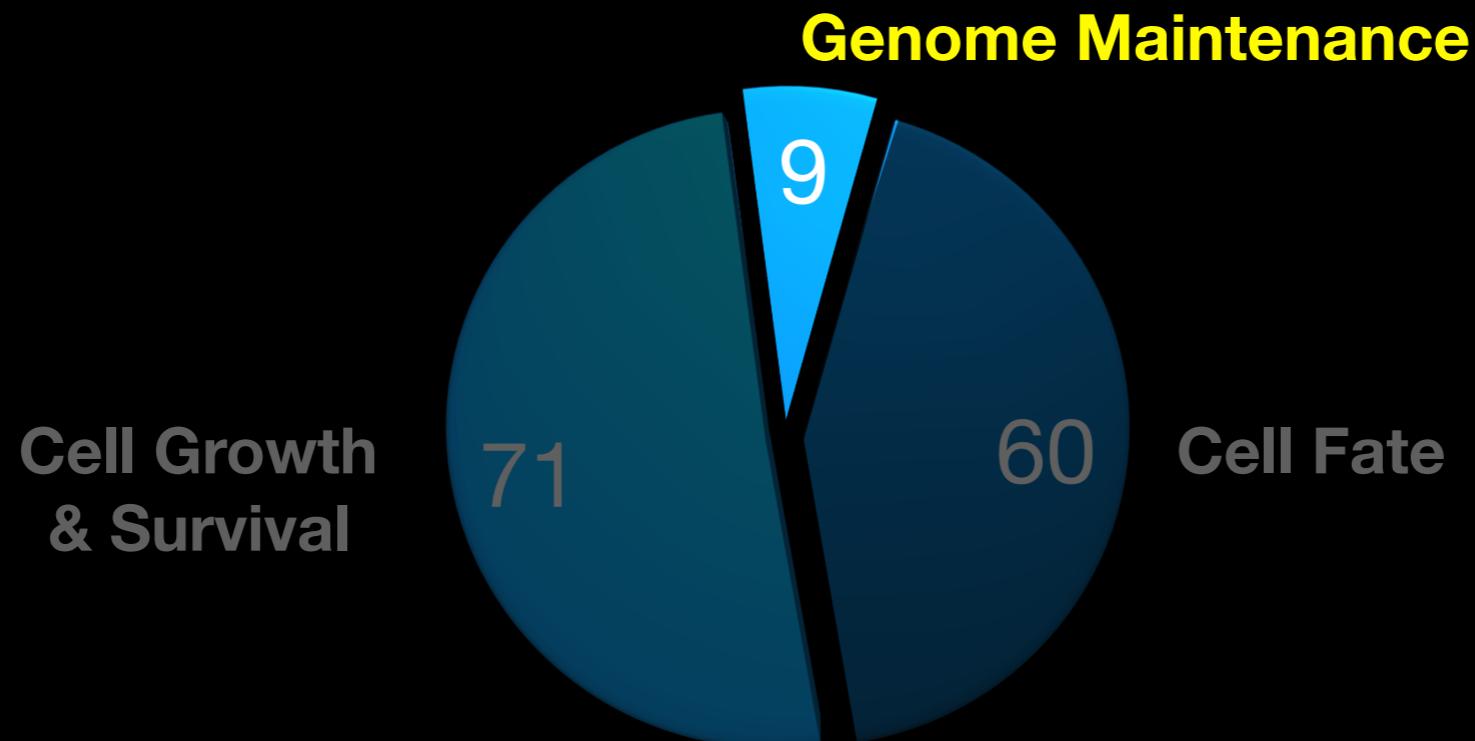
- p53 normally shuts down cell division when a cell is stressed (e.g. by DNA damage)
- When DNA is damaged, p53 activates genes that stop cell growth or trigger the cell to die.
- Thus, p53 guards against changes to cells that might lead to tumor formation.
- It appears necessary to inactivate p53 to develop many forms of cancer.

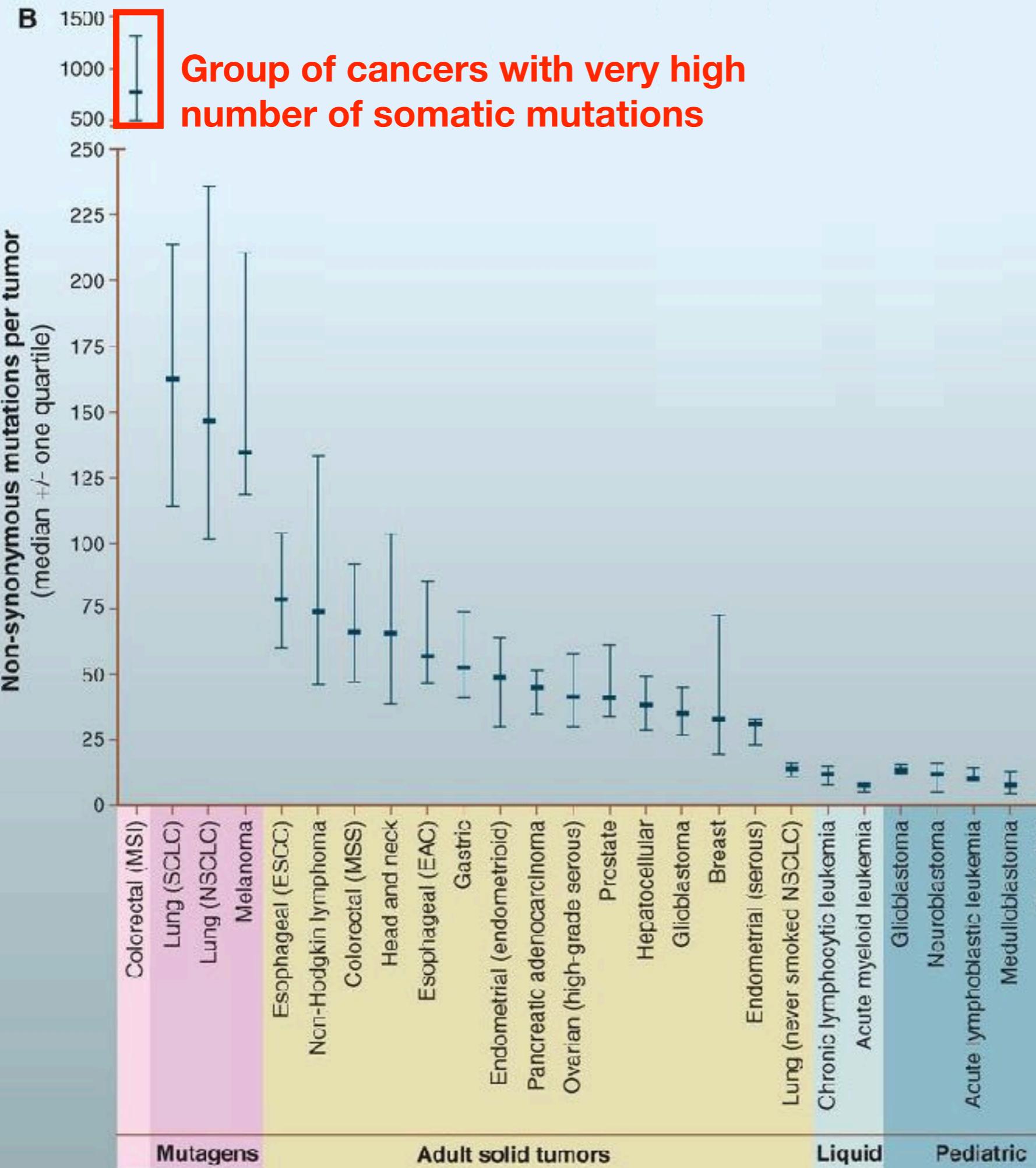


Functions of the 140 cancer genes

Current genomics approaches have identified ~140 cancer genes. Of which there are:

Three main categories





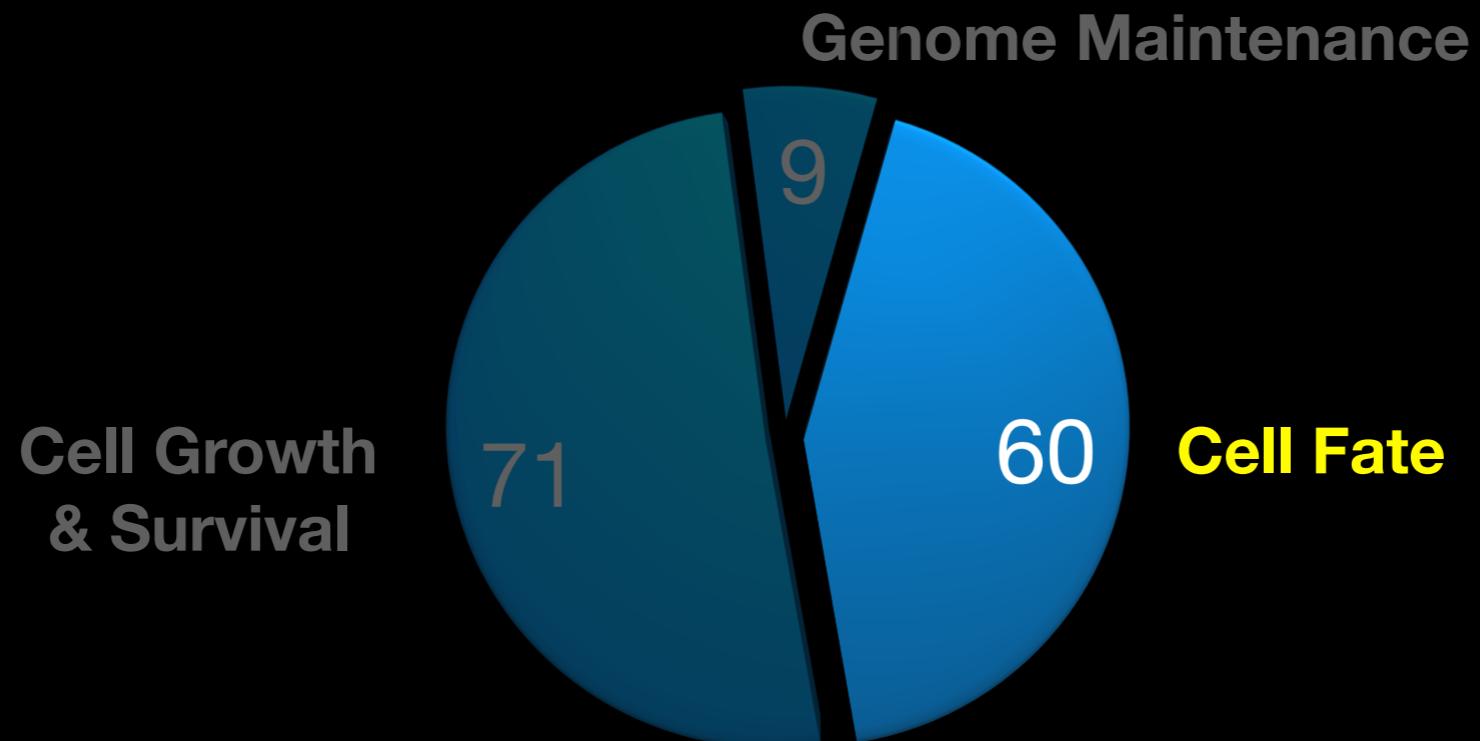
Linked to mutations in DNA repair genes.

Vogelstein et al.
Science (2013)

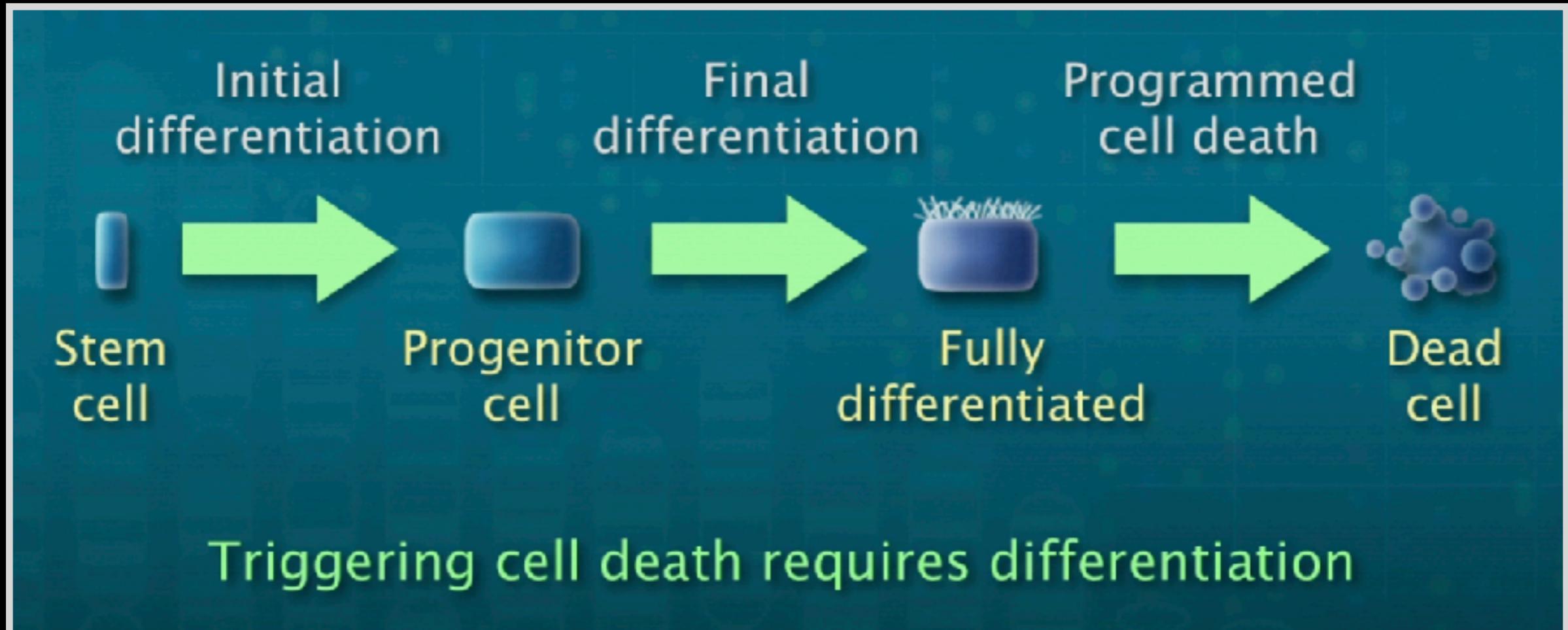
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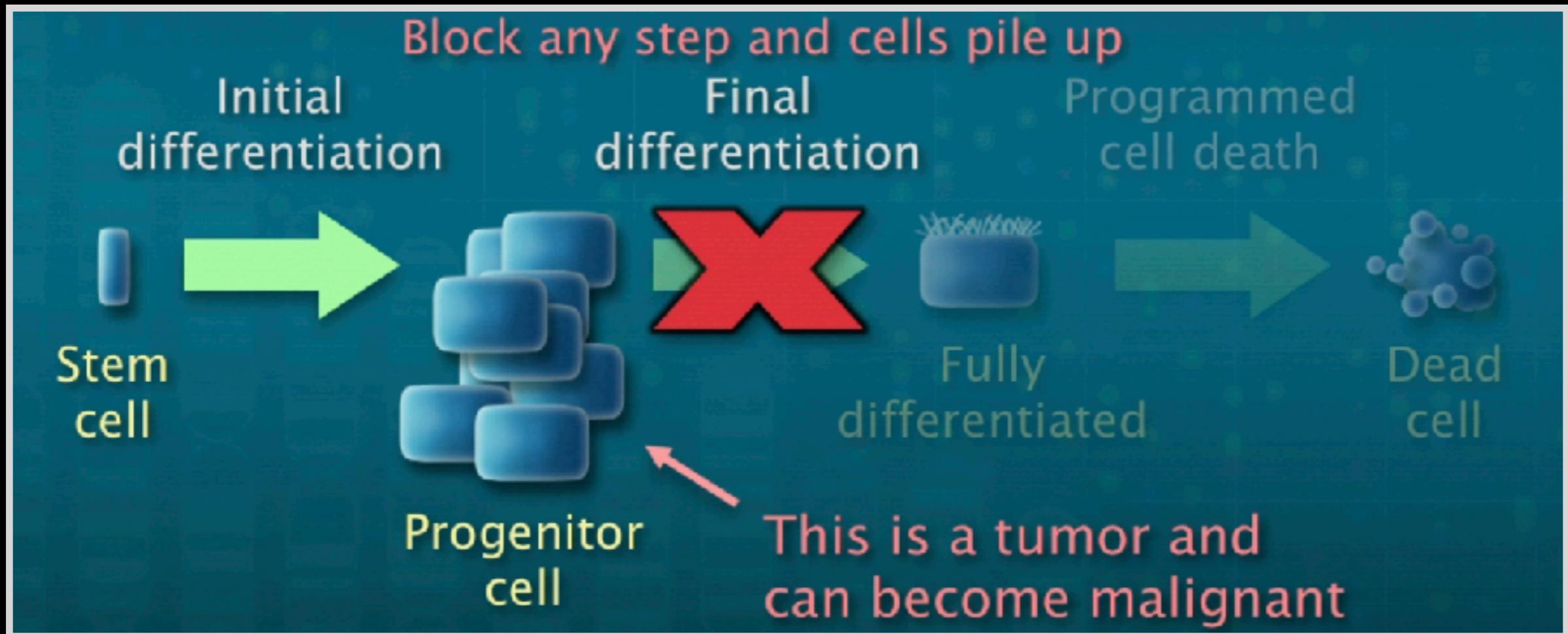
Three main categories



How Can Mutations in Cell Fate Genes Cause Cancer?



How Can Mutations in Cell Fate Genes Cause Cancer?



Disrupting the normal processes of differentiation and maturation of the intestinal epithelial cells can lead to cancer.



Clevers Lab|Digizyme

http://molecularmovies.com/movies/kellermcgill_clonalconveyorbelt.mov

Hands-on time!

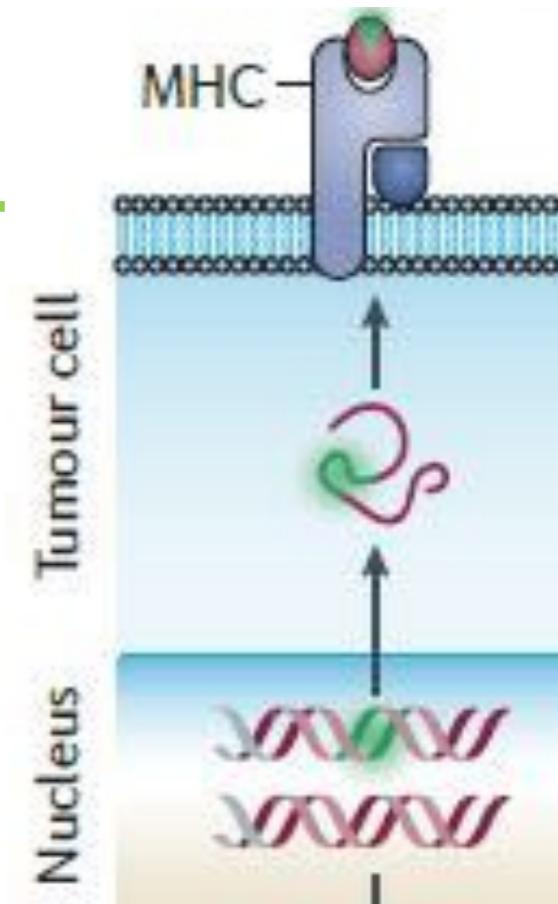
https://bioboot.github.io/bimm143_W18/lectures/#18

Part 1 Only Please

Cancer Immunotherapy

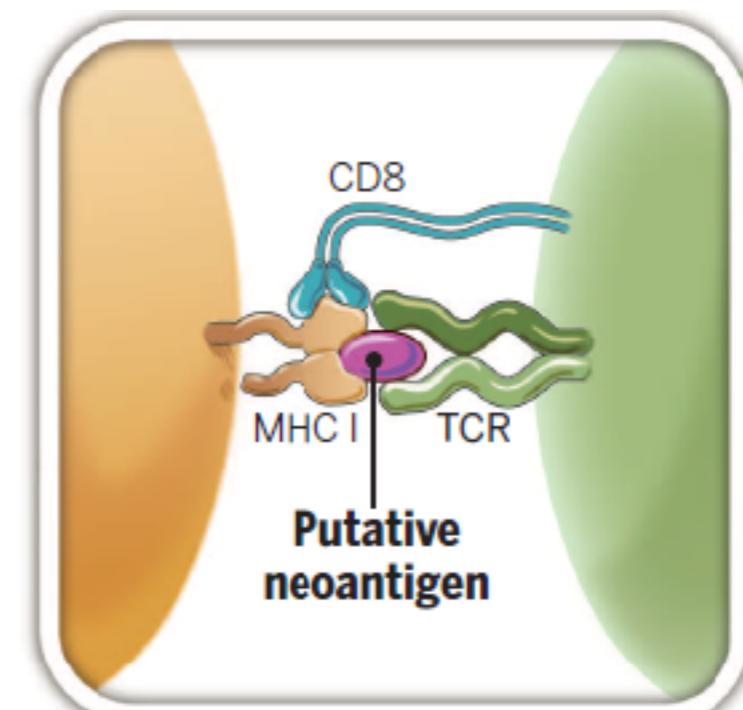
Neoepitopes (Neoantigens)

- Cancers genomes accumulate mutations
- Mutations in coding regions are translated in mutated protein sequences
- Mutated peptides can be presented as epitopes on MHC to T cells



Neoepitopes are presumably recognized by tumor-infiltrating lymphocytes (**TILs**)

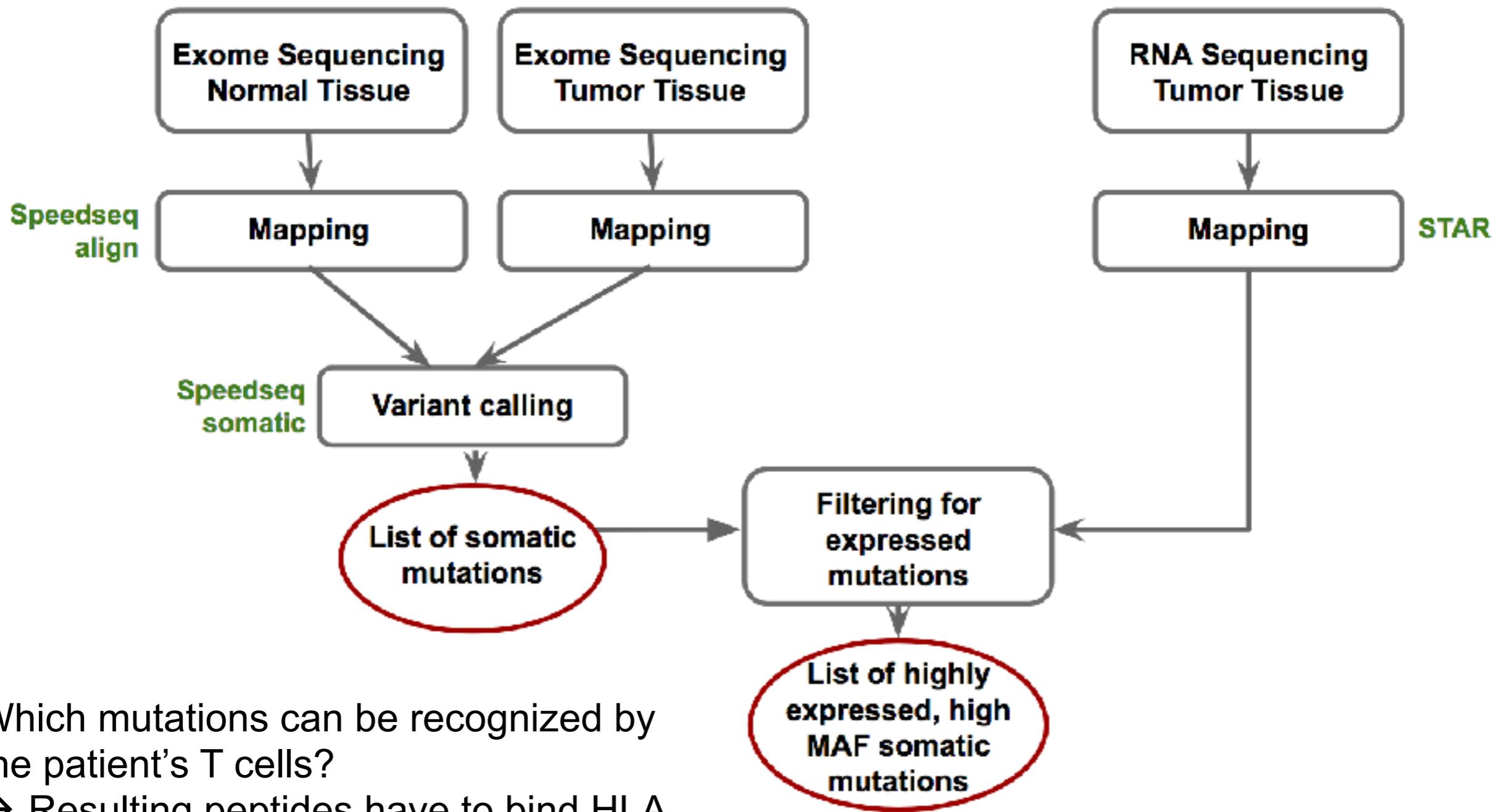
Neoepitopes are highly tumor-specific!



Cancer Immunotherapy

- Vaccination: Introduce or boost an immune response against a specific target (antigen)
- Cancer cells contain non-self antigens that *could* be recognized by T cells, but presence of cancer means this mechanism has failed, typically by the tumor suppressing immune responses
- Checkpoint blockade treatments: Block immune suppressive mechanisms to boost T cell immune responses against cancer cells.
- Problem: Checkpoint blockade is unspecific, and will also boost unwanted autoimmune responses
- Personalized Cancer Immunotherapy: Boost anti-tumor response with vaccine containing peptides corresponding to cancer mutations that can be recognized by T cells.
→ How can such a vaccine be designed?

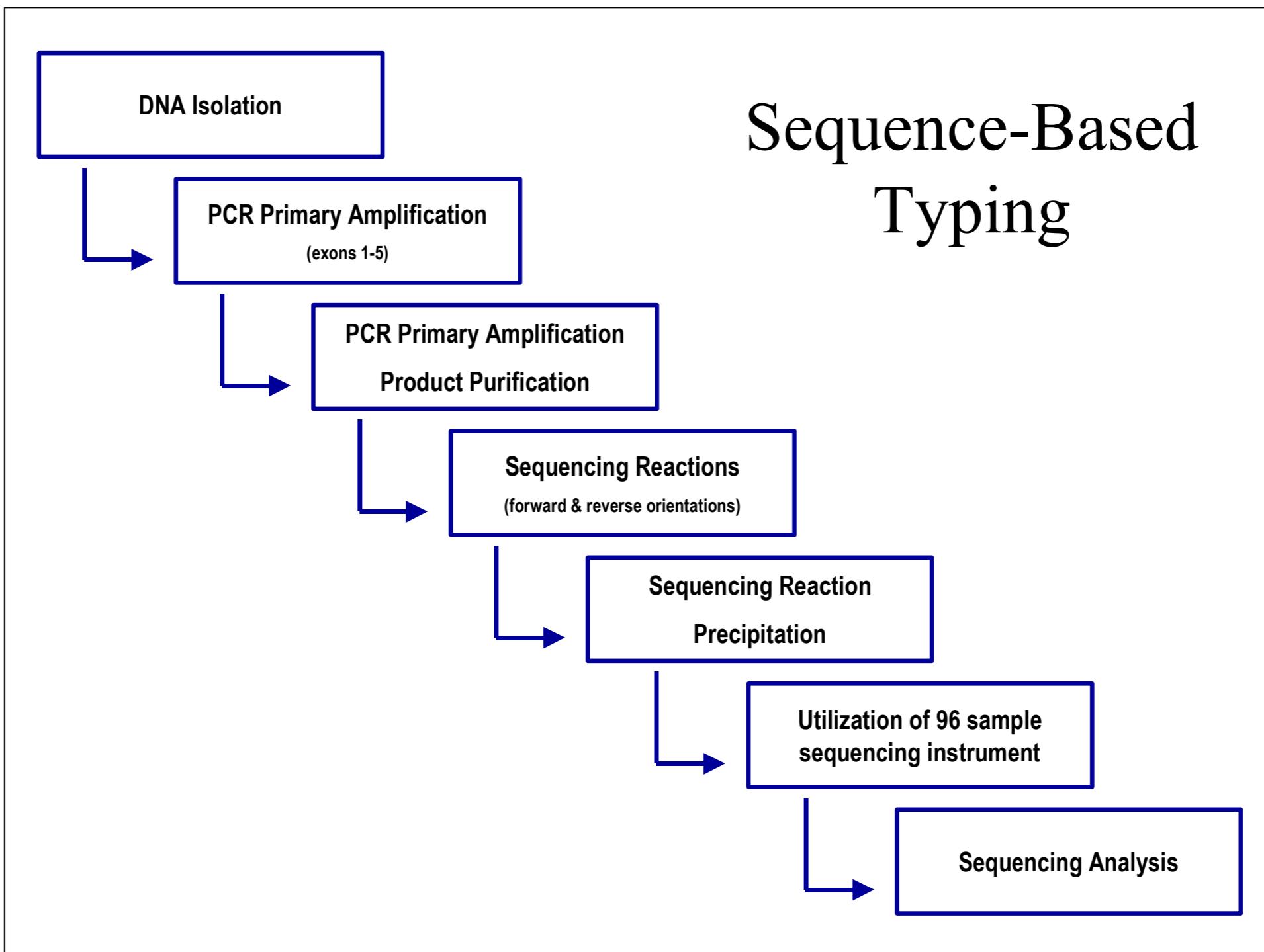
DNA and RNA sequencing identifies tumor specific somatic mutations



Which mutations can be recognized by the patient's T cells?

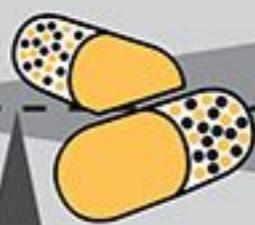
→ Resulting peptides have to bind HLA molecules of the patient

HLA Typing: Targeted sequencing of HLA locus



•http://www.ashi-hla.org/publicationfiles/ASHI_Quarterly/25_2_2001/highthrusbt3.htm

TRADITIONAL CANCER THERAPIES



DRUGS OR RADIATION

Kills **Cancerous Cells**

Kills **Healthy Cells**



CANCER IMMUNOTHERAPIES



Unleash



Patient's Immune System

IMMUNOTHERAPY

Selectively Kills
Cancerous Cells

Healthy Cells



Hands-on time!

https://bioboot.github.io/bimm143_W18/lectures/#18

Part 2