

BGGN 213

Cancer Genomics & Immunoinformatics

Lecture 18

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UC San Diego

<http://thegrantlab.org/bggn213>

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

Towards personalized cancer treatments

Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells

Cancer Immunoinformatics

Hands-on analysis to design personalized cancer vaccines

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>

It is estimated that cancer will strike 40% of people at some point in their lifetime with frequently devastating effects.

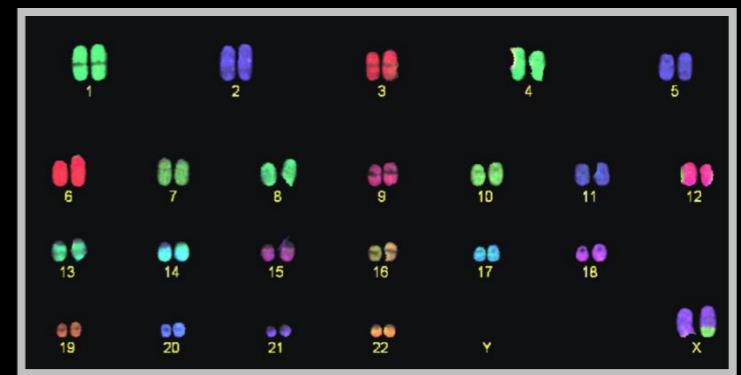
What is Cancer?

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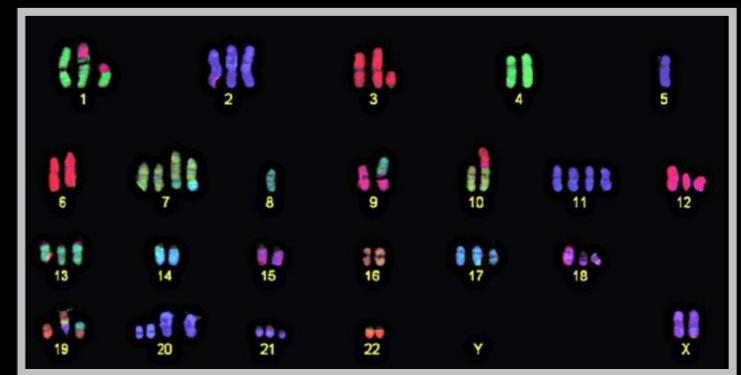
Source: <https://www.cancer.gov>

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.



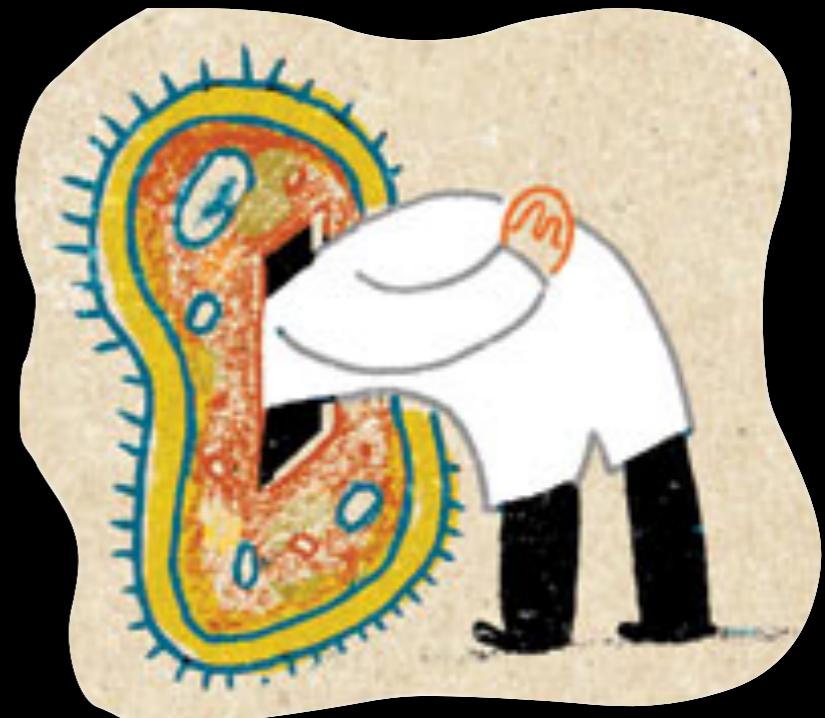
Healthy 46 chromosomes



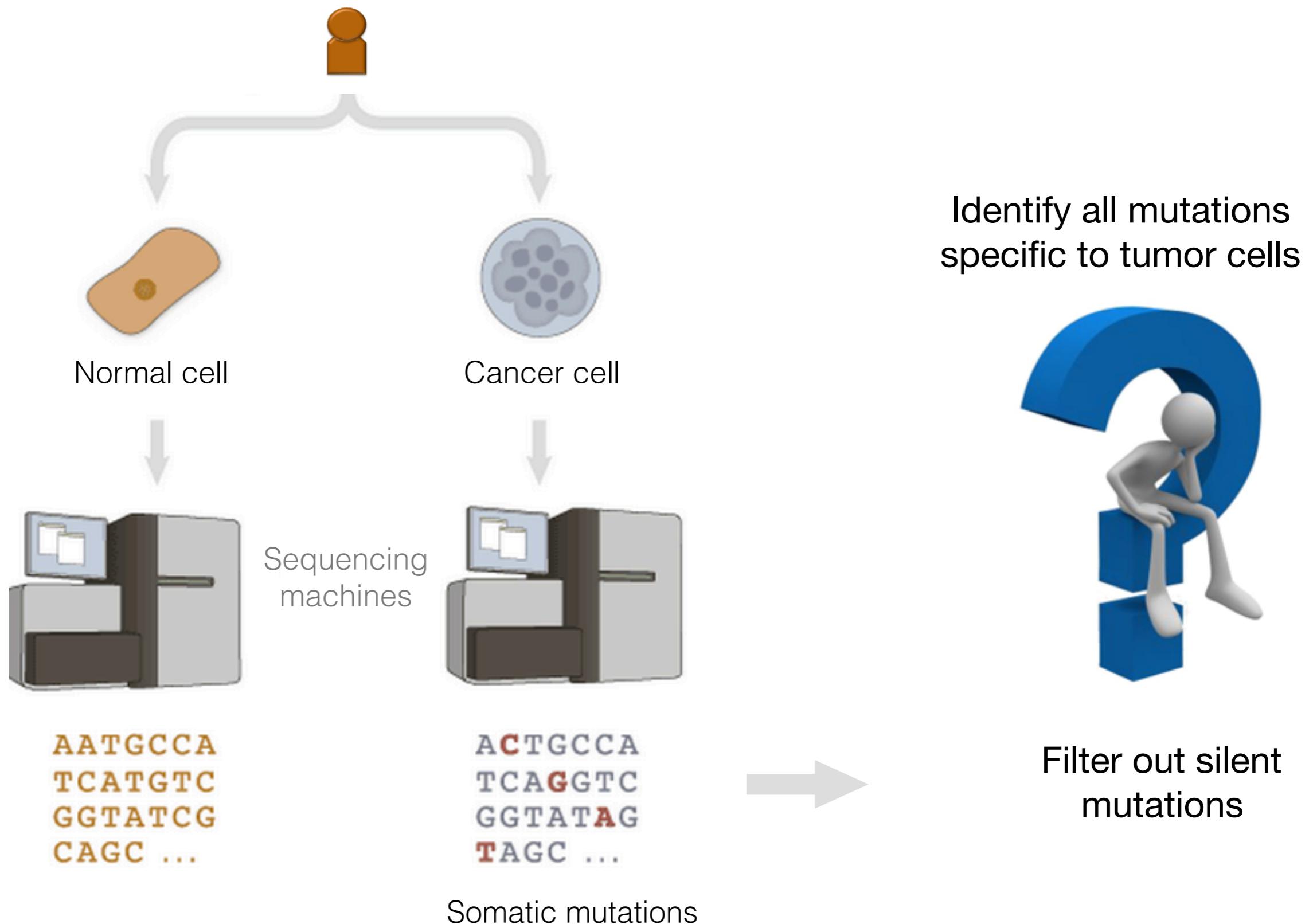
Example cancer 59 chromosomes

Goals of Cancer Genome Research

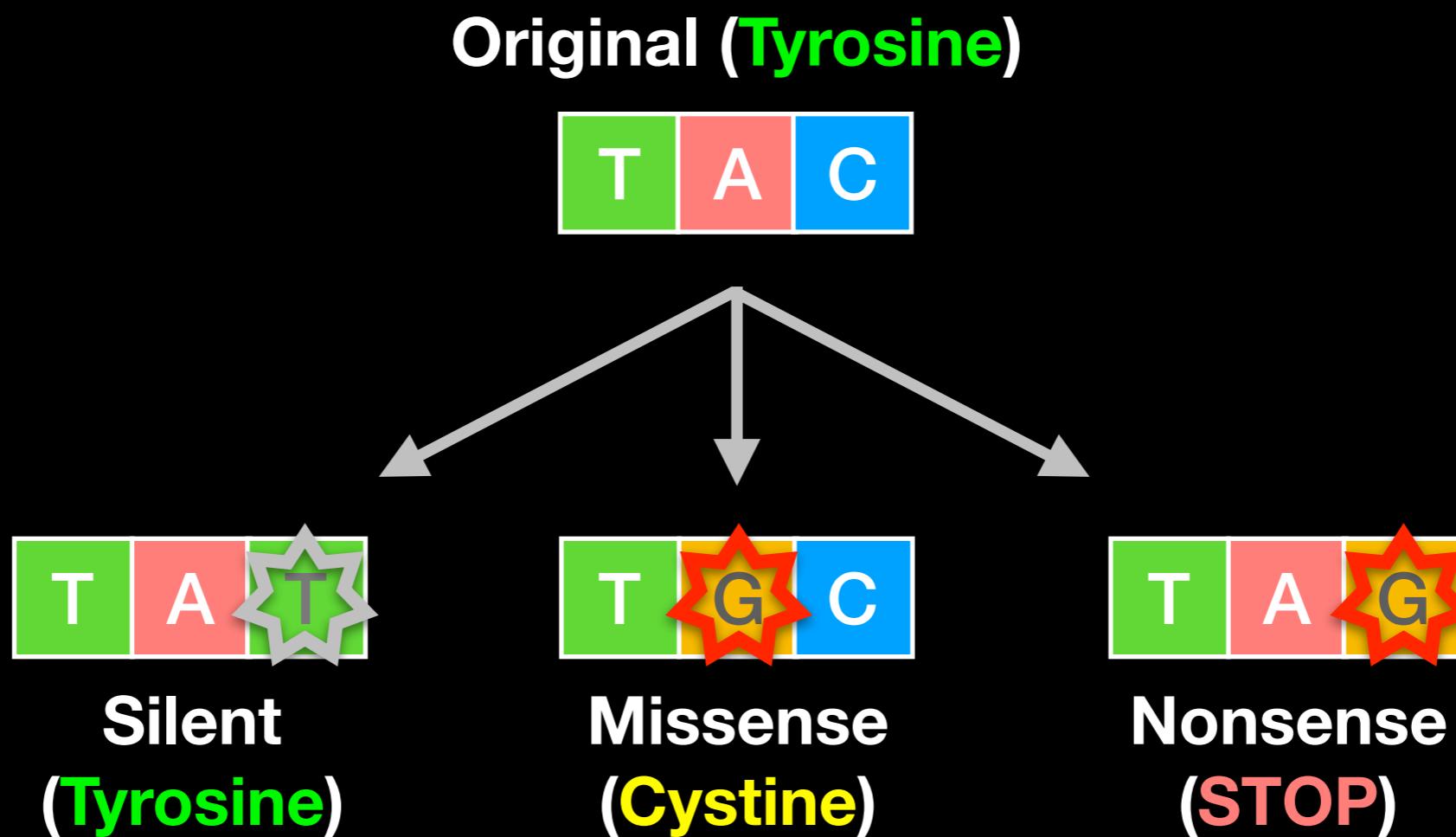
- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches



Finding Cancer Associated Mutations



Mutations detected: Point mutations



Mutations detected: Indels

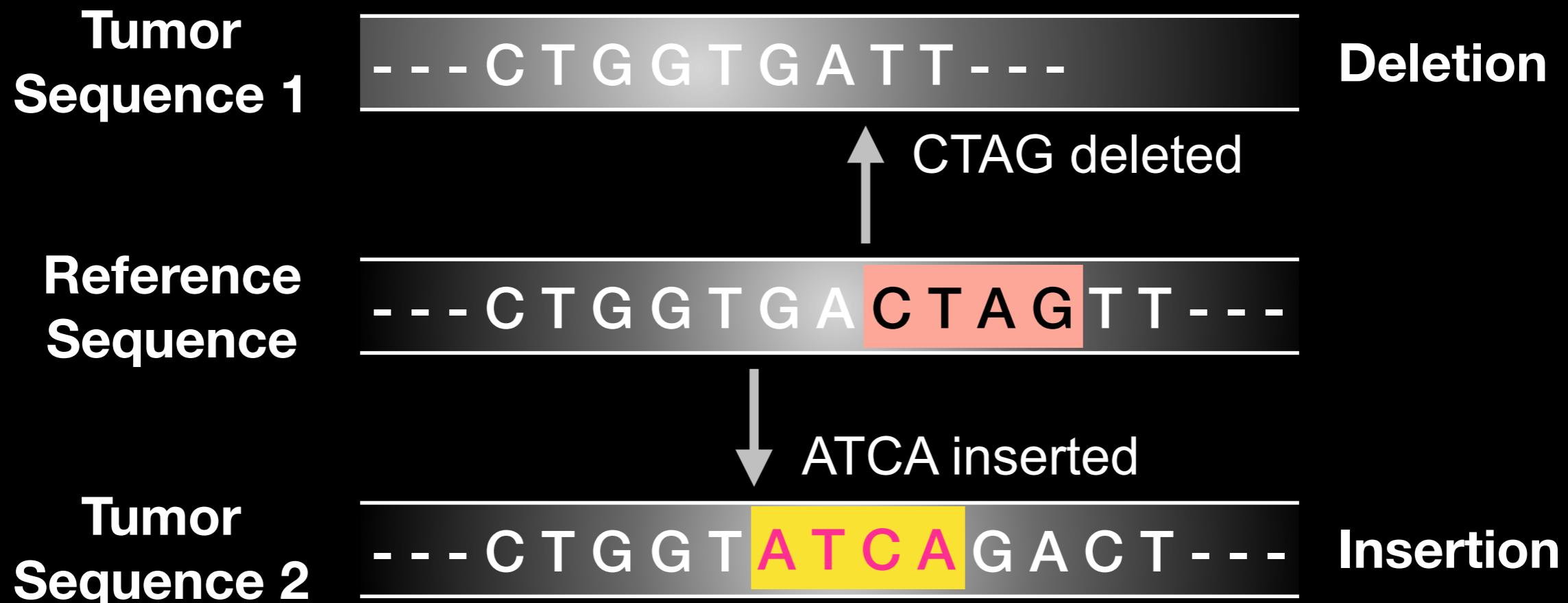
Reference
Sequence

--- C T G G T G A C T A G T T ---

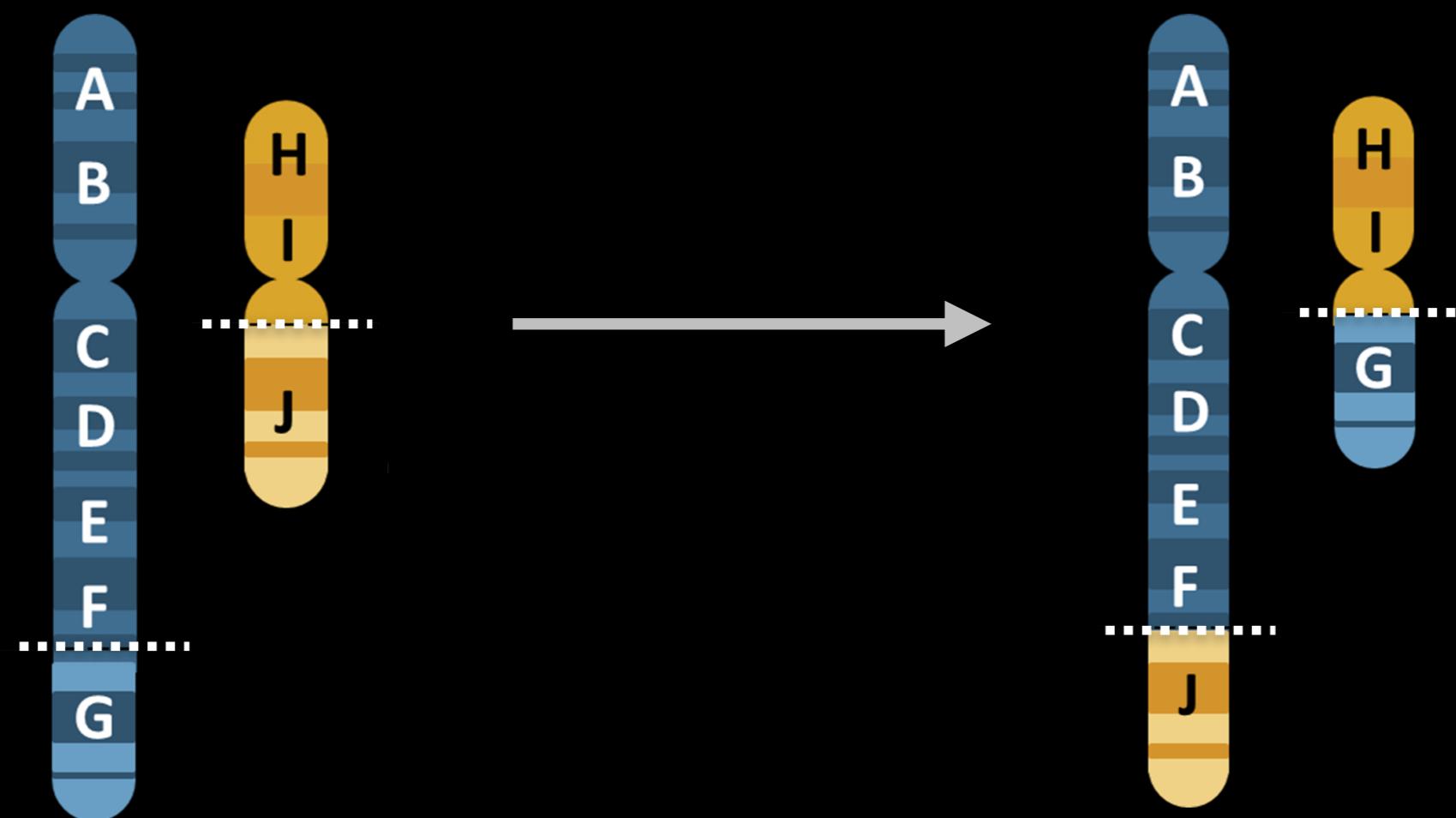
Mutations detected: Indels

The diagram illustrates a deletion mutation. On the left, 'Tumor Sequence 1' is shown as a grey box containing the sequence:
- - - C T G G T G A T T - - -
On the right, 'Deletion' is written. Below it, a white arrow points upwards from the sequence, indicating the position of the deletion. The deleted sequence 'CTAG' is highlighted in a red box. On the far left, 'Reference Sequence' is shown as a grey box containing the sequence:
- - - C T G G T G A C T A G T T - - -

Mutations detected: Indels



Mutations detected: Translocations

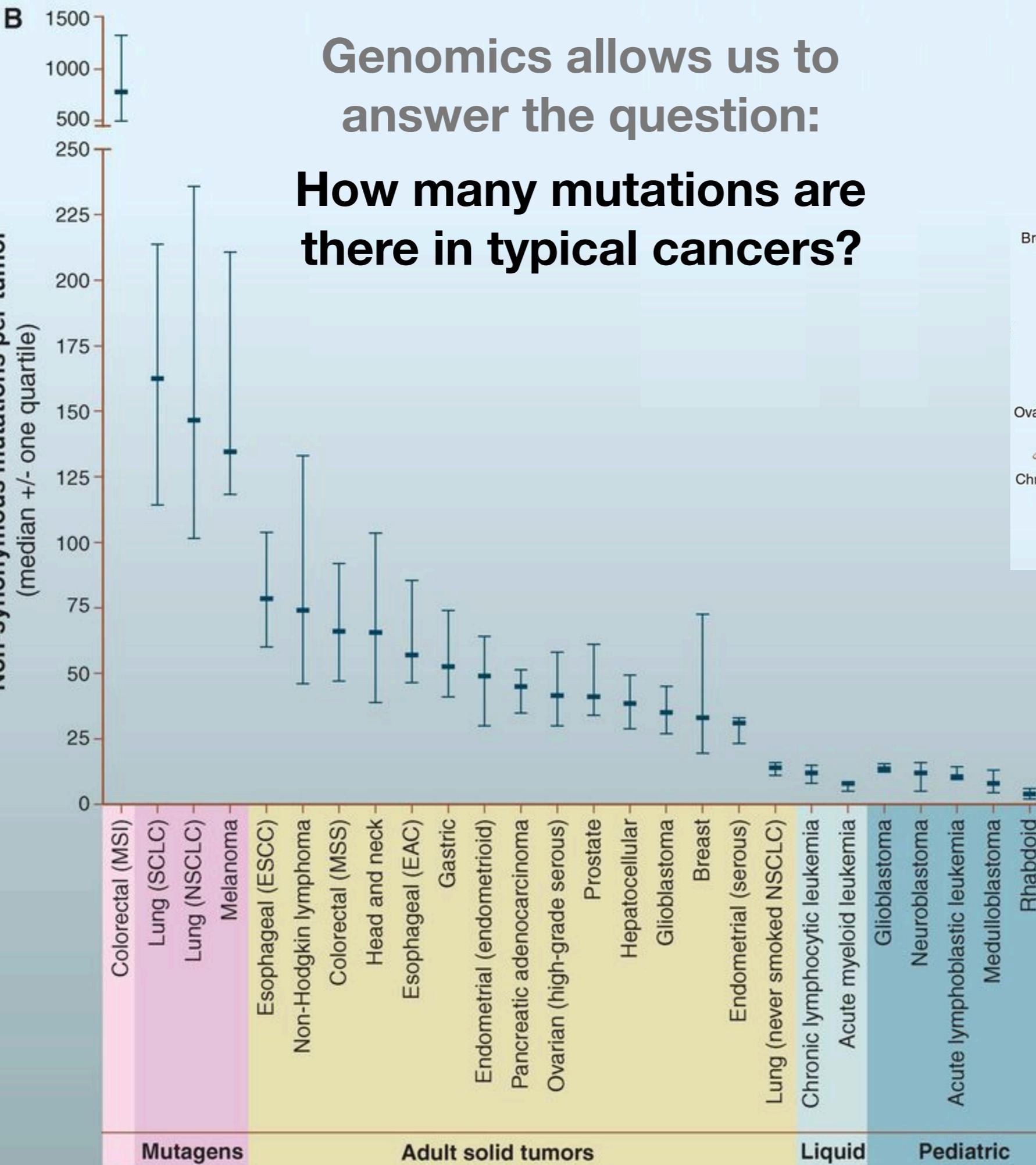


What can go wrong in cancer genomes?

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

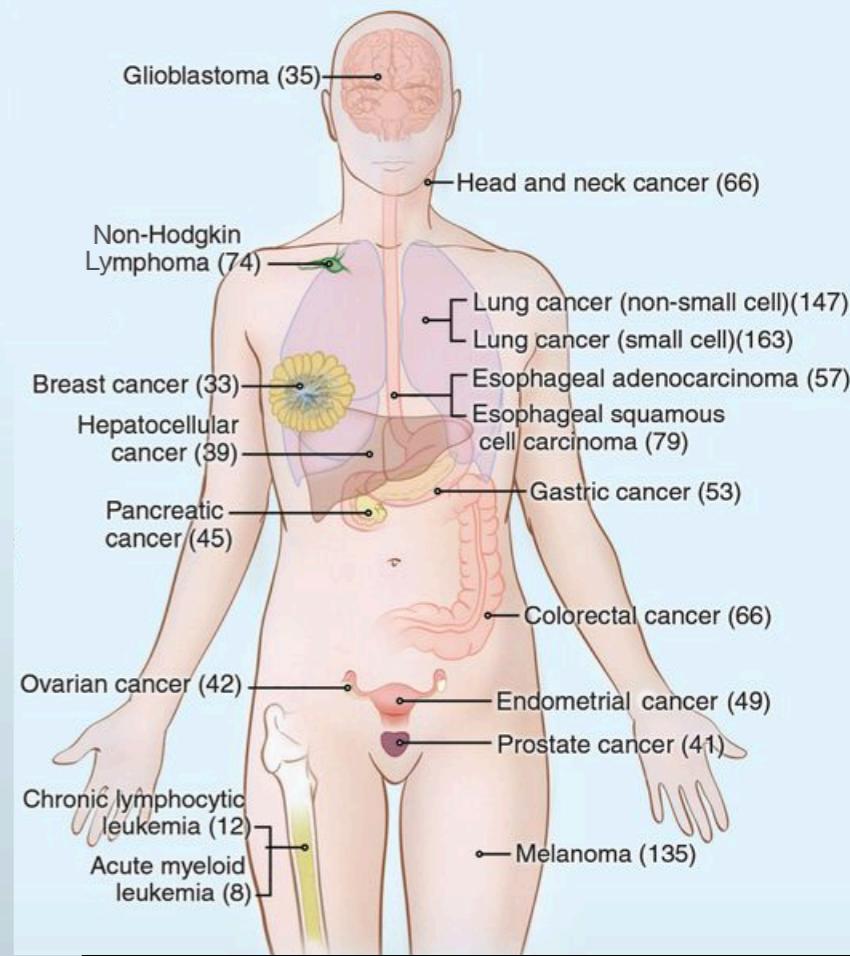
WGS = whole genome sequencing, WXS = whole exome sequencing

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



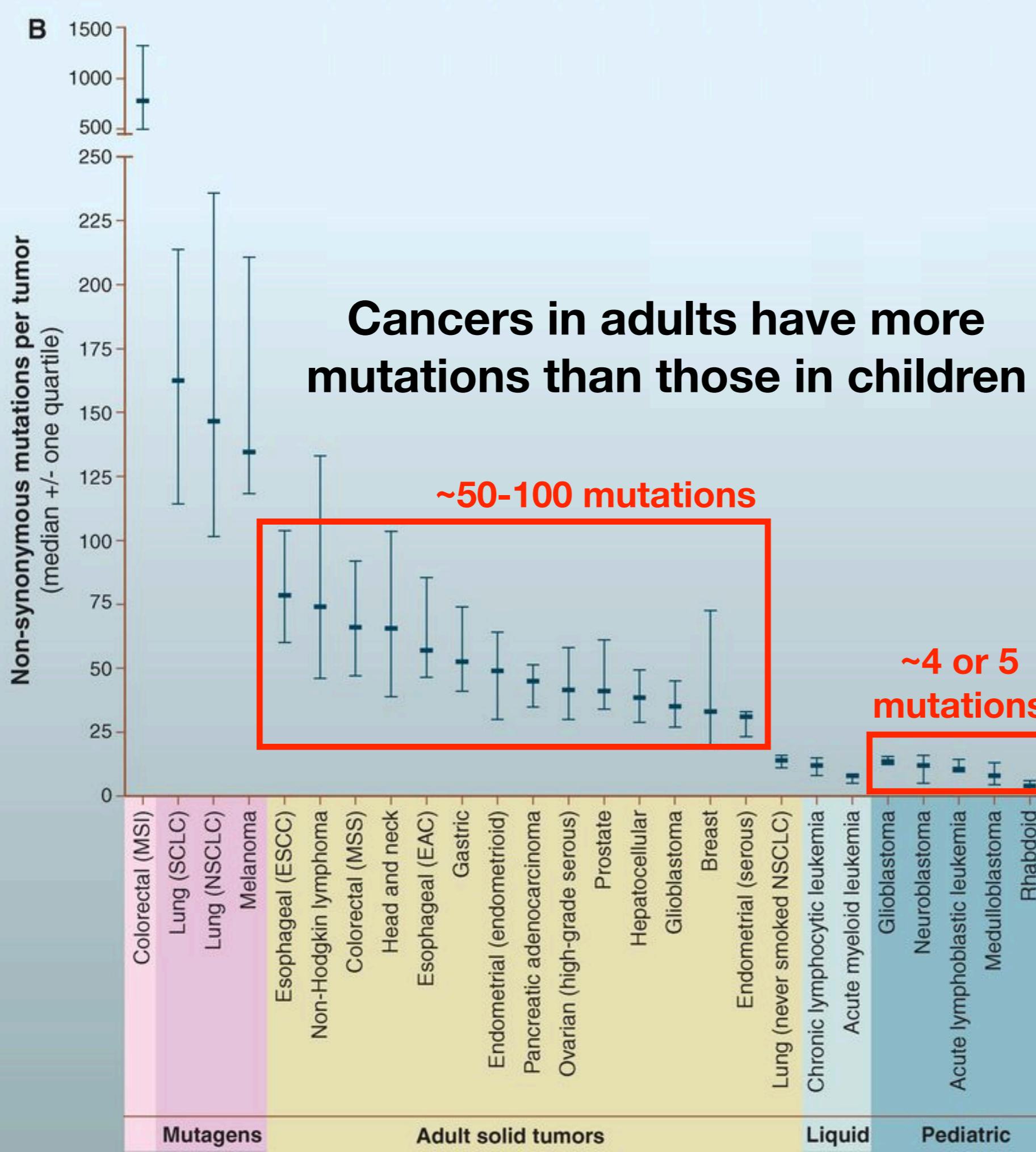
Genomics allows us to answer the question:

How many mutations are there in typical cancers?

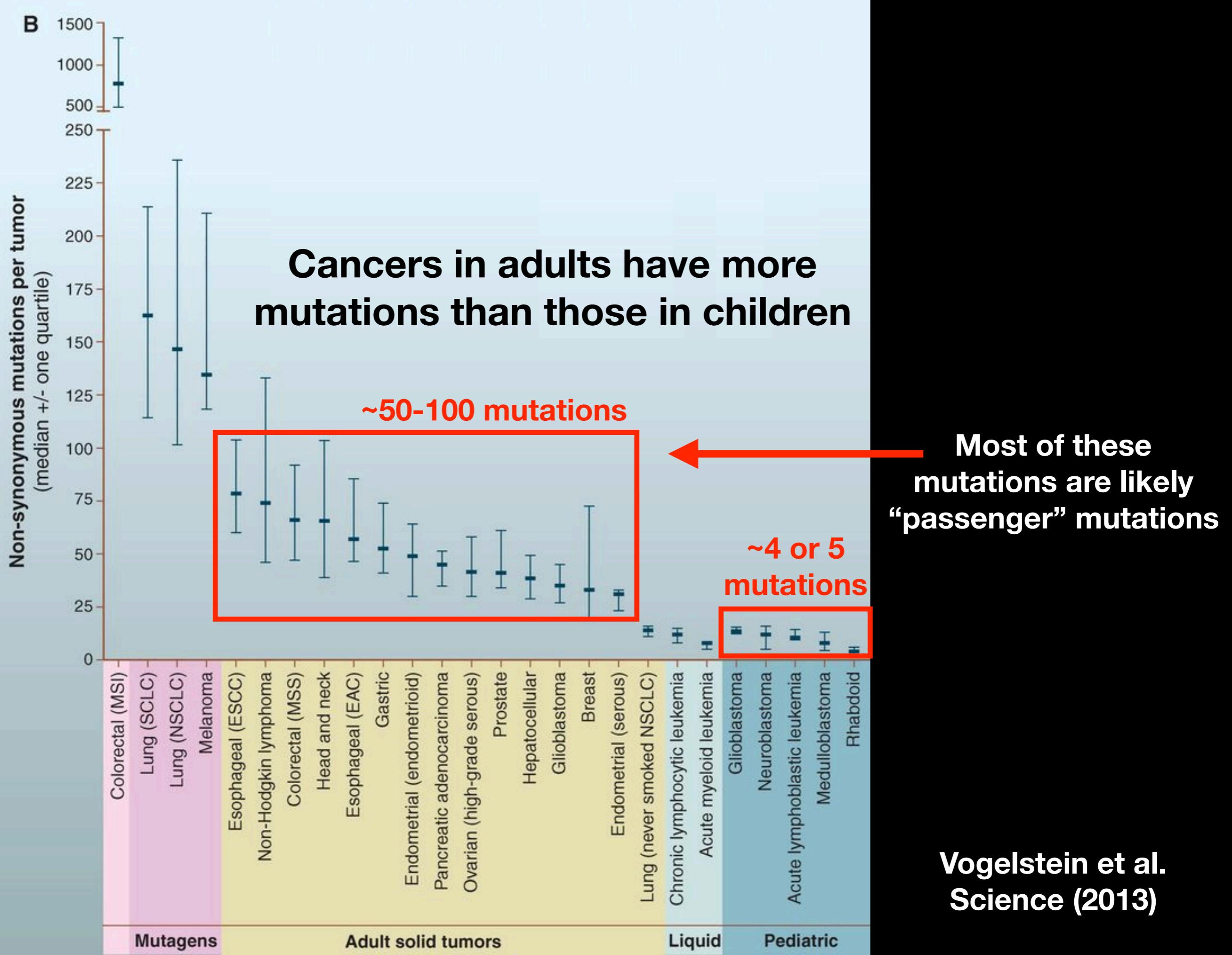


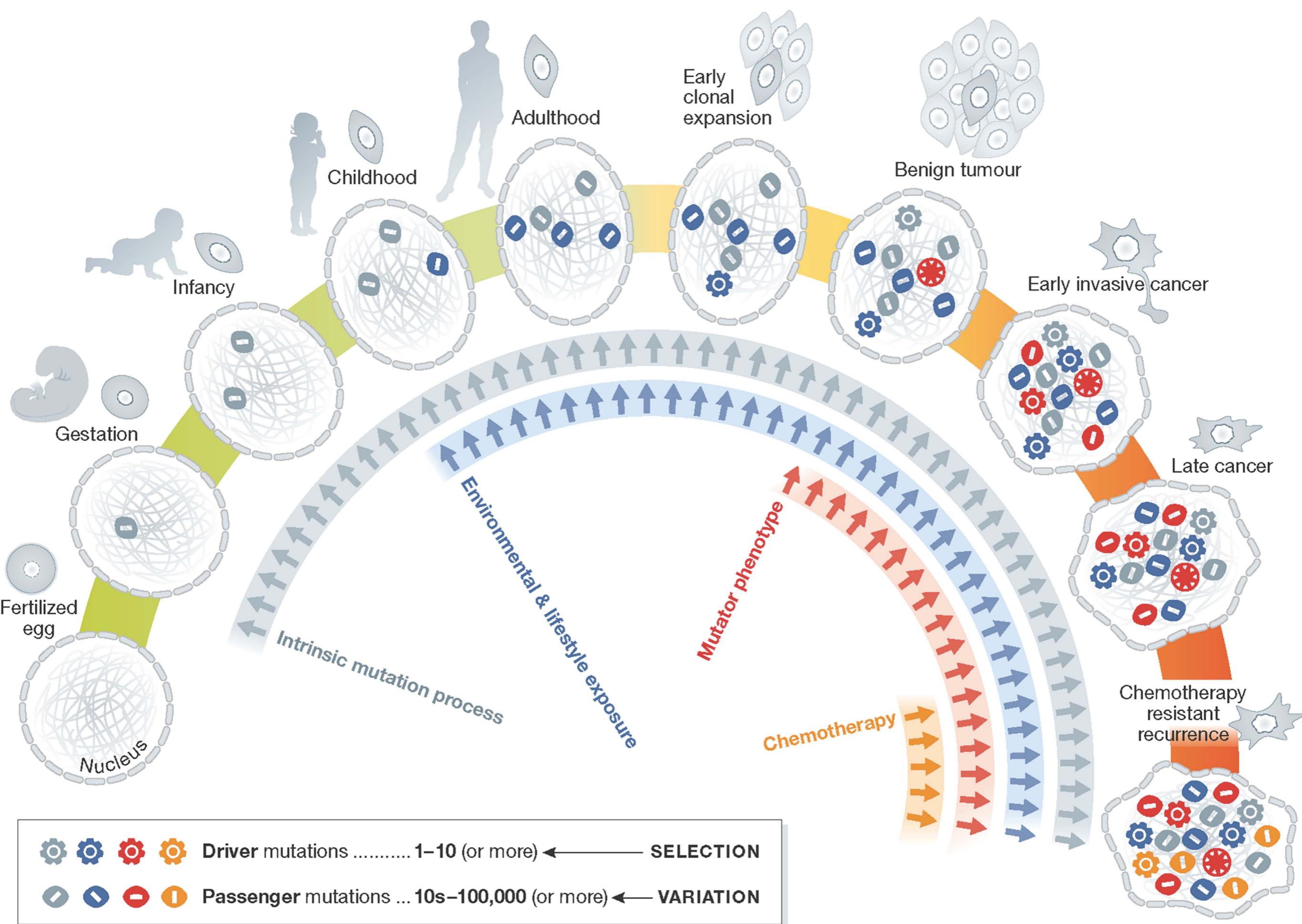
Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

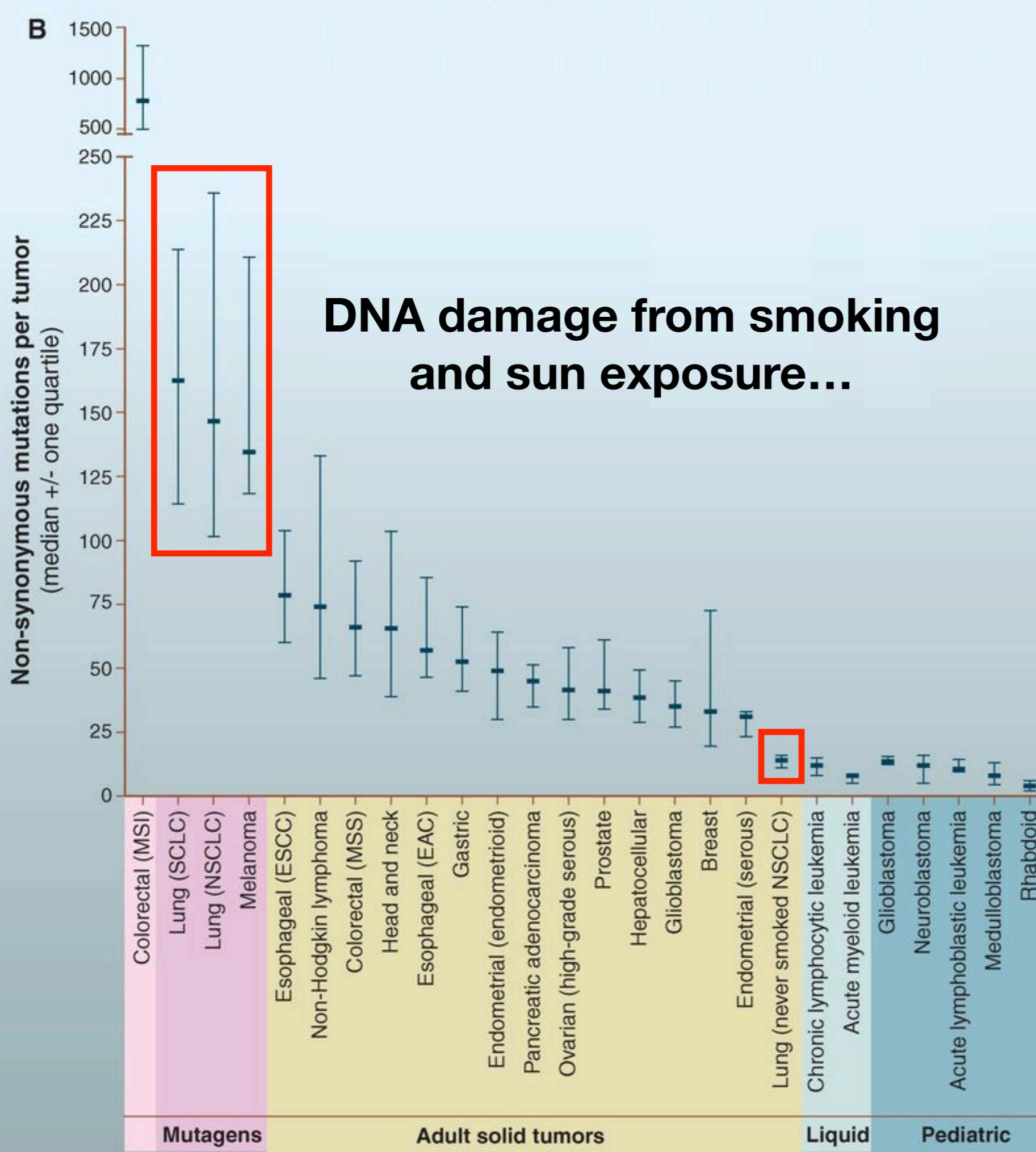
Vogelstein et al.
Science (2013)



Vogelstein et al.
Science (2013)

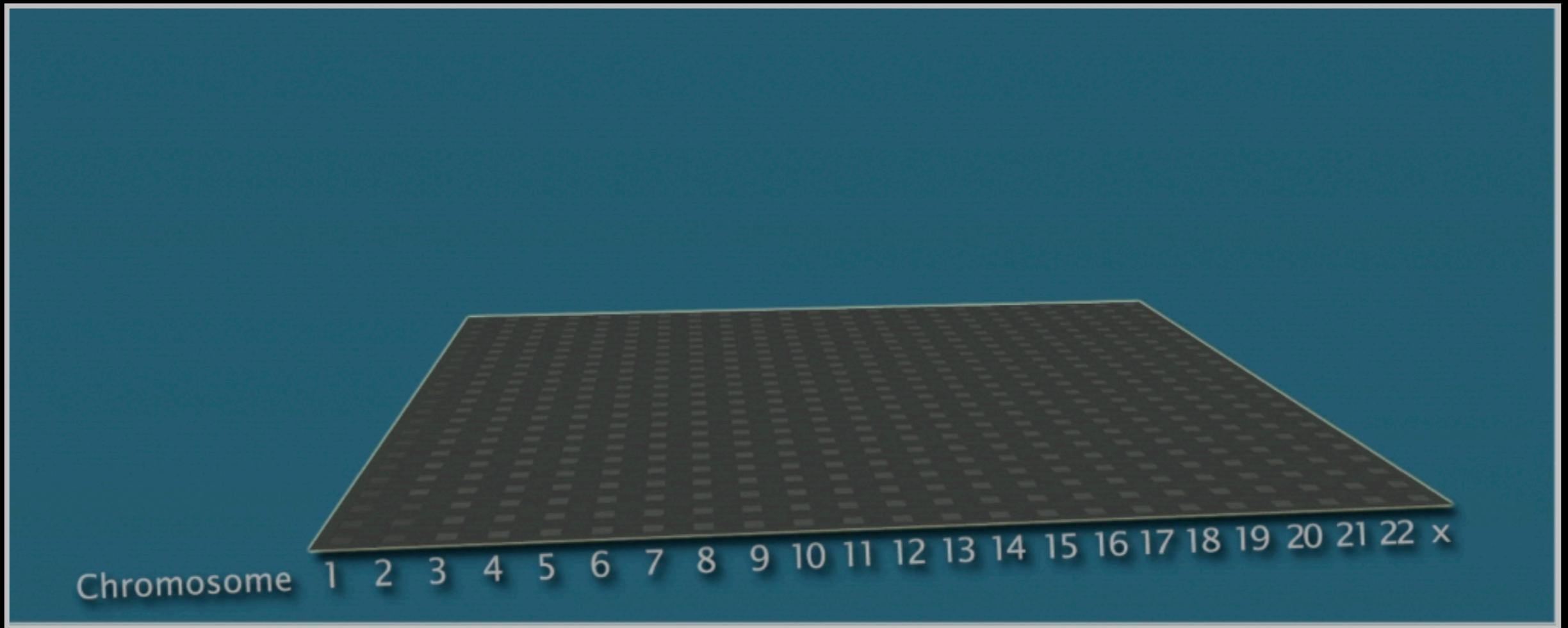






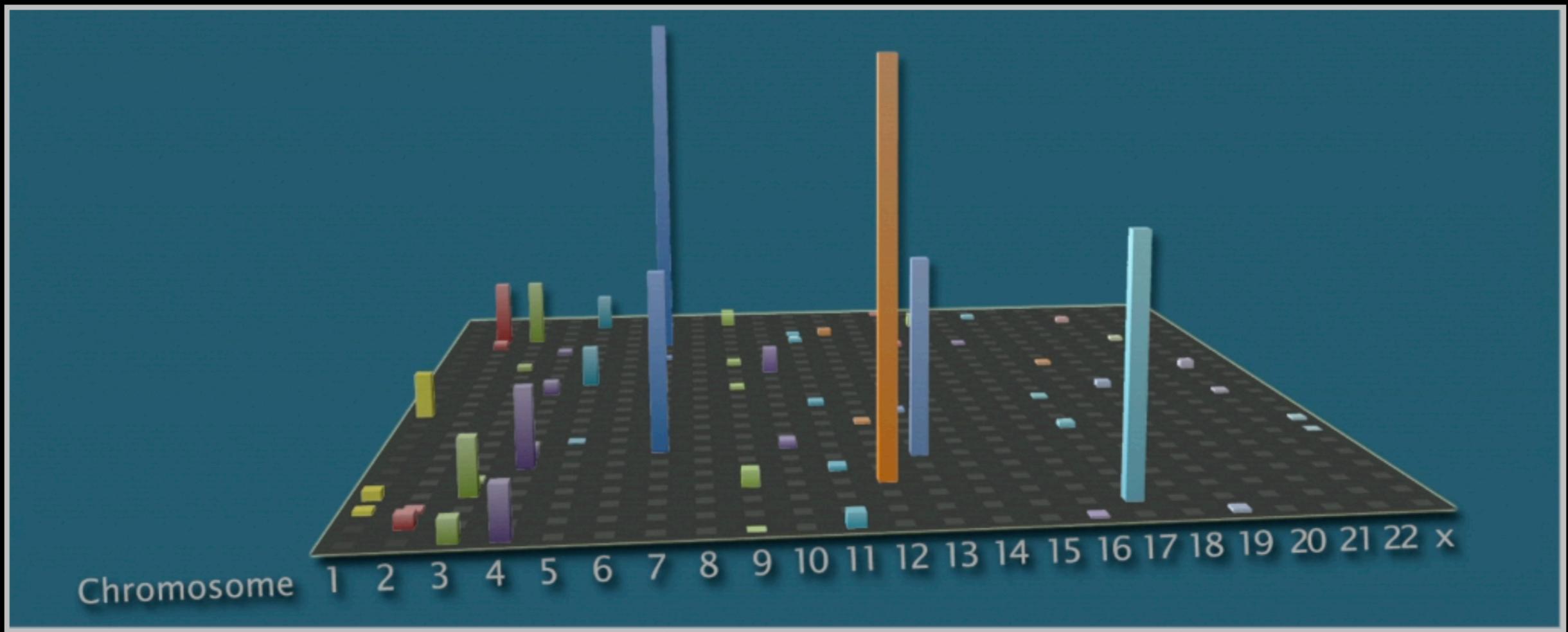
Vogelstein et al.
Science (2013)

Genomic approaches can identify the genes most commonly mutated in cancer



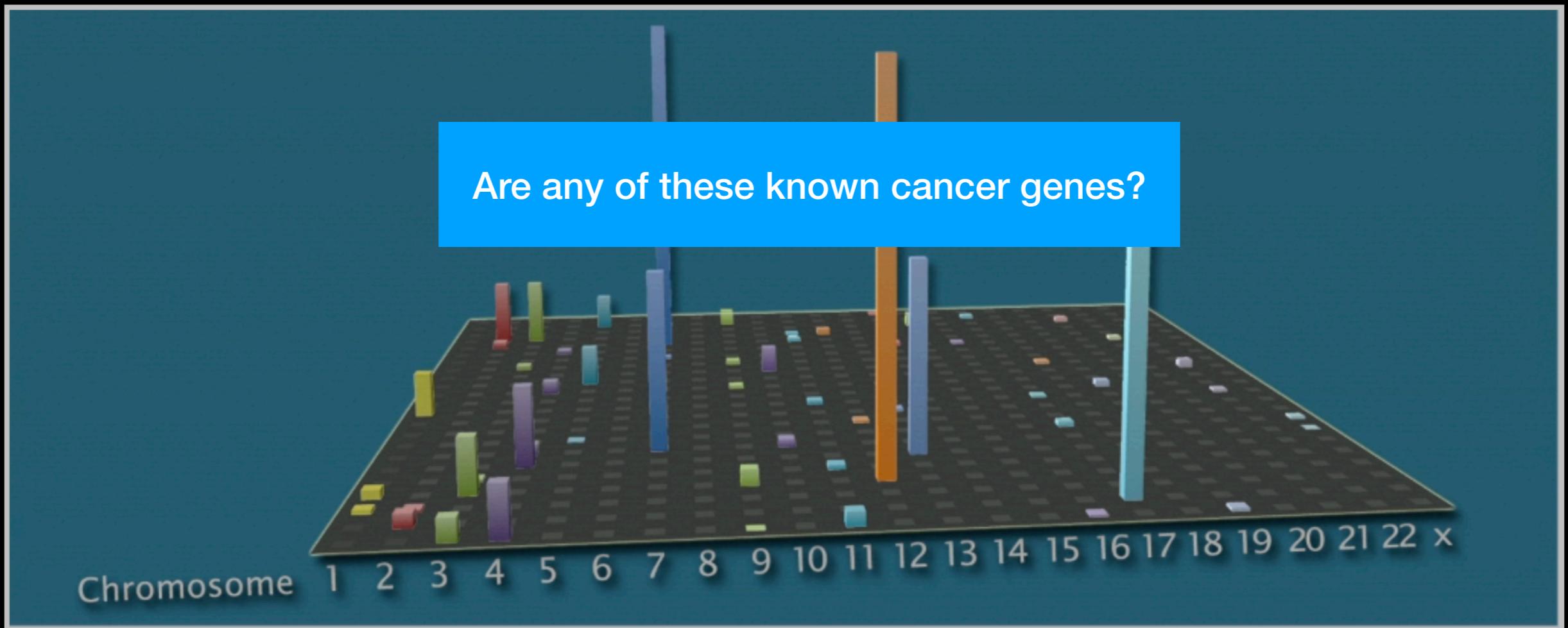
Arrange all genes in a matrix, ordered by chromosomes

Identifying genes most commonly mutated in cancer



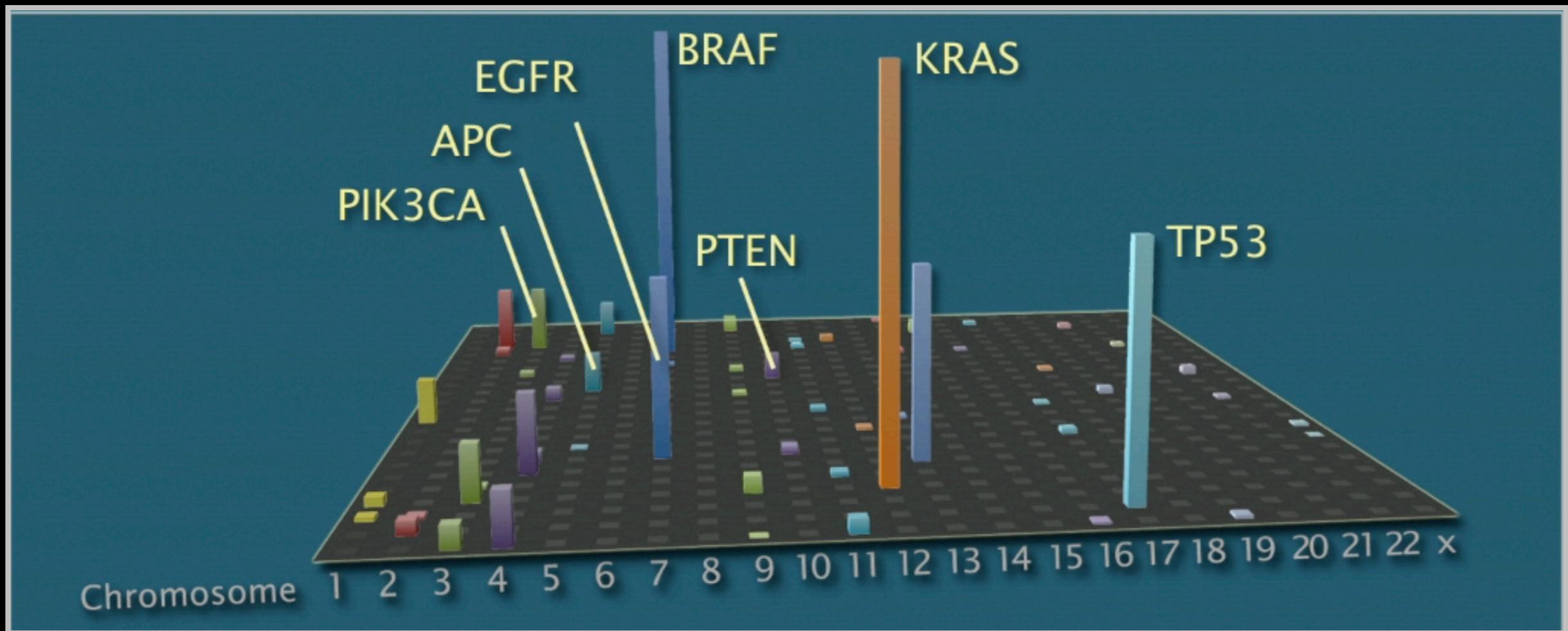
Add all data together to see which genes are most often mutated

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



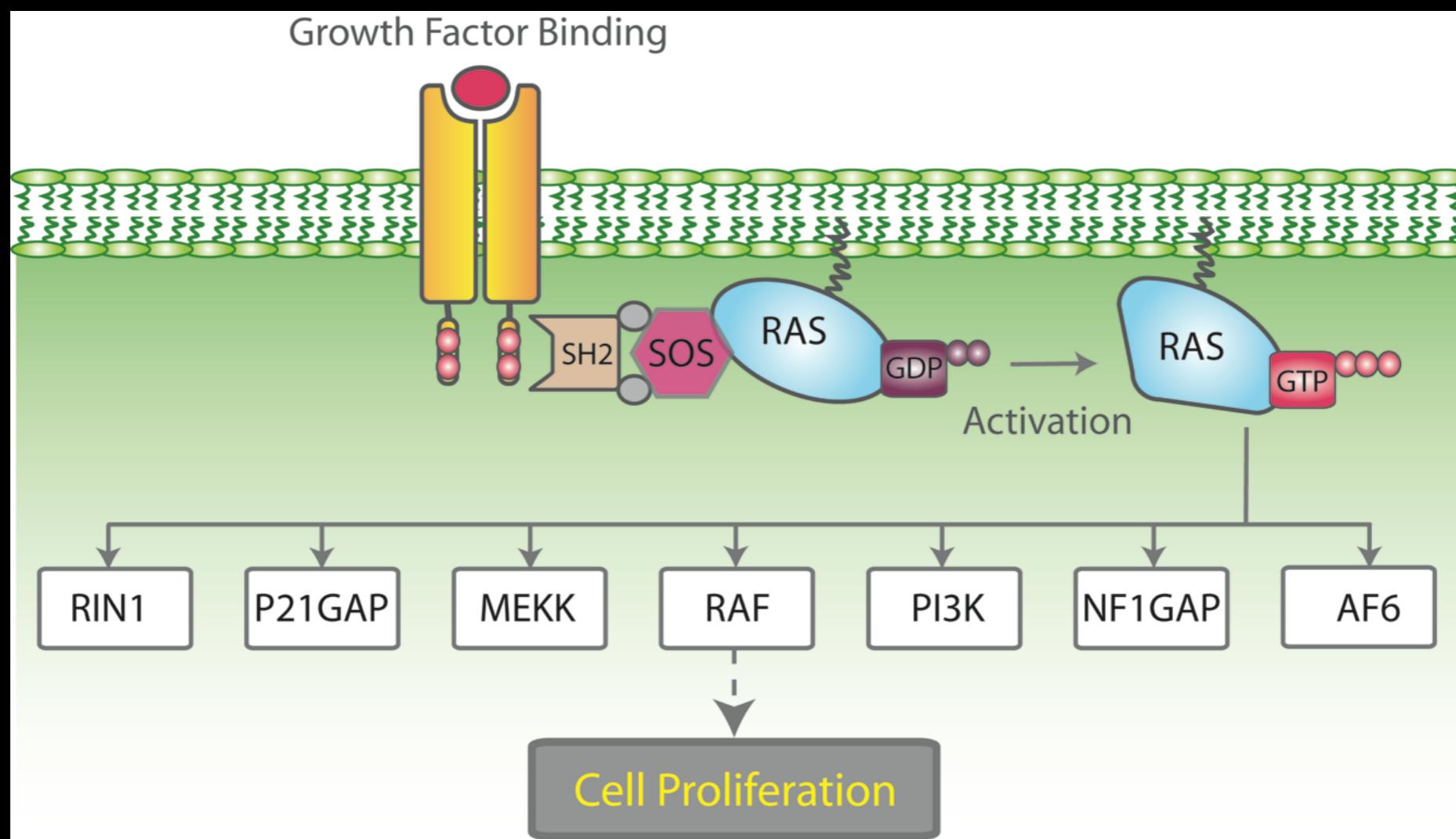
Many are famous proto-oncogenes, many others are new cancer genes!

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.

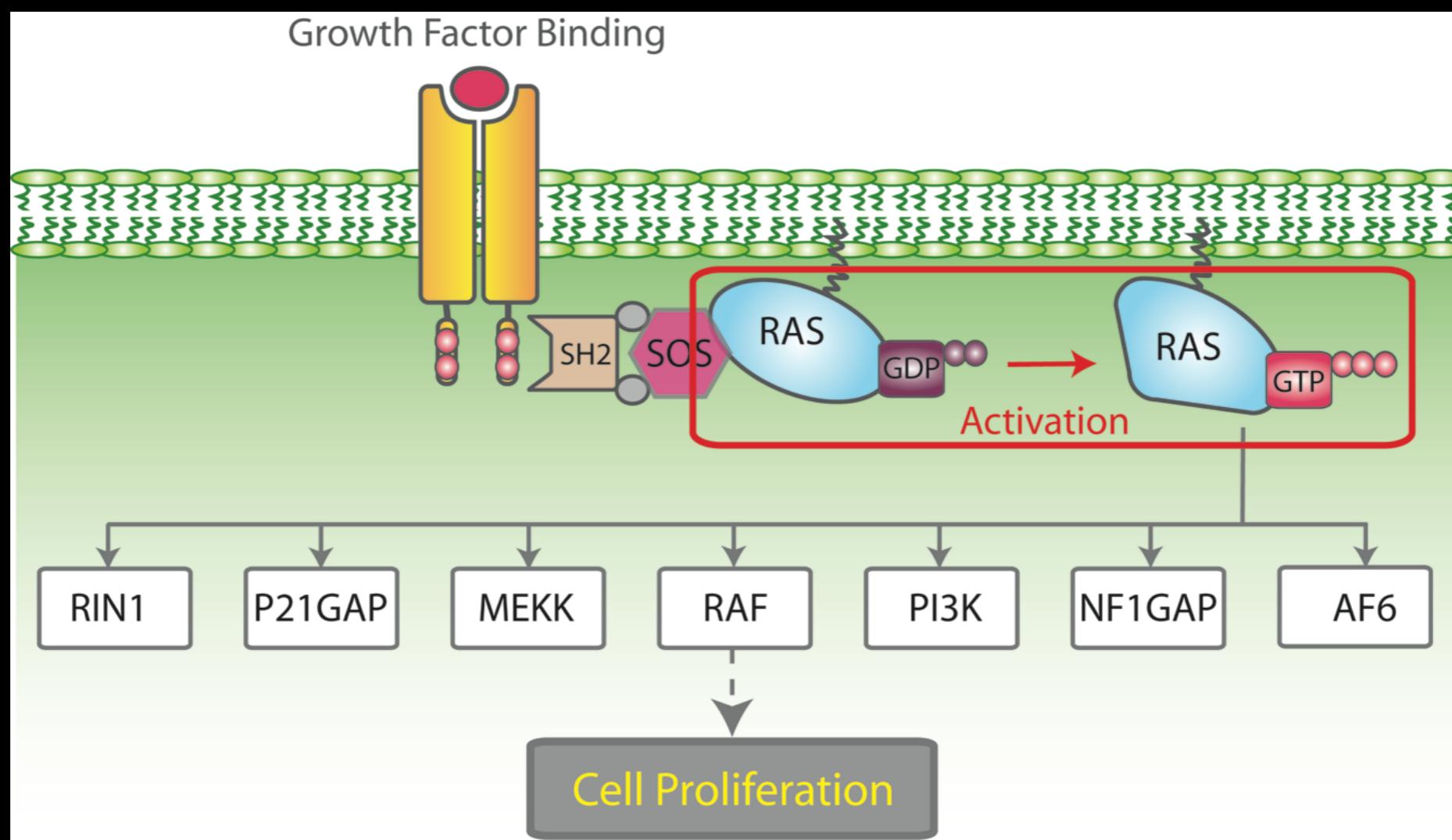
Cell growth and survival genes

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

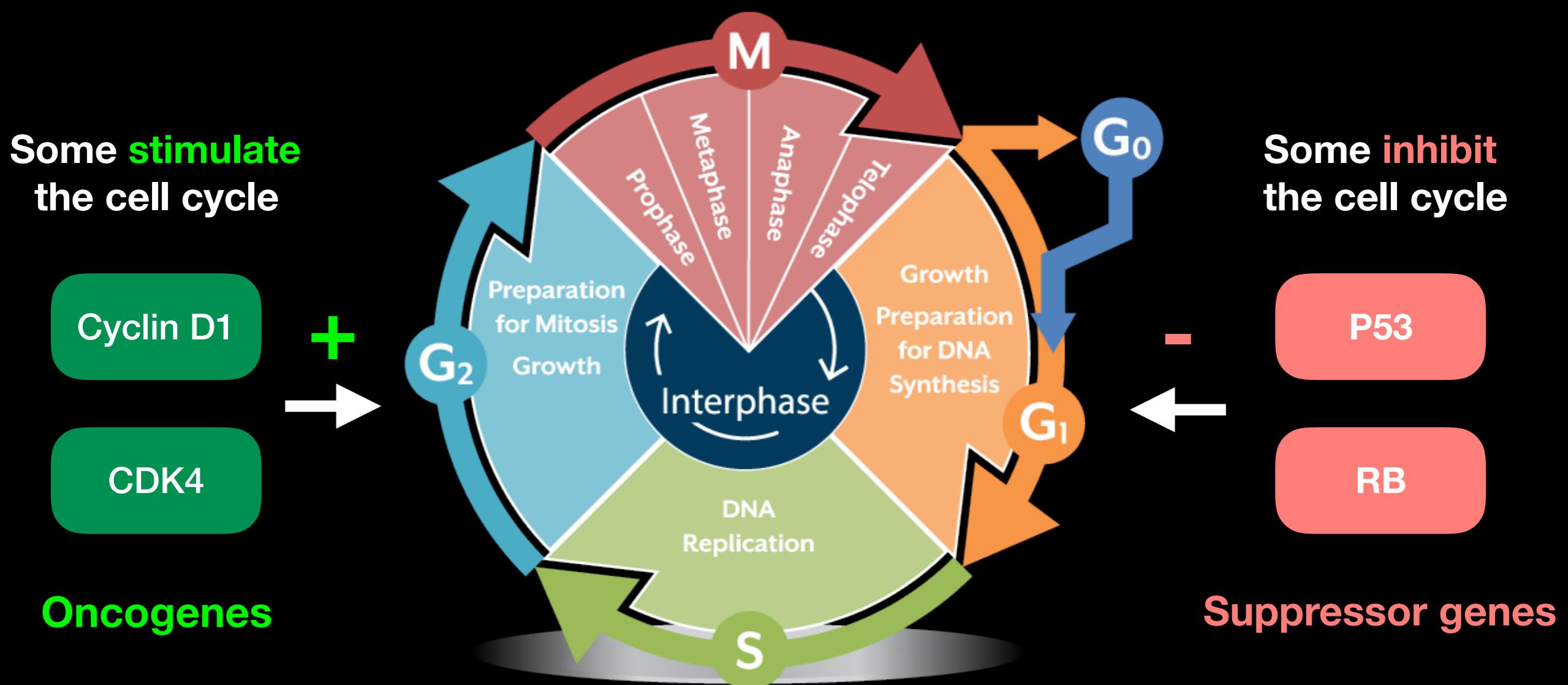


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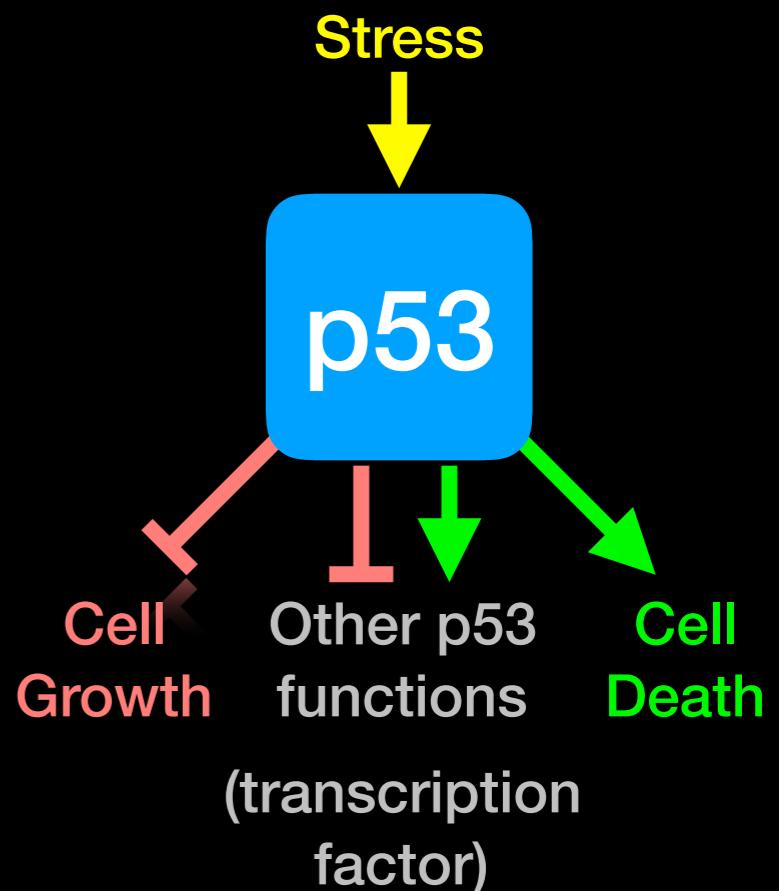
Regulators of Cell Cycle and Cell Death



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.

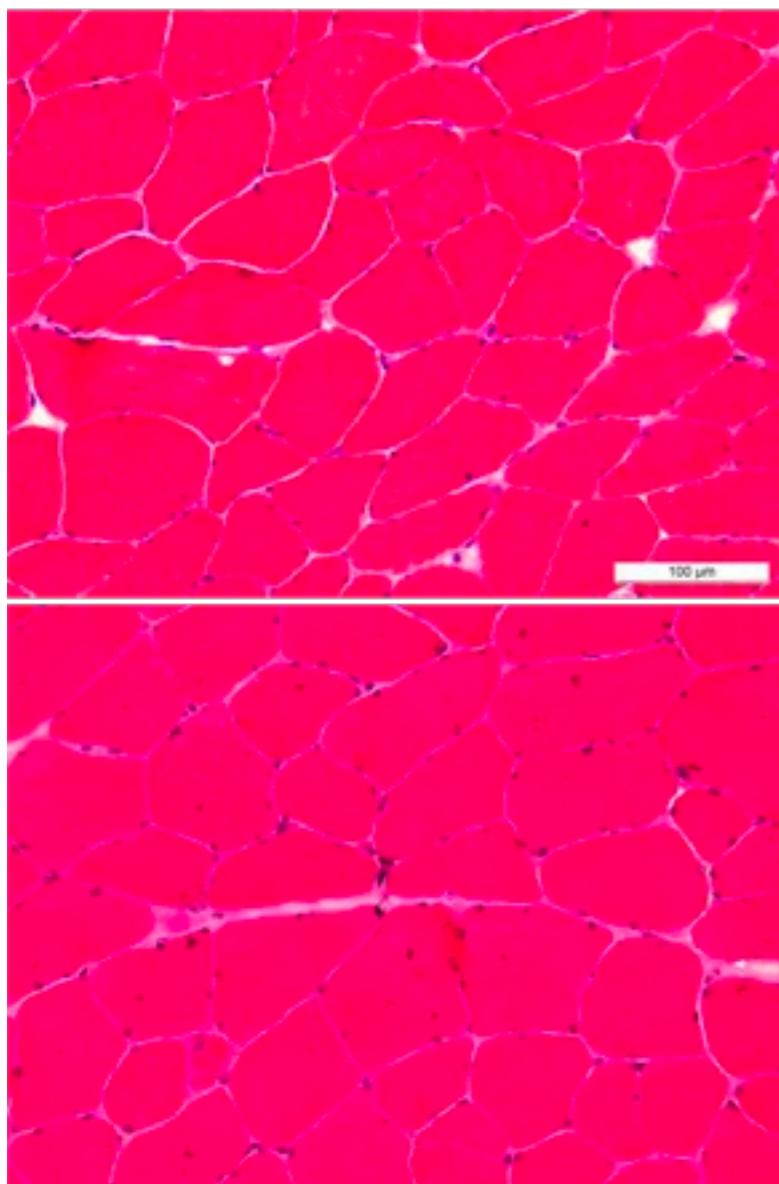


Hands-on time!

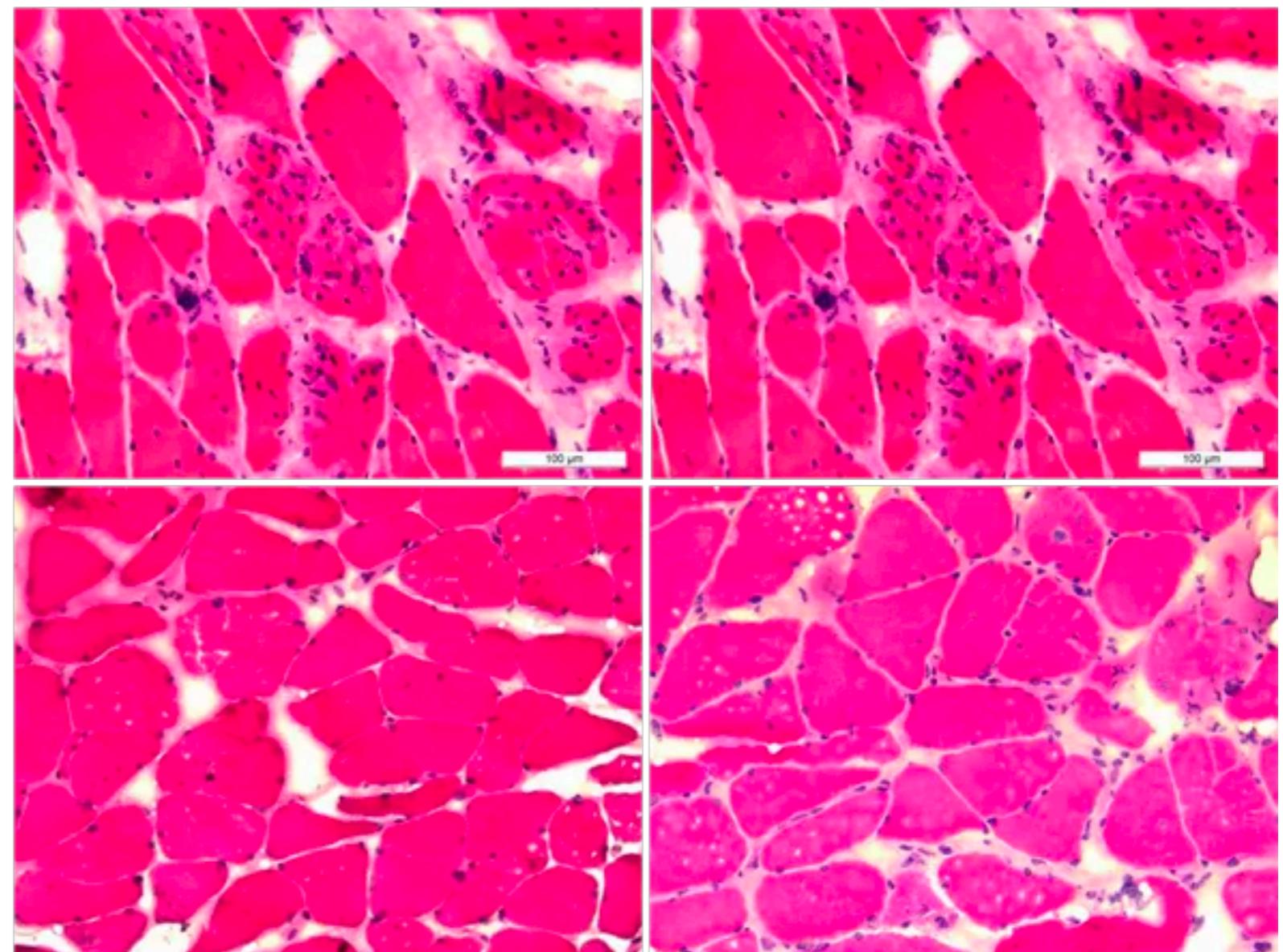
https://bioboot.github.io/bggn213_W19/lectures/#17

Part 1 Only Please

Control



Pancreatic Cancer



Representative H&E micrographs of rectus abdominis biopsies are displayed for two patients without cancer (*left*) and four patients with pancreatic cancer (*right*)

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Genomic Data

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Recap on how the immune system normally detects cancer cells and how we can predict mutations that can be recognized by T cells

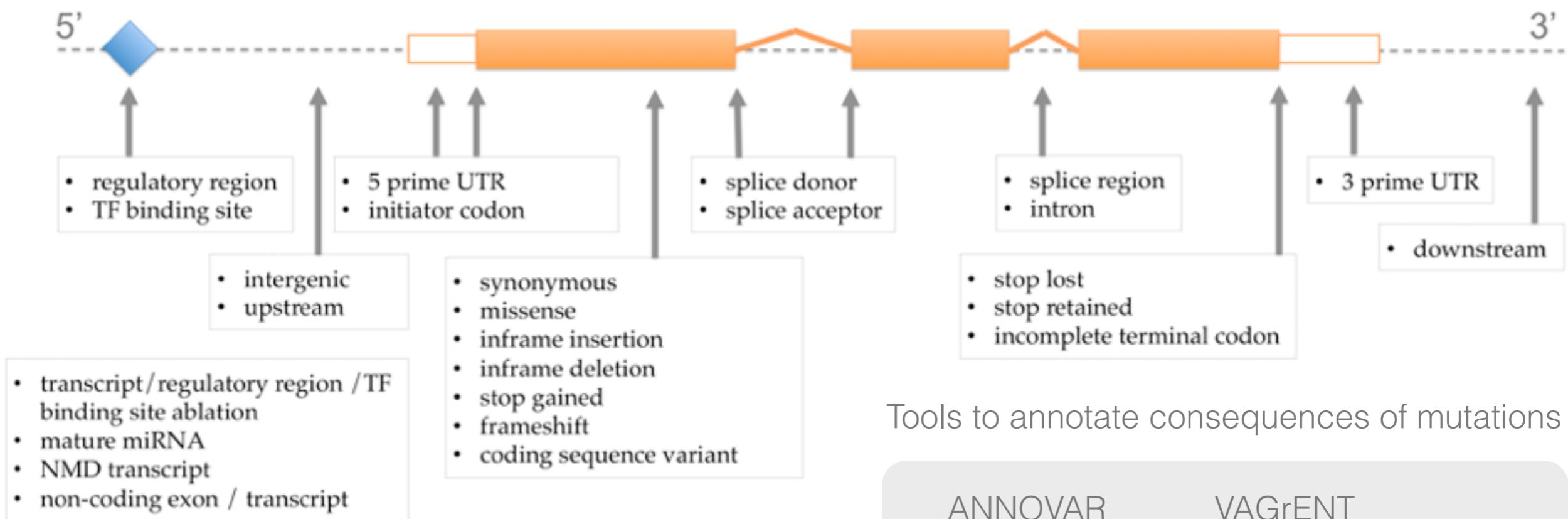
Cancer
Immunoinformatics

Hands-on analysis to design personalized cancer vaccines

1. Predict consequences of mutations

ACTGCCTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATTGCTACTGCATCTCGGGTTAACTC
GACGTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTTTGTGCACCTCTGTACGCGCGAGTTGGCA
CTGTCGCCCTGTGTGCATGTGCACTGTCT**T**CGCTGCACTGCTACGTCTACCGTCGACTTCAAATCG**C**TT
AACCCGTACTCCCATTGCTACTGCATCTCGGGTTAACTCGACGTTT**G**CATGCATGTGTGCACCCCAATATATA
TGCA**A**CTTTGTGCACCTCTGTACGCGCGAGTTGGCACTGTGCCCTGTGTGCATGTGCACTGTCT**TC**GA

Map mutations into genome annotations to predict its possible effect



Tools to annotate consequences of mutations

ANNOVAR

VAGrENT

Ensembl VEP

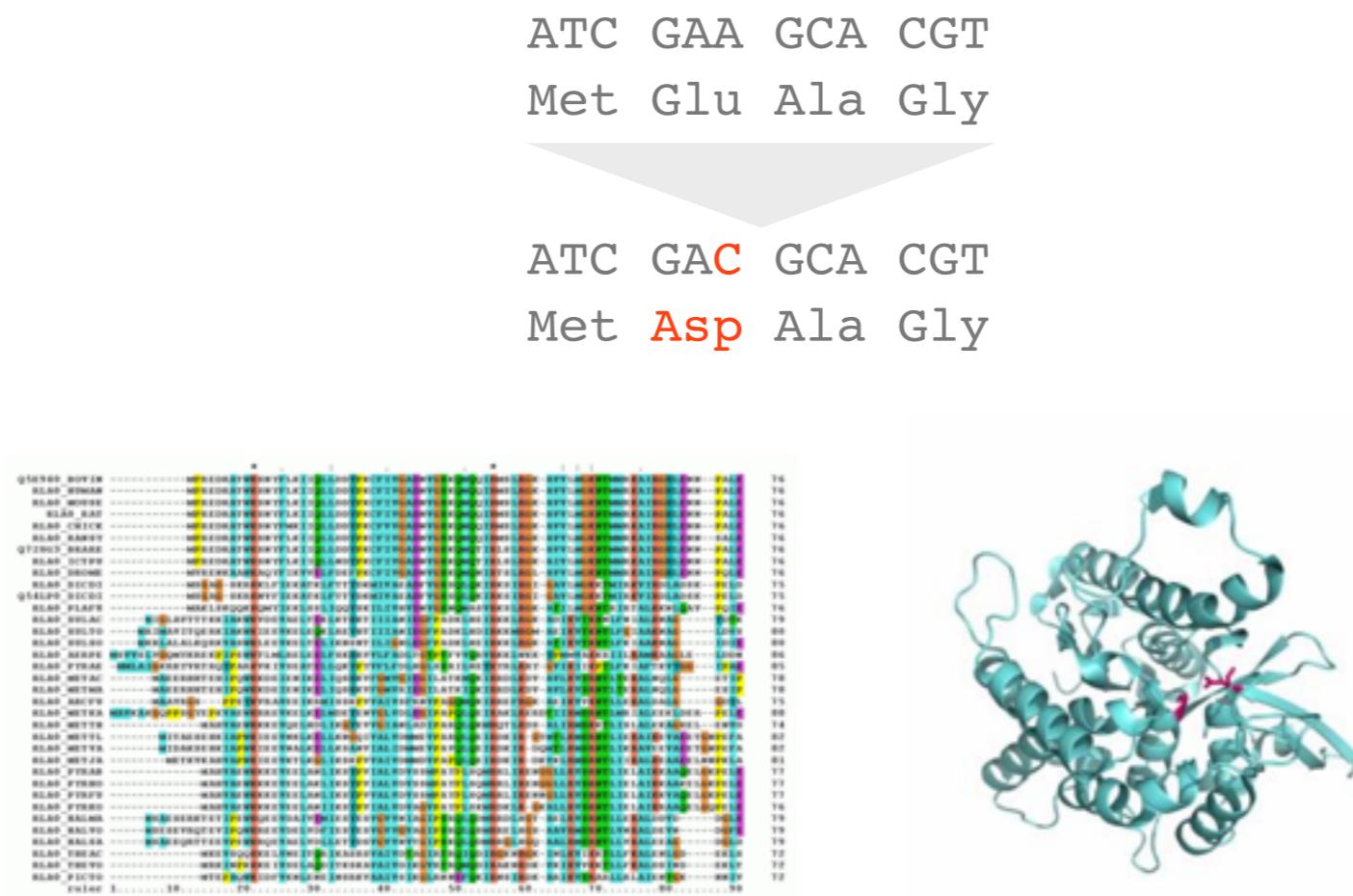
ASOoVIR

snpEff

annTools

2. Assess the functional impact of nsSNVs

nsSNVs = non-synonymous Single Nucleotide Variant (missense)



Computational methods to assess the functional impact of nsSNVs

MutationTaster

LogRe

MutPred

SNPs&GO

CanPredict

Condel

CHASM

SNPeffect

SIFT

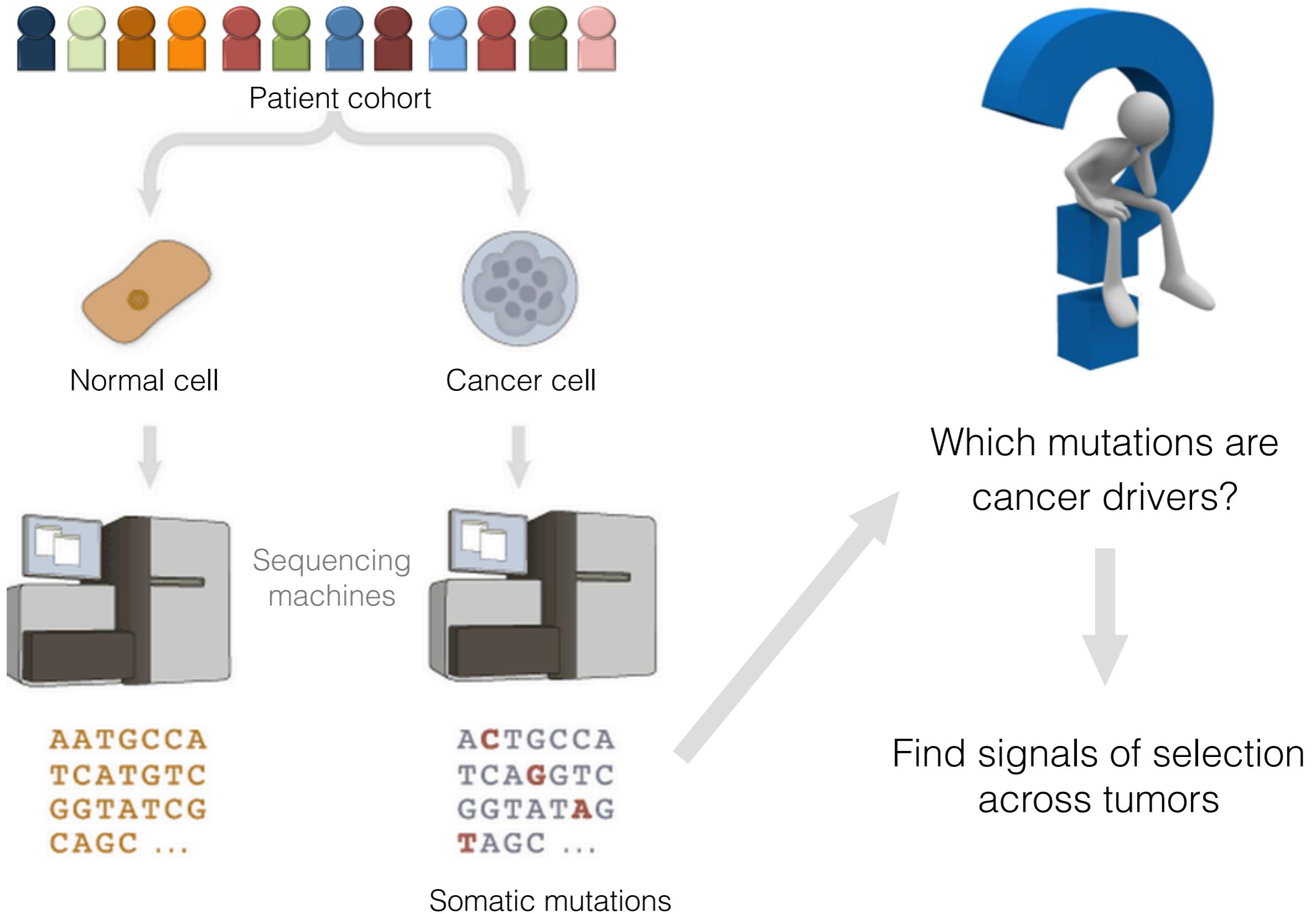
PolyPhen2

MutationAssessor

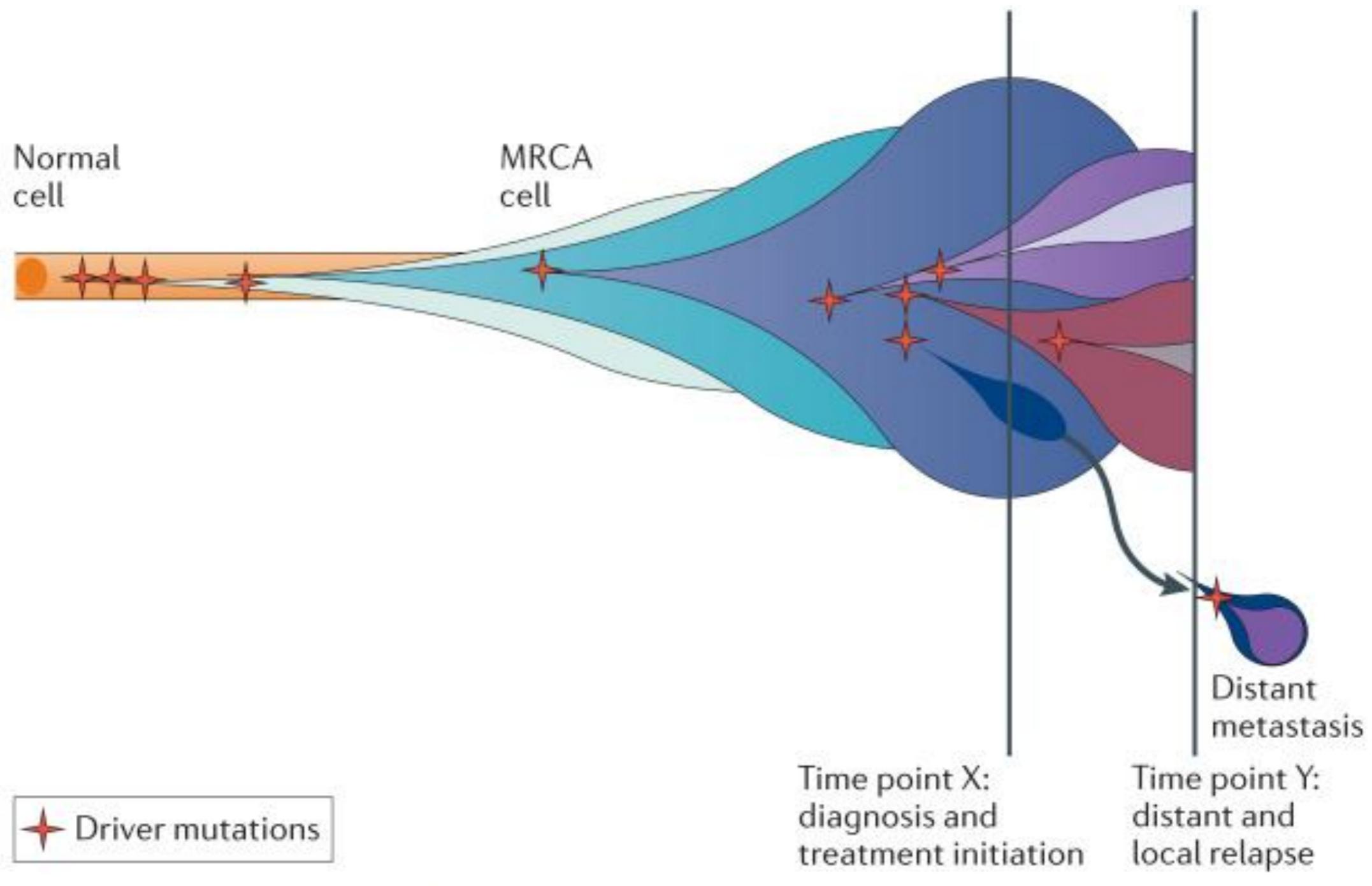
PMut

transFIC

3. Identify cancer drivers from somatic mutations



Cancer is an evolutionary process



How to differentiate drivers from passengers?

ACTG**C**TACGTCTACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATTGCTACTGC
ATCTCGGGTTAACTCGACGTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTT
TTGTGCACCTCTGTCACGCGAGTTGGCACTGTGCCCTGTGTGCATGTGCACTGT
CTC**T**CGCTGCACTGCCCTACGTCTACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCC
ATGCTACTGCATCTCGGGTTAACTCGACGTTT**G**CATGCATGTGTGCACCCCAATATA
TATGCA**A**CTTTGTGCACCTCTGTCACGCGAGTTGGCACTGTGCCCTGTGTGCA
TGTGCACTGTCT**T**CGAGTTT**G**CATGCATGTGTGCACTGTGCACCTCTGTTACGTCT

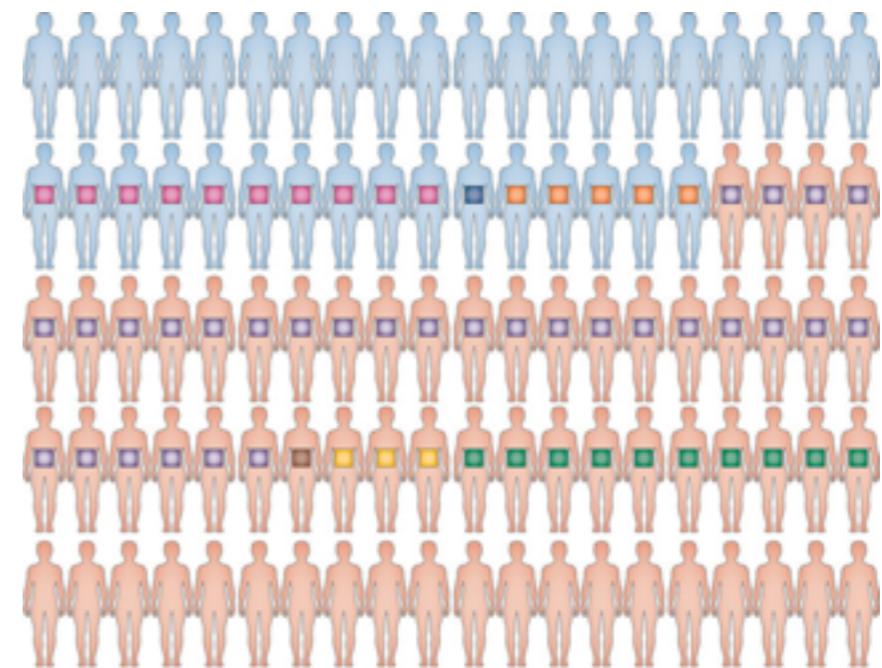


How to differentiate drivers from passengers?

```
ACTGCCTACGTCTACCGTCGACTTCAAATCGCTTAACCCGTACTCCCATGCTACTGC  
ATCTCGGGTTAACTCGACGTTTTCATGCATGTGTGCACCCCAATATATATGCAACTT  
TTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTGCCCTGTGTGCATGTGCACTGT  
CTCTCGCTGCACTGCCTACGTCTACCGTCGACTTCAAATCGCTTAACCCGTACTCCC  
ATGCTACTGCATCTCGGGTTAACTCGACGTTTGCATGCATGTGTGCACCCCAATATA  
TATGCAACTTTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTGCCCTGTGTGCA  
TGTGCACTGTCTTCGAGTTTGCATGCATGTGTGCACTGTGCACCTCTGTTACGTCT
```



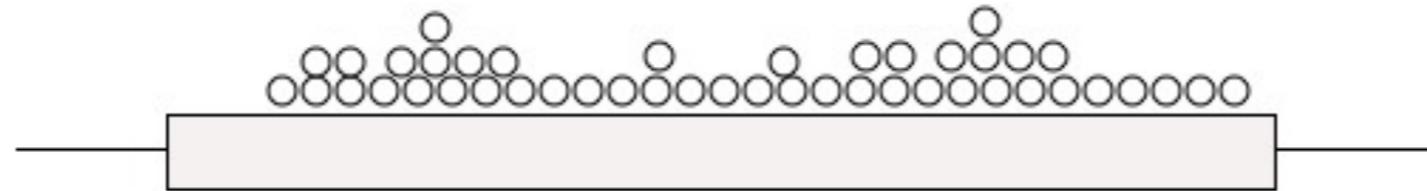
Find signals of positive selection across tumour re-sequenced genomes



Signals of positive selection

Recurrence

MuSiC-SMG / MutSigCV

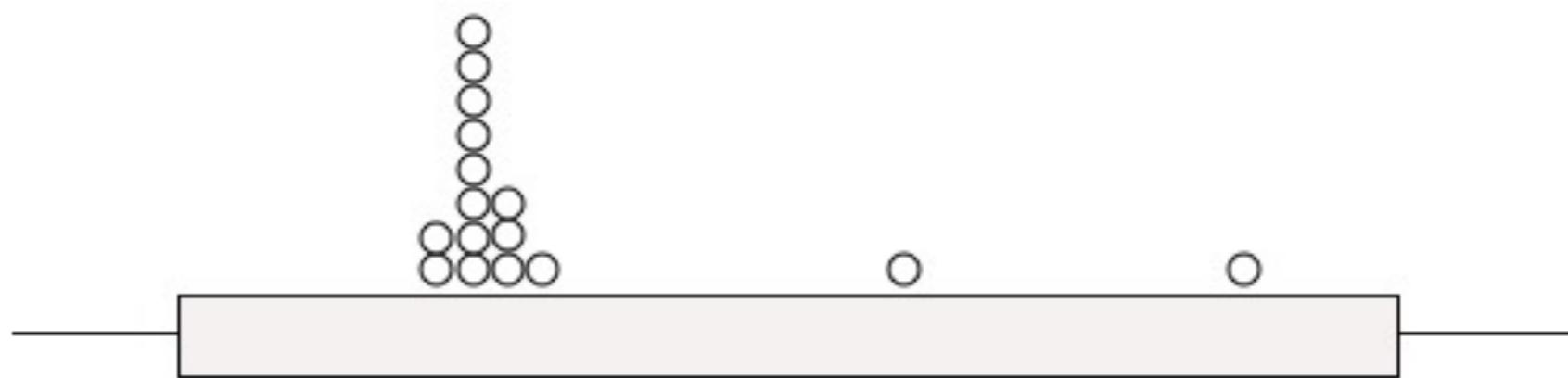


○ Mutation

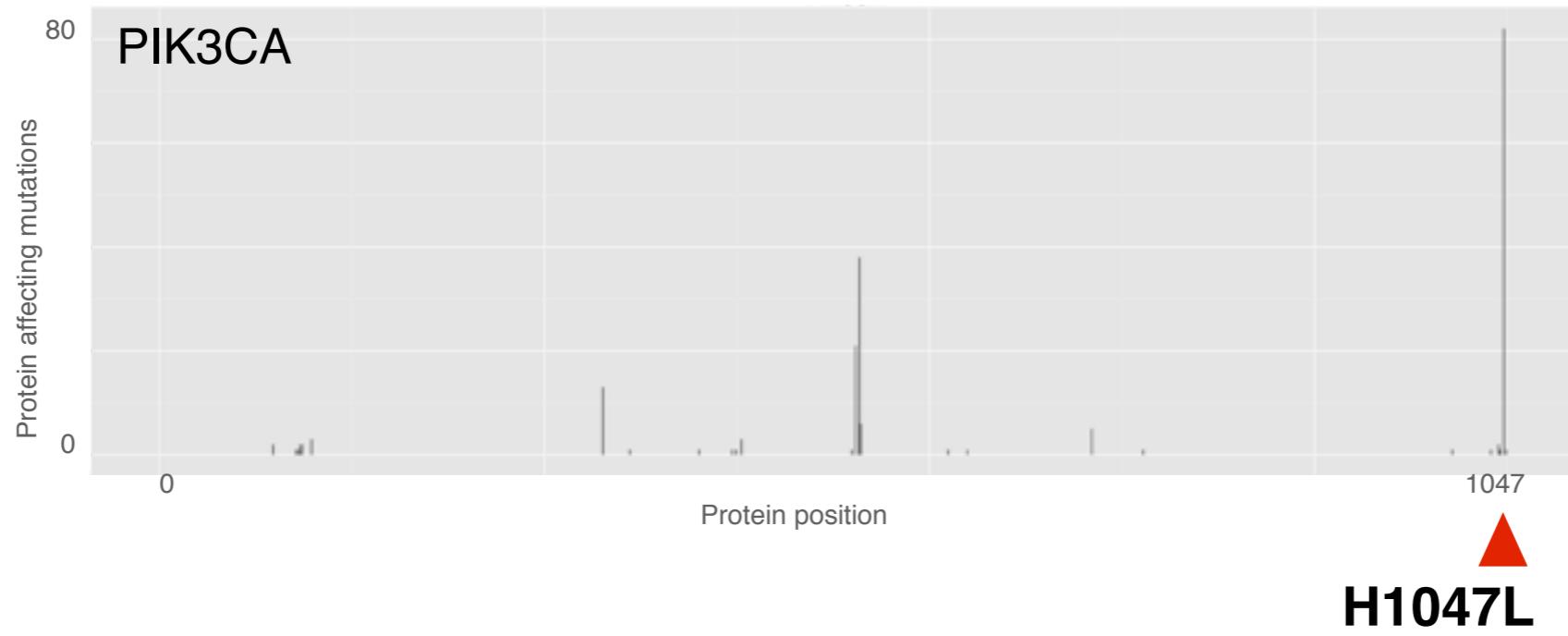
Identify genes mutated more frequently than background mutation rate

Mutation clustering

OncodriveCLUST



○ Mutation



PIK3CA is recurrently mutated in the same residue in breast tumours

<http://www.intogen.org/mutations/analysis>

IntOGen Mutations Analysis

 Download

To interpret catalogs of cancer somatic mutations.

Cohort analysis



Use this if you have a list of somatic mutations for a cohort of tumors and want to identify driver mutations, genes and pathways.

 [View an example](#)

 [Analyse your data](#)

Single tumor analysis



Use this if you have a list of somatic mutations for a single tumor and want to rank them based on their implication in cancer development.

 [View an example](#)

 [Analyse your data](#)