



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>

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

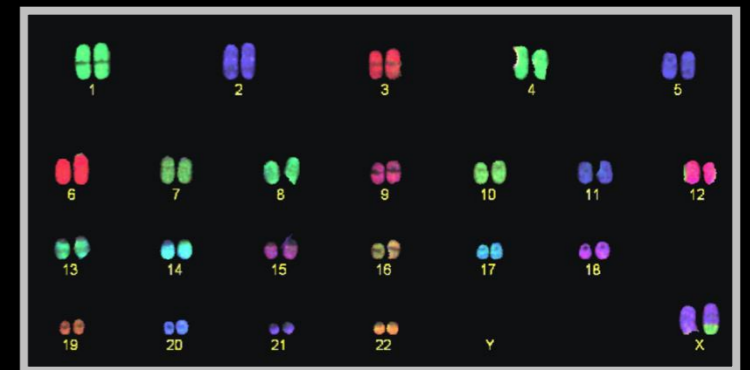
What is Cancer?

“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>

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

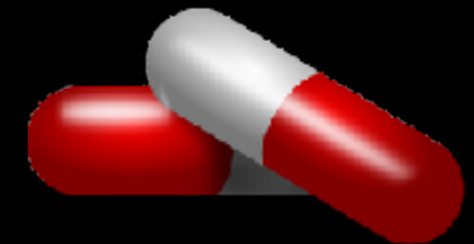


Motivation for adopting a genomics approach...

- Cancer is caused by mutations to specific genes

AGCT → AGAT

- Knowing which genes and proteins enables the development of **targeted treatments**



- 1st major Goal:
Define ALL cancer genes!

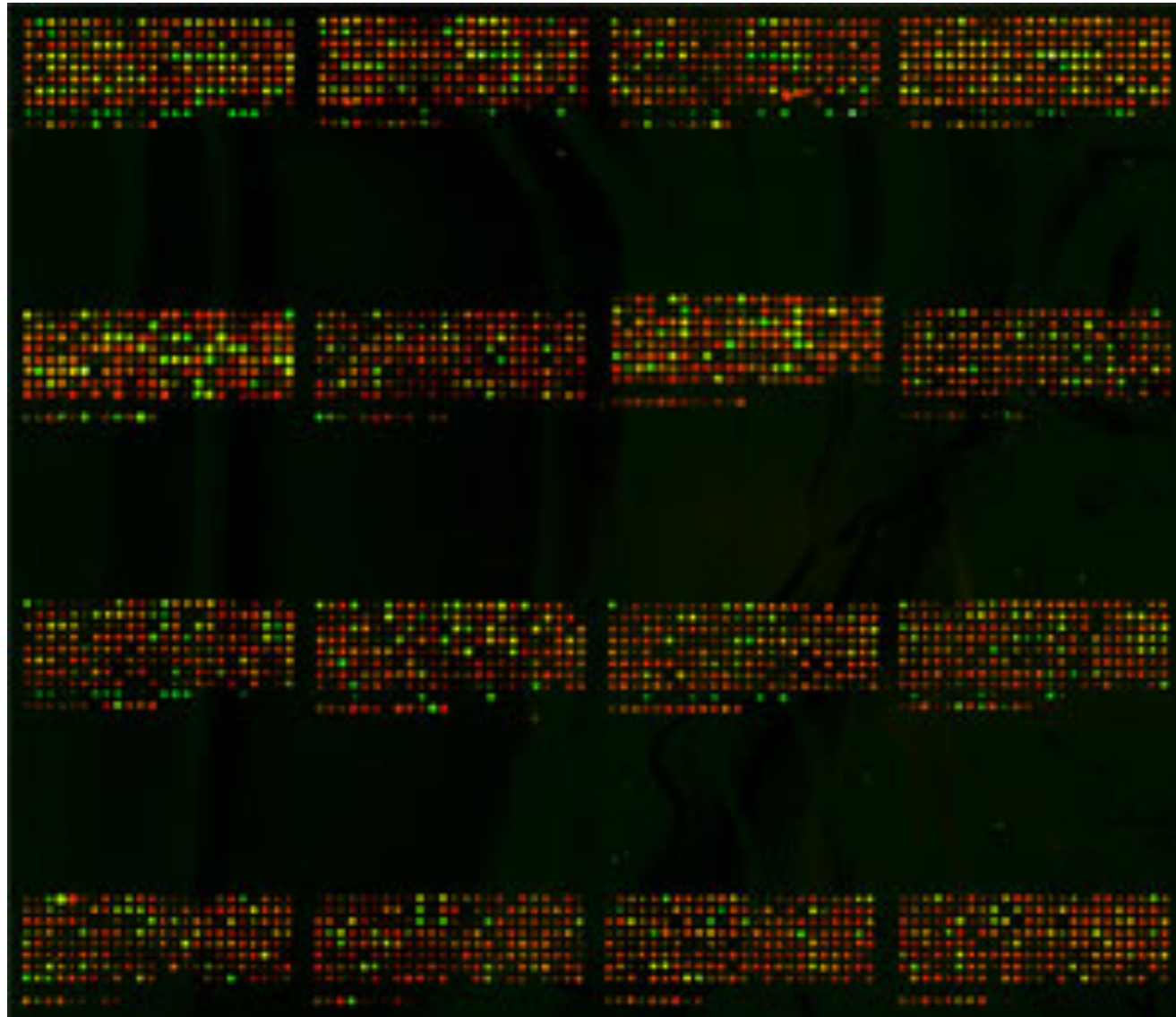


Use A Cancer Genomics Approach

Arrays

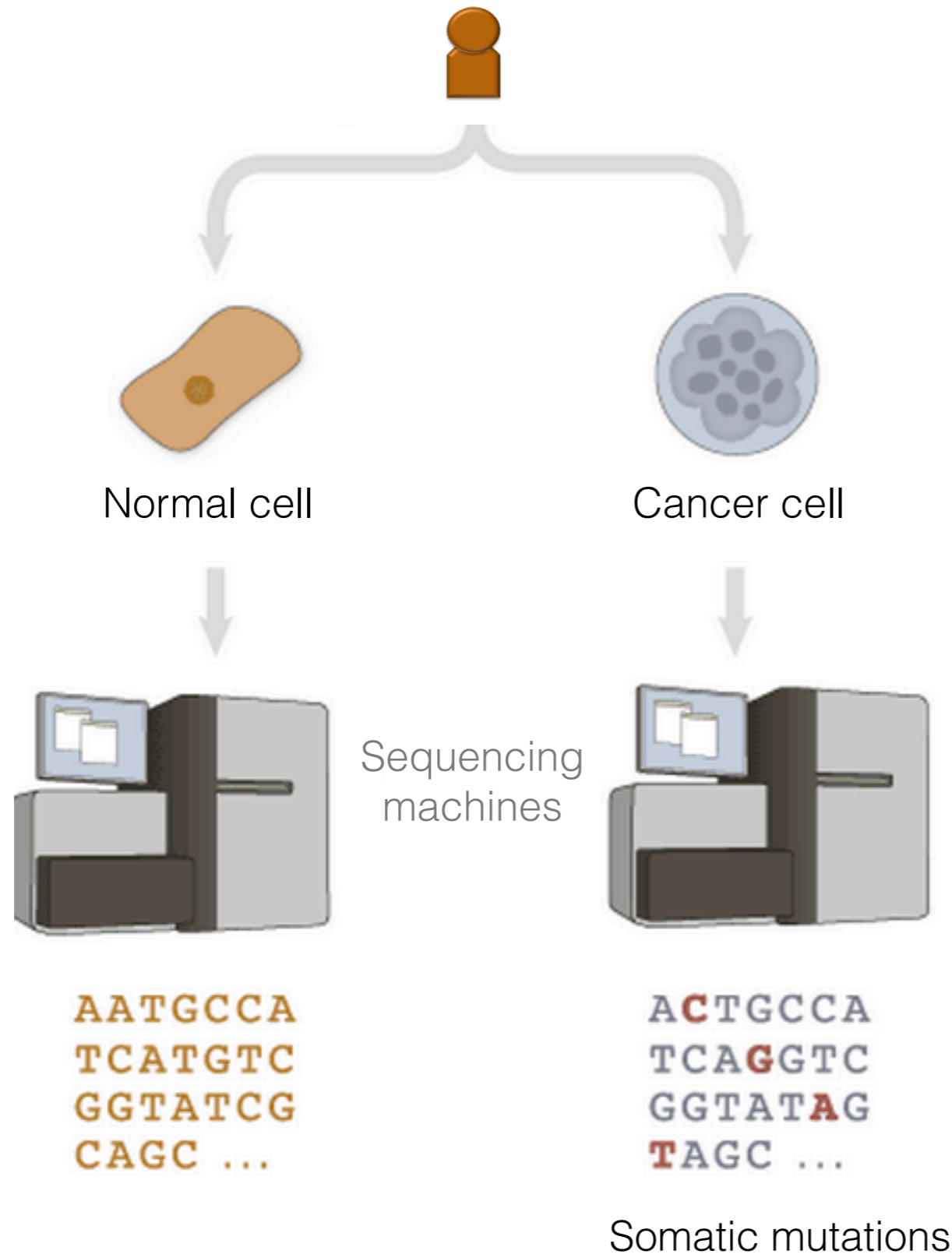


Parallel Sequencing



```
ACTCAGCCCCAGCGGAGGTGAAGGACGTCCTTCCCCAGGAGCCGGTGAGA
AGCGCAGTCGGGGGCACGGGGATGAGCTCAGGGGCCTCTAGAAAGATGTA
GCTGGGACCTCGGGAAGCCCTGGCCTCCAGGTAGTCTCAGGAGAGCTACT
CAGGGTTCGGGCTTGGGGAGAGGAGGAGCGGGGGTGAGGCCAGCAGCAGGG
GACTGGACCTGGGAAGGGCTGGGCAGCAGAGACGACCCGACCCGCTAGAA
GGTGGGGTGGGGAGAGCATGTGGACTAGGAGCTAAGCCACAGCAGGACCC
CCACGAGTTGTCACTGTCAATTTATCGAGCACCTACTGGGTGTCCCCAGTG
TCCTCAGATCTCCATAACTGGGAAGCCAGGGGCAGCGACACGGTAGCTAG
CCGTCGATTGGAGAACTTTAAAATGAGGACTGAATTAGCTCATAAATGGA
AAACGGCGCTTAAATGTGAGGTTAGAGCTTAGAATGTGAAGGGAGAATGA
GGAATGCGAGACTGGGACTGAGATGGAACCGGCGGTGGGGAGGGGGAGGG
GGTGTGGAATTTGAACCCCGGGAGAGAAAGATGGAATTTTGGCTATGGAG
GCCGACCTGGGGATGGGGAAATAAGAGAAGACCAGGAGGGAGTTAAATAG
GGAATGGGTTGGGGGCGGCTTGGTAACTGTTTGTGCTGGGATTAGGCTGT
TGCAGATAATGGAGCAAGGCTTGGAAAGGCTAACCTGGGGTGGGGCCGGGT
TGGGGTTCGGGCTGGGGGCGGGAGGAGTCCTCACTGGCGGTTGATTGACAG
TTTCTCCTTCCCCAGACTGGCCAATCACAGGCAGGAAGATGAAGGTTCTG
TGGGCTGCCCCGACCCGCTAGAAGGTGGGGTGGGGAGAGCATGTGGACTA
GGAGCTAAGCCACAGCAGGACCCCCACGAGTTGTCACTGTCAATTTATCGA
GCACCTACTGGGTGTCCCCAGTGTCTCAGATCTCCATAACTGGGAAGCC
AGGGGCAGCGAC
```

Finding Cancer Associated Mutations

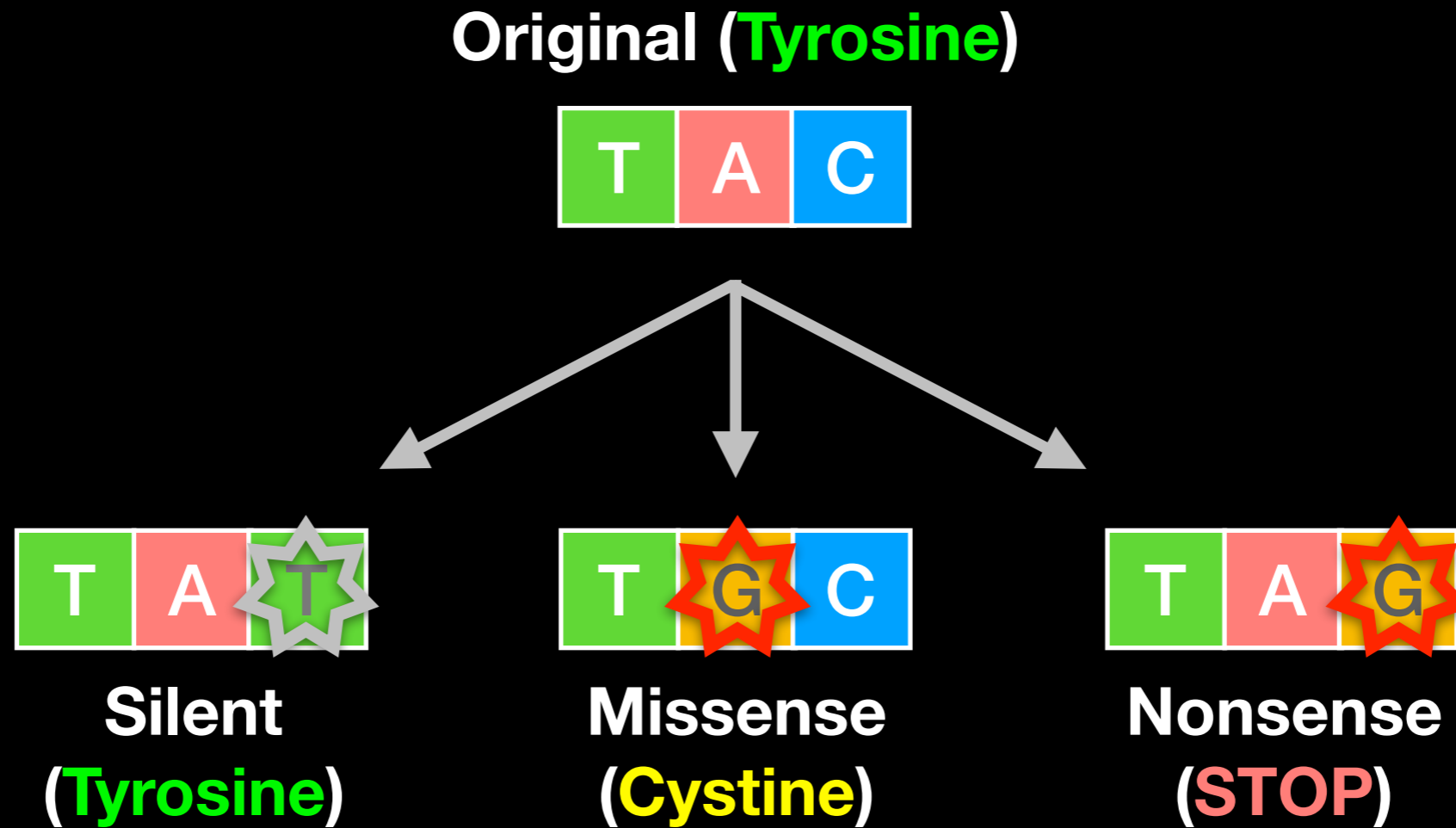


Identify all mutations specific to tumor cells

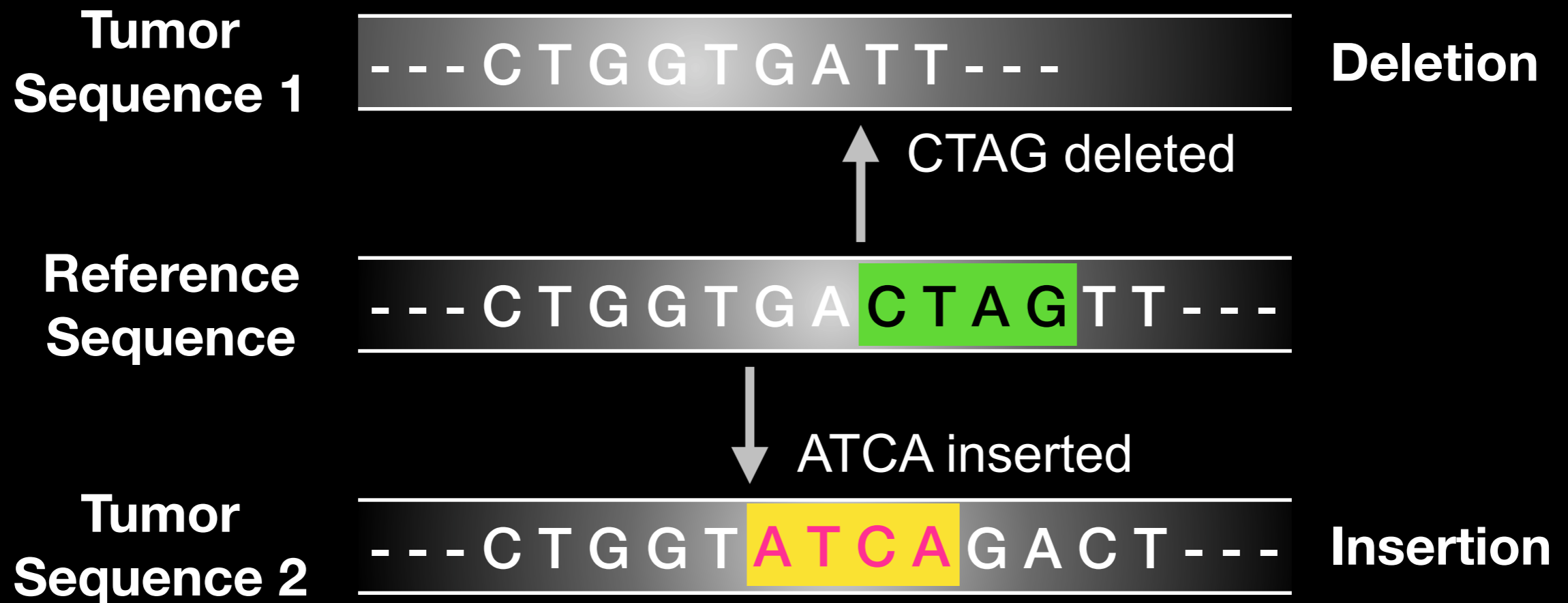


Filter out silent mutations

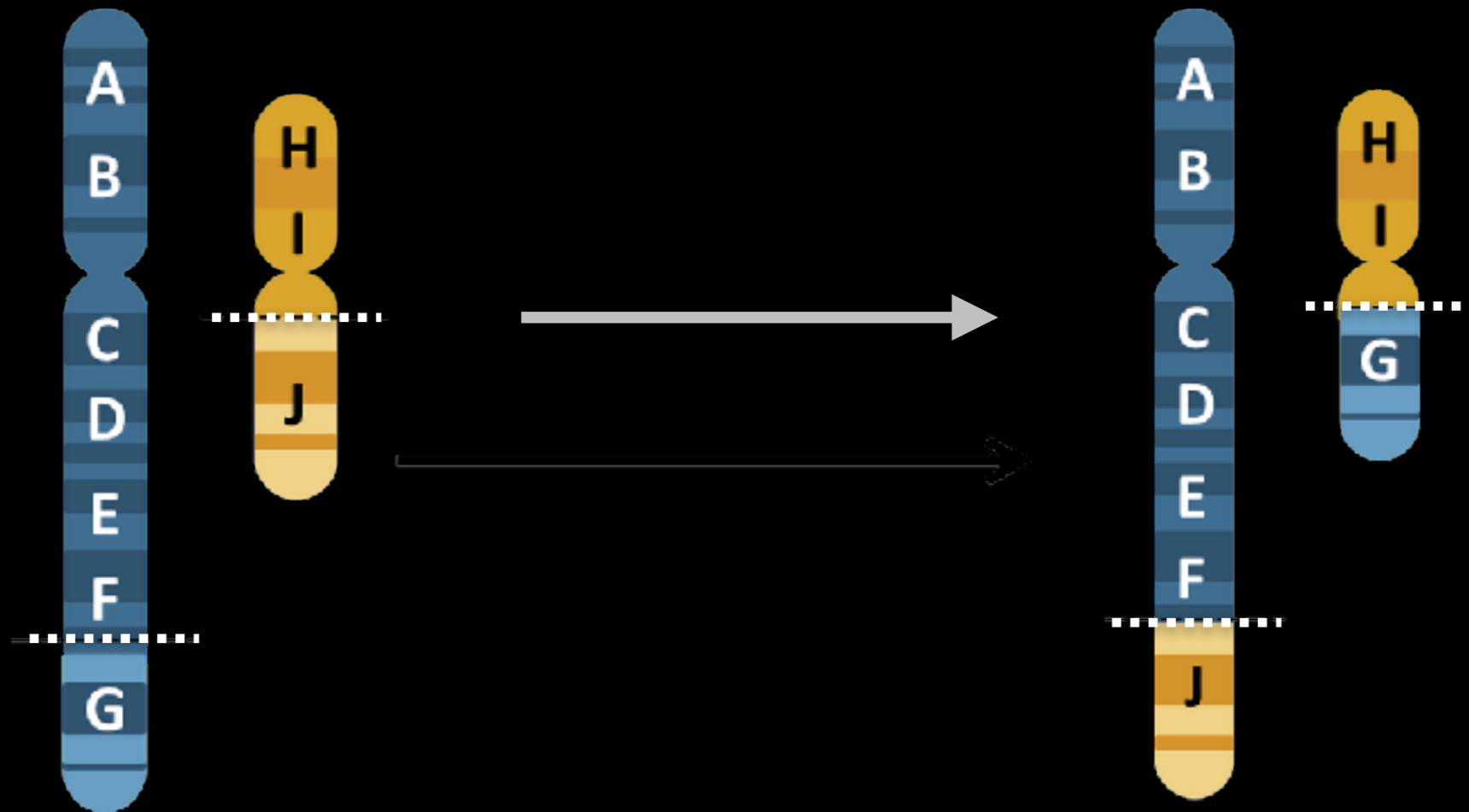
Mutations detected: Point mutations



Mutations detected: Indels



Mutations detected: Translocations



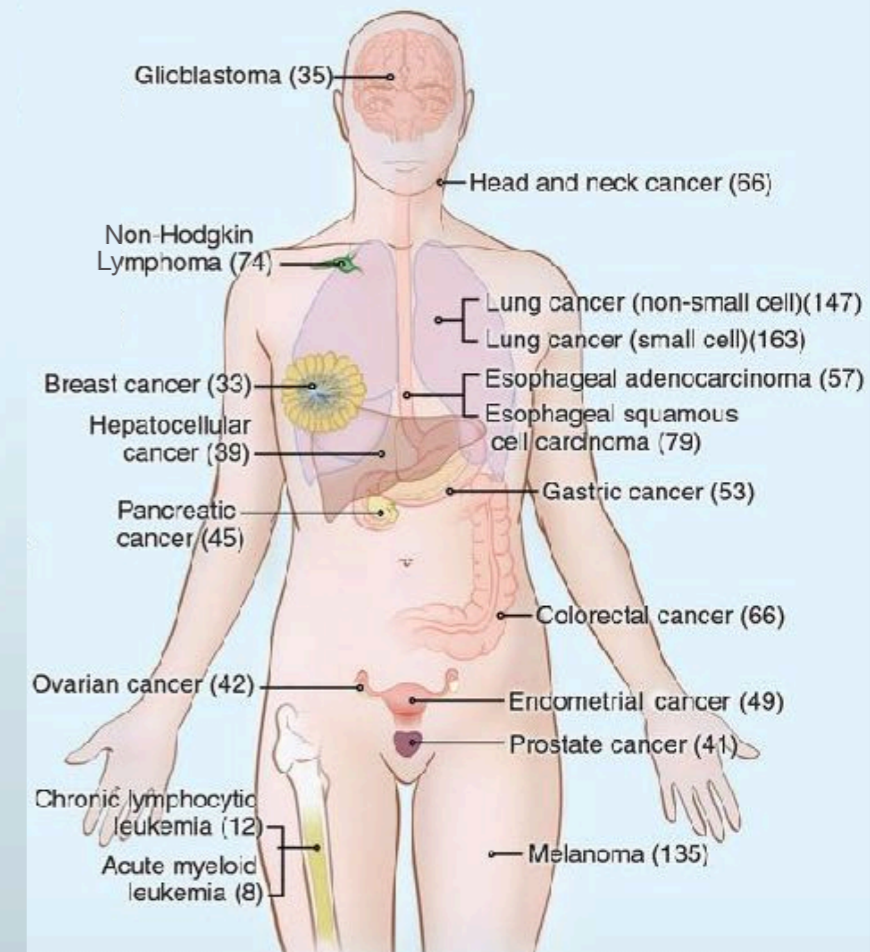
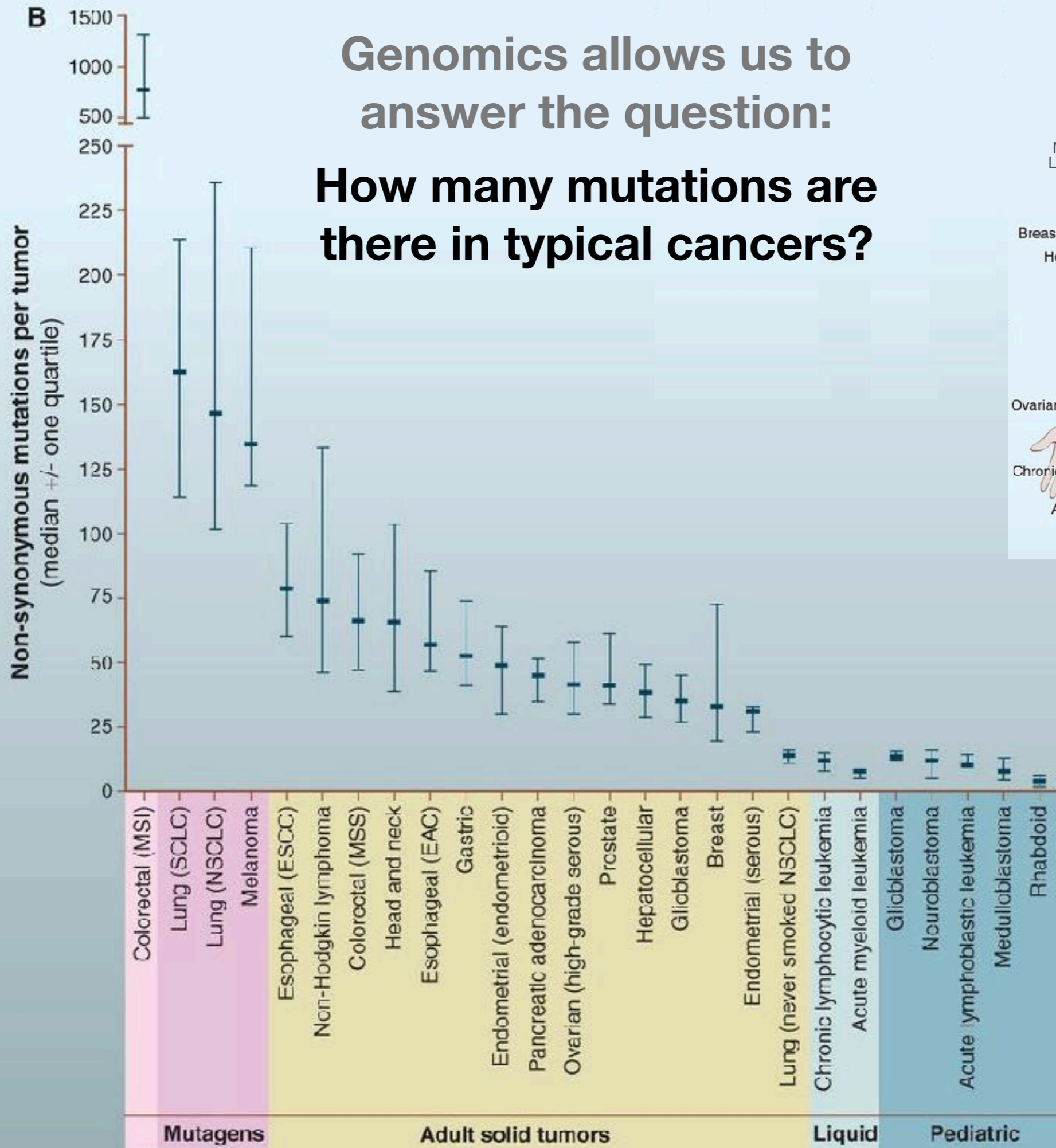
What can go wrong in cancer genomes?

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

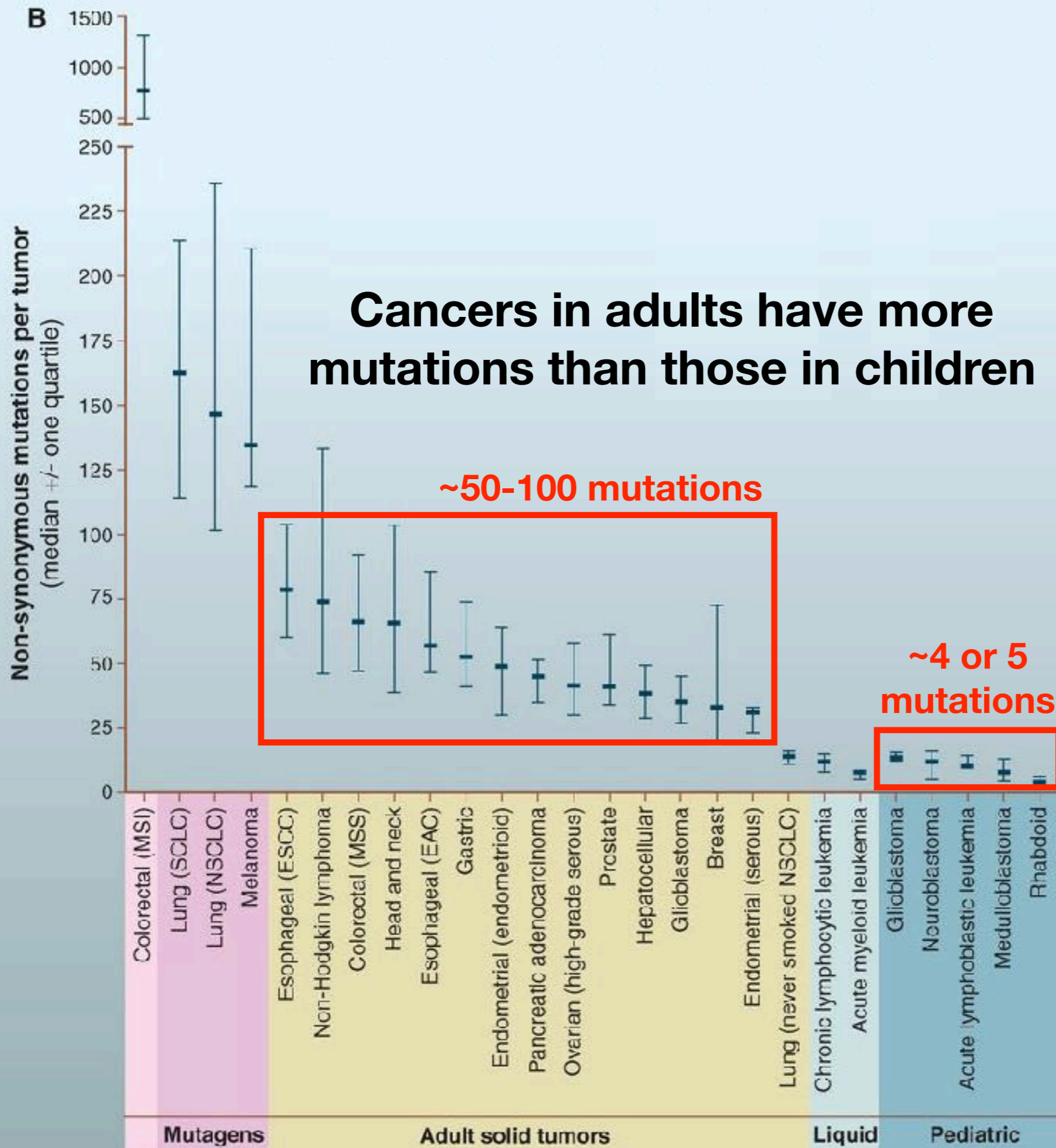
RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

Genomics allows us to answer the question: How many mutations are there in typical cancers?

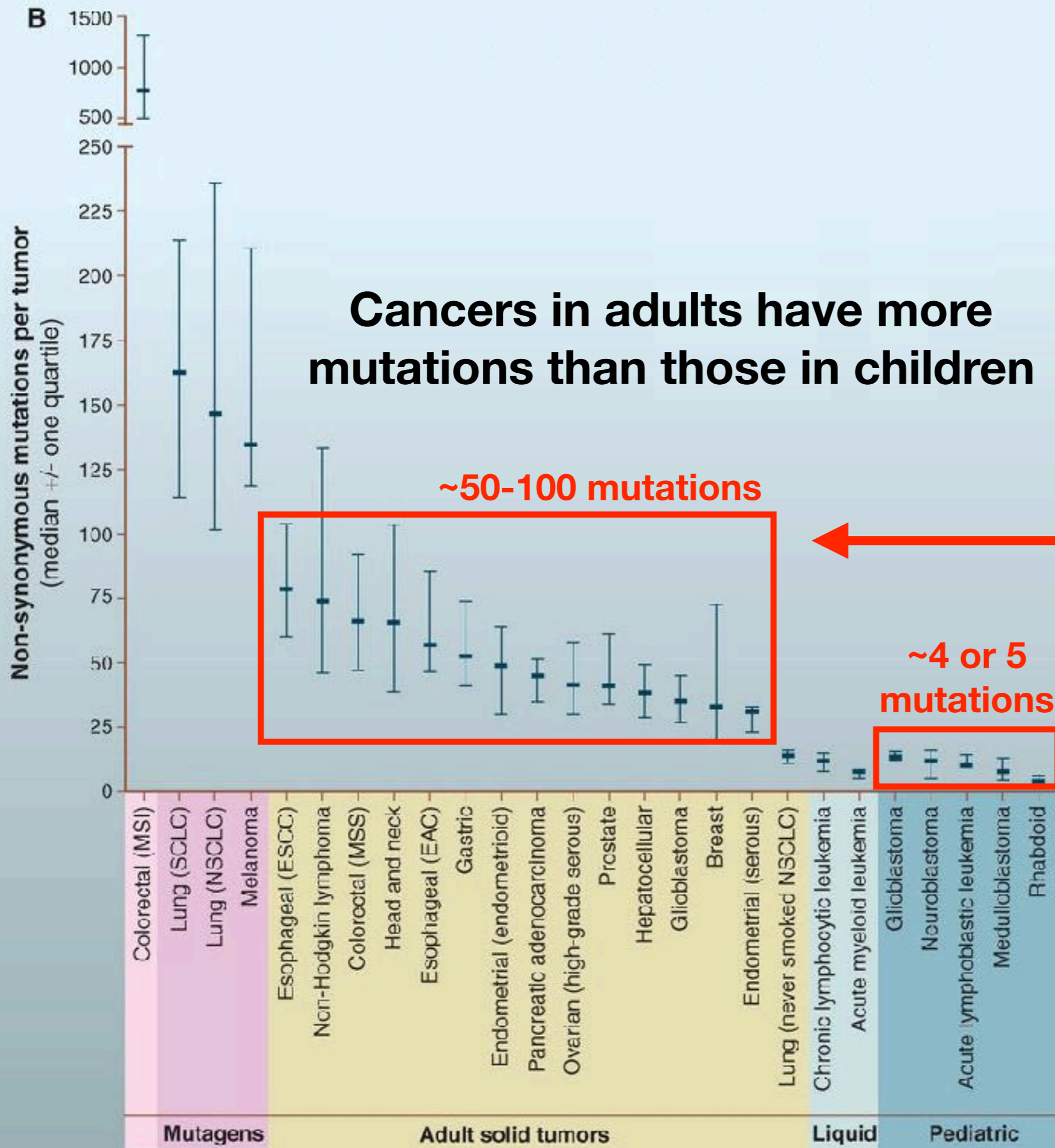


Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al. Science (2013)

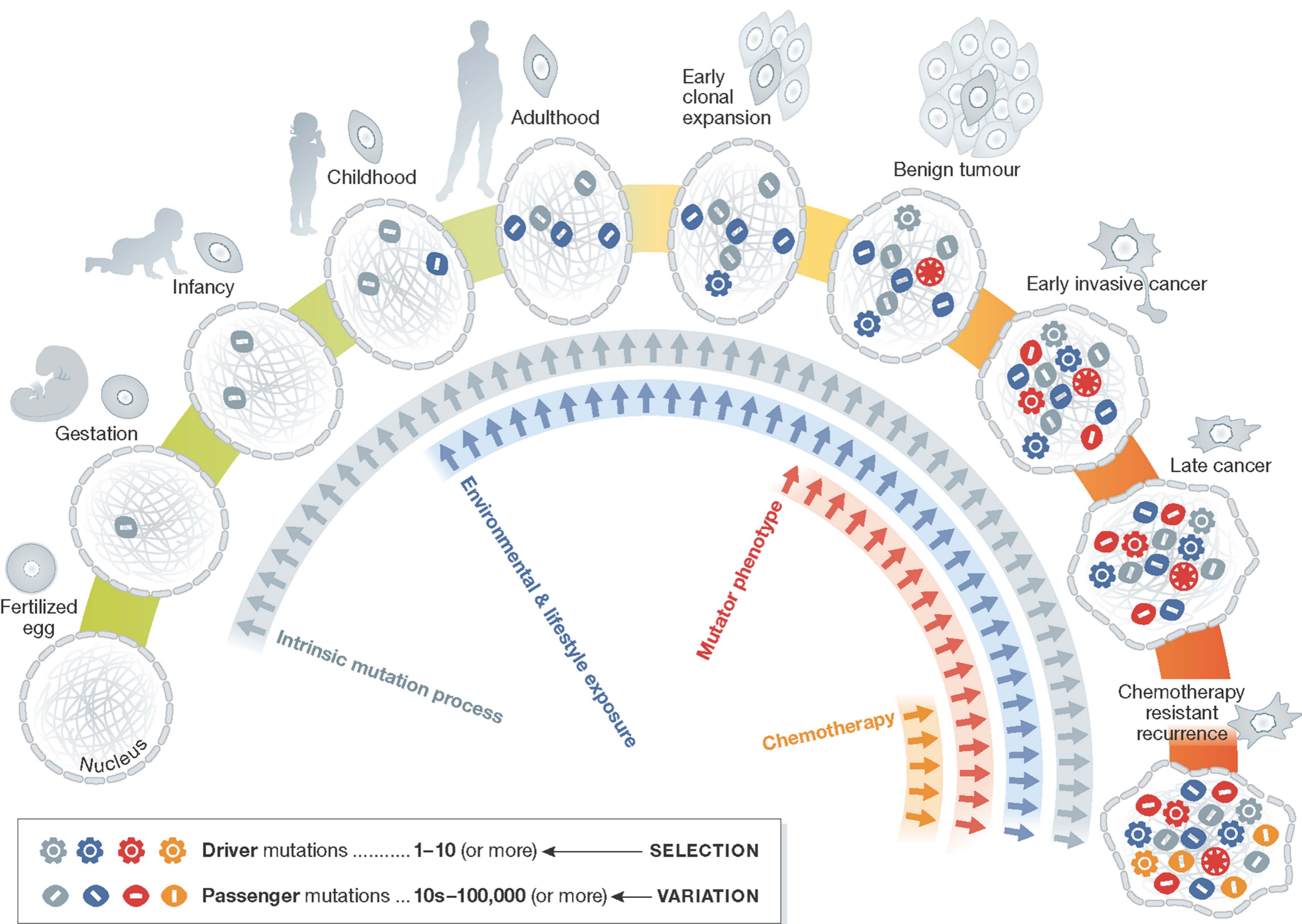


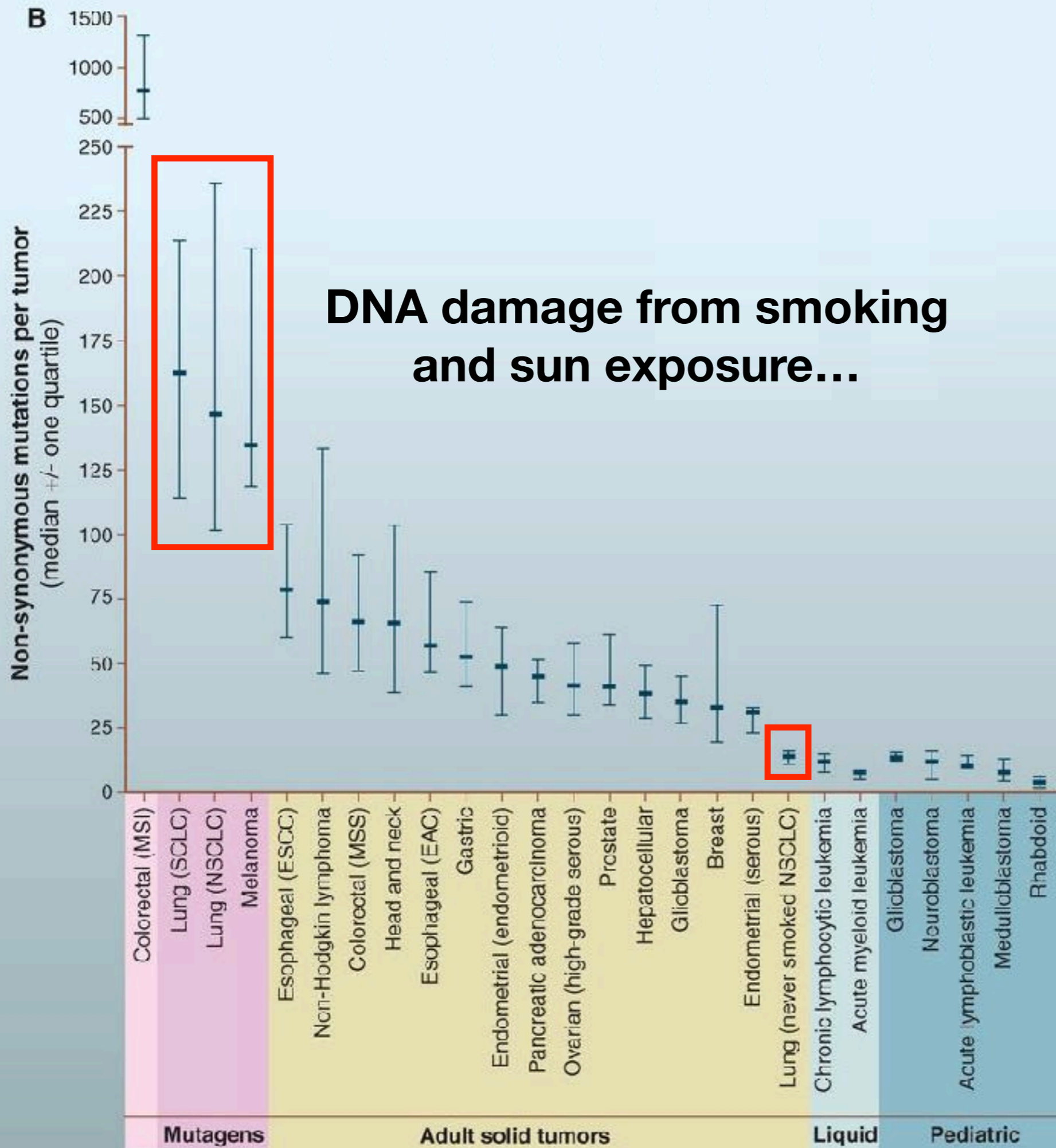
**Vogelstein et al.
Science (2013)**



Most of these mutations are likely “passenger” mutations

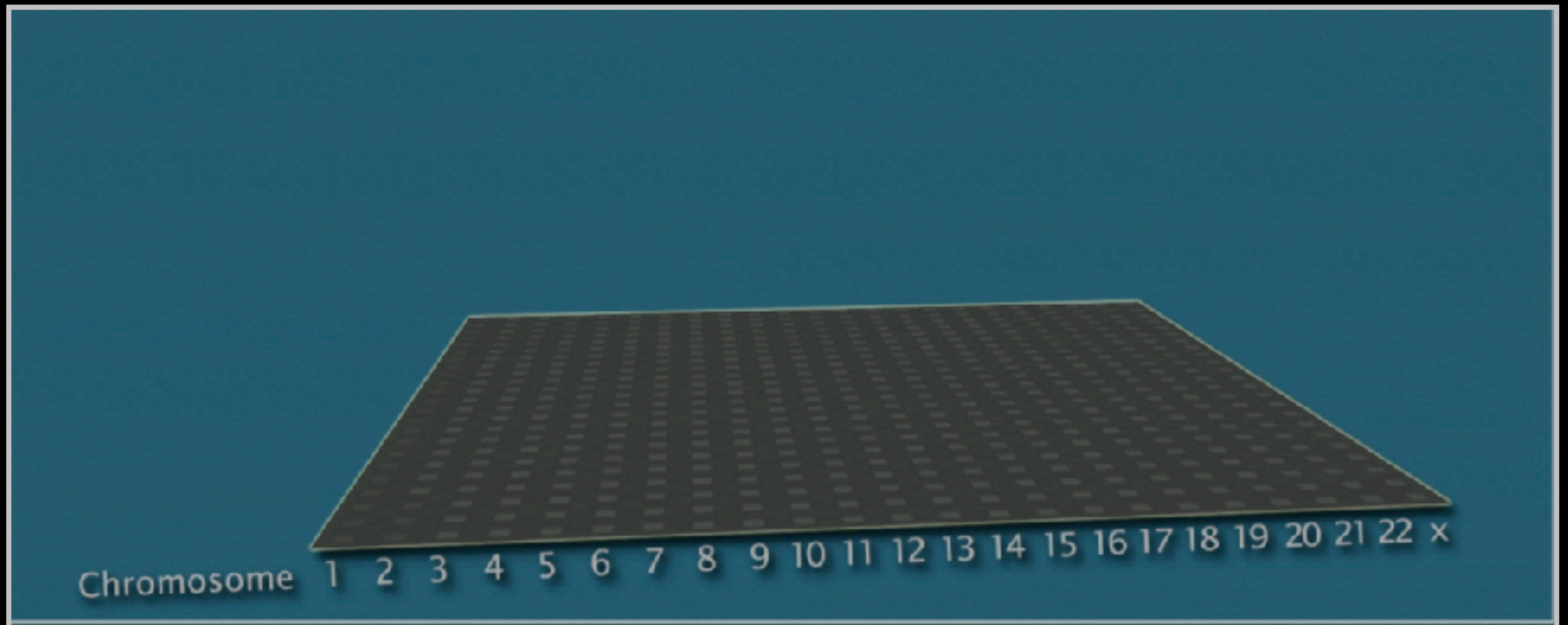
Vogelstein et al.
Science (2013)





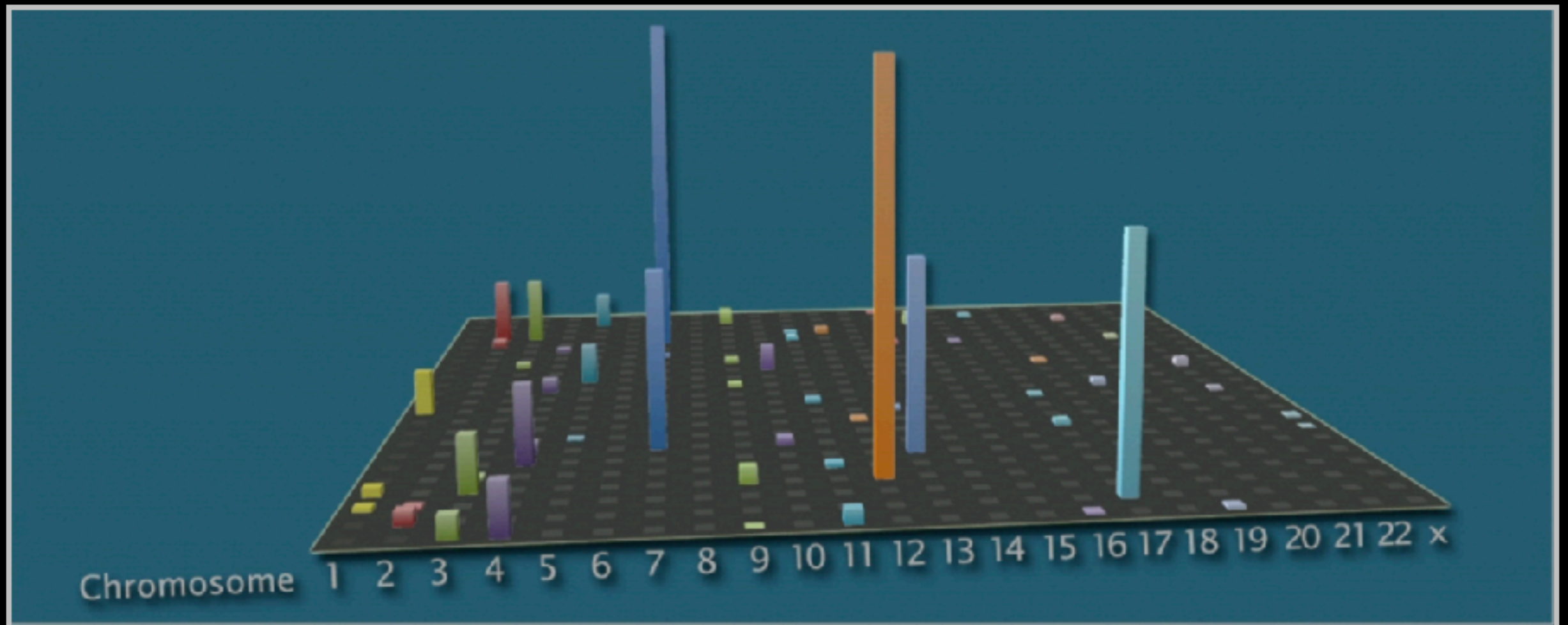
Vogelstein et al.
Science (2013)

Genomic approaches can identify the genes most commonly mutated in cancer



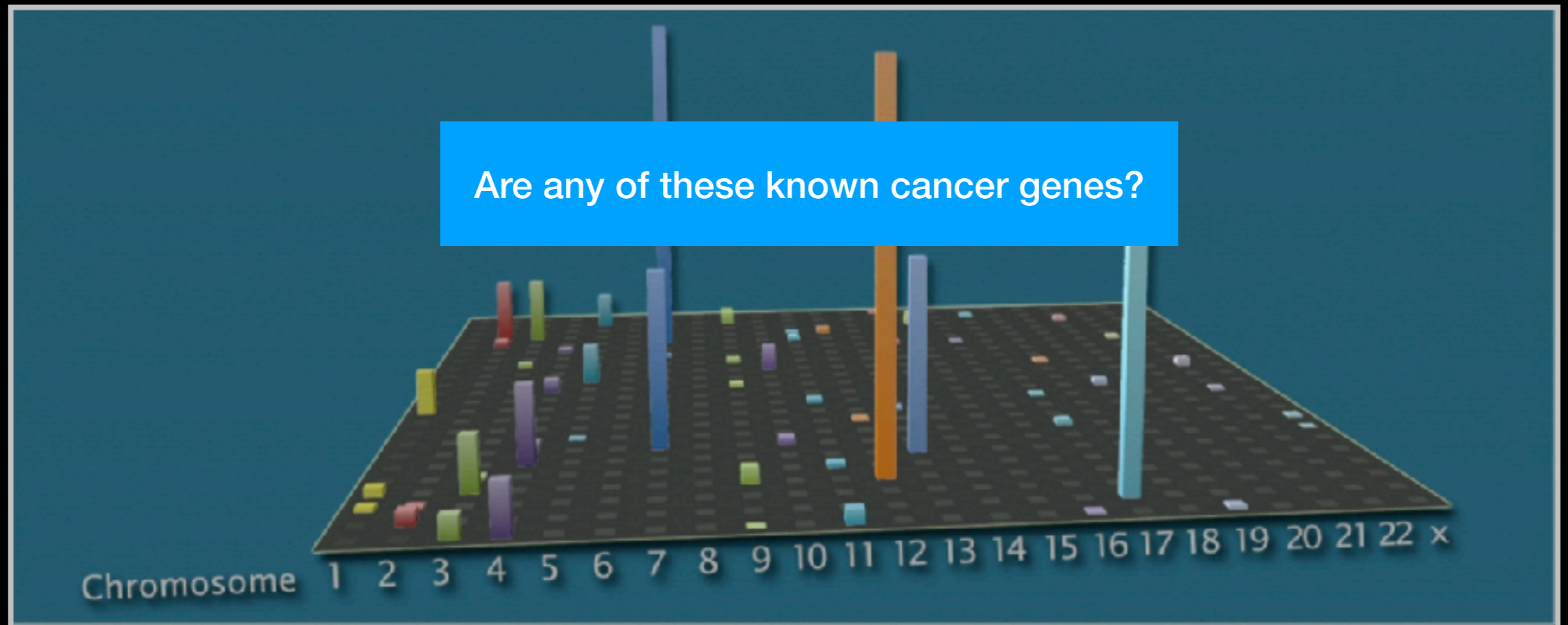
Arrange all genes in a matrix, ordered by chromosomes

Identifying genes most commonly mutated in cancer



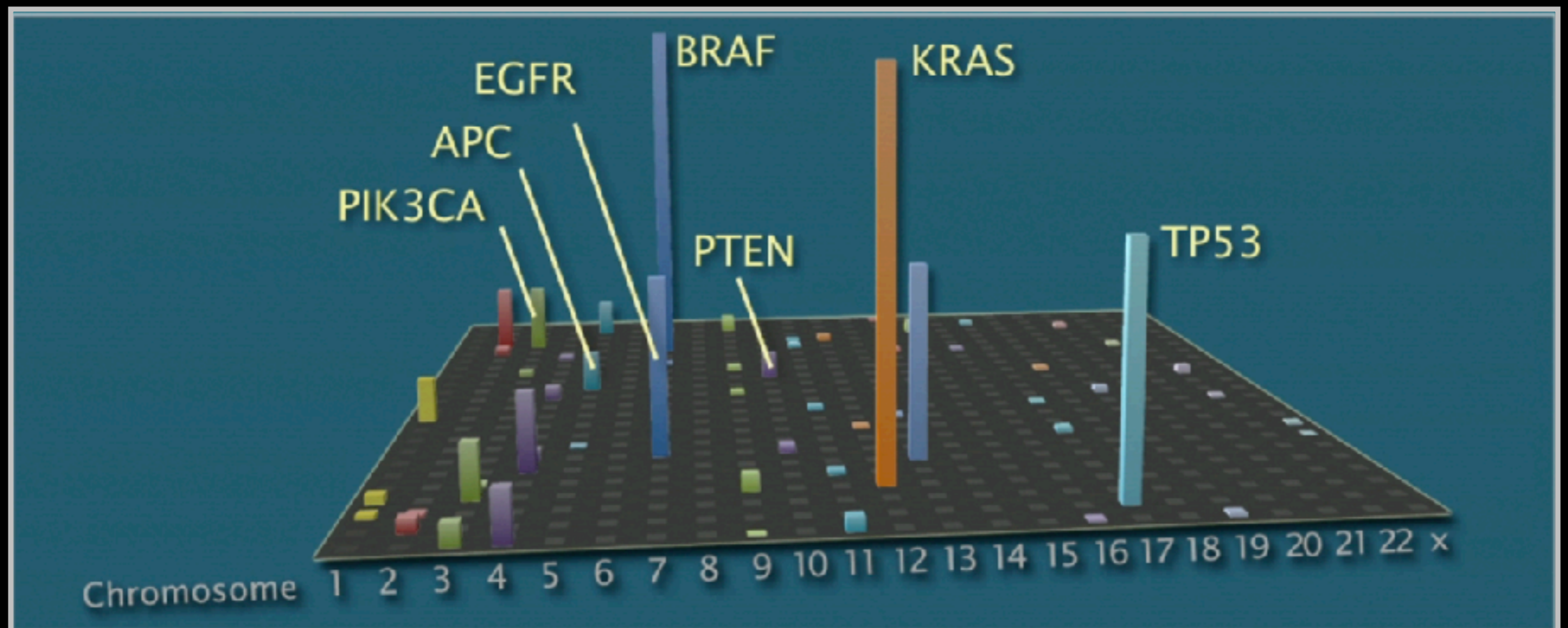
Add all data together to see which genes are most often mutated

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



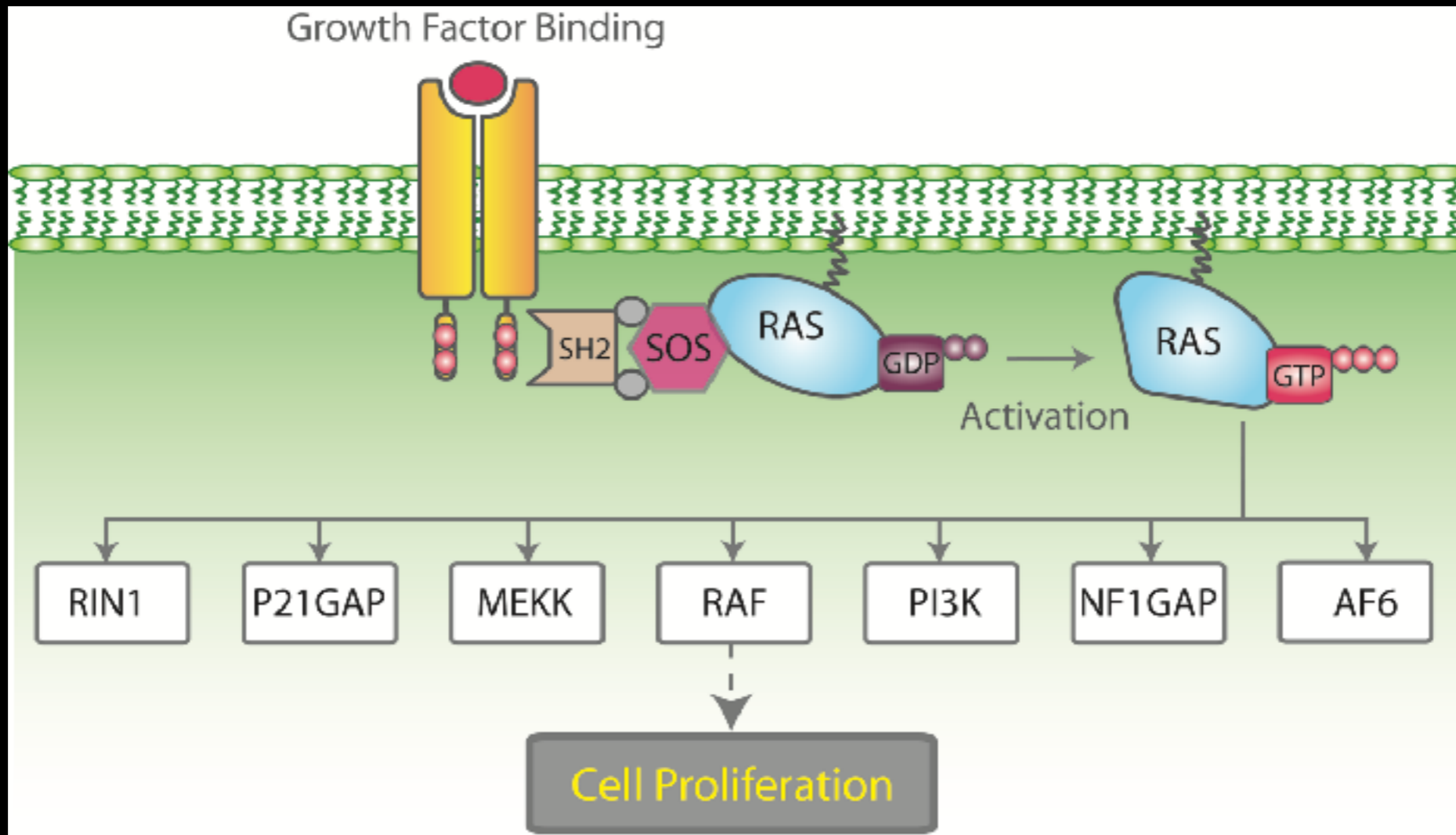
Many are famous proto-oncogenes, many others are new cancer genes!

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.

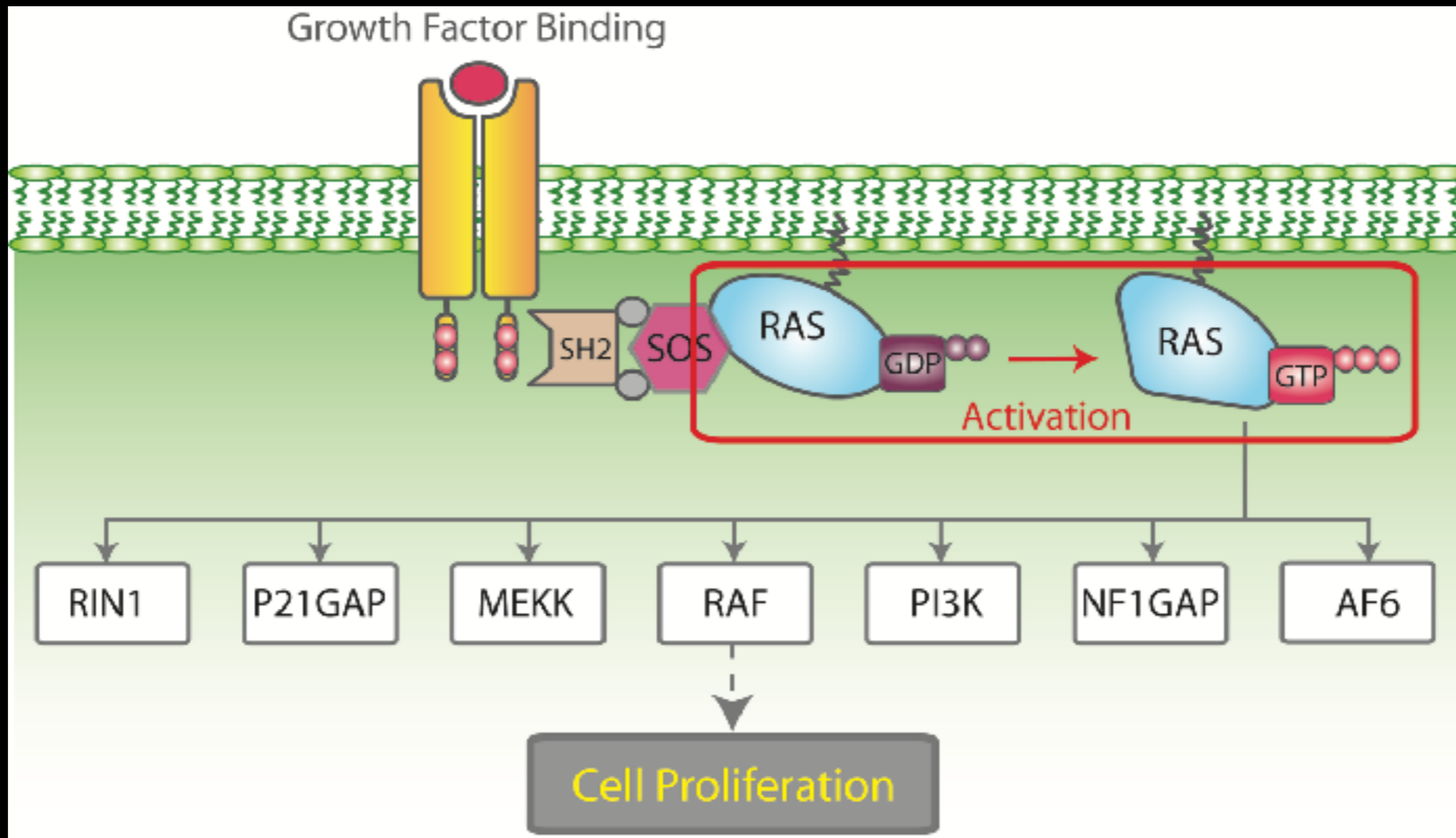
Cell growth and survival genes

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

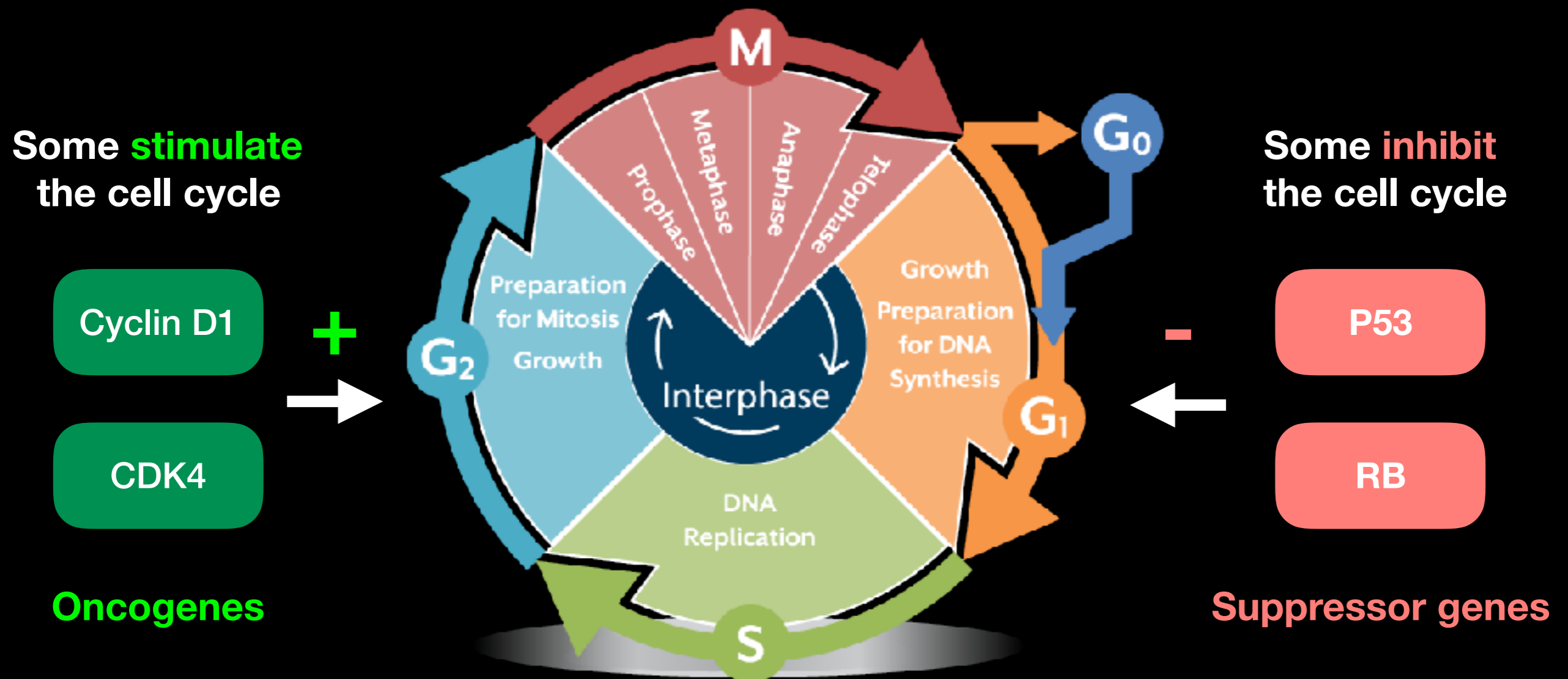


Cell growth and survival genes

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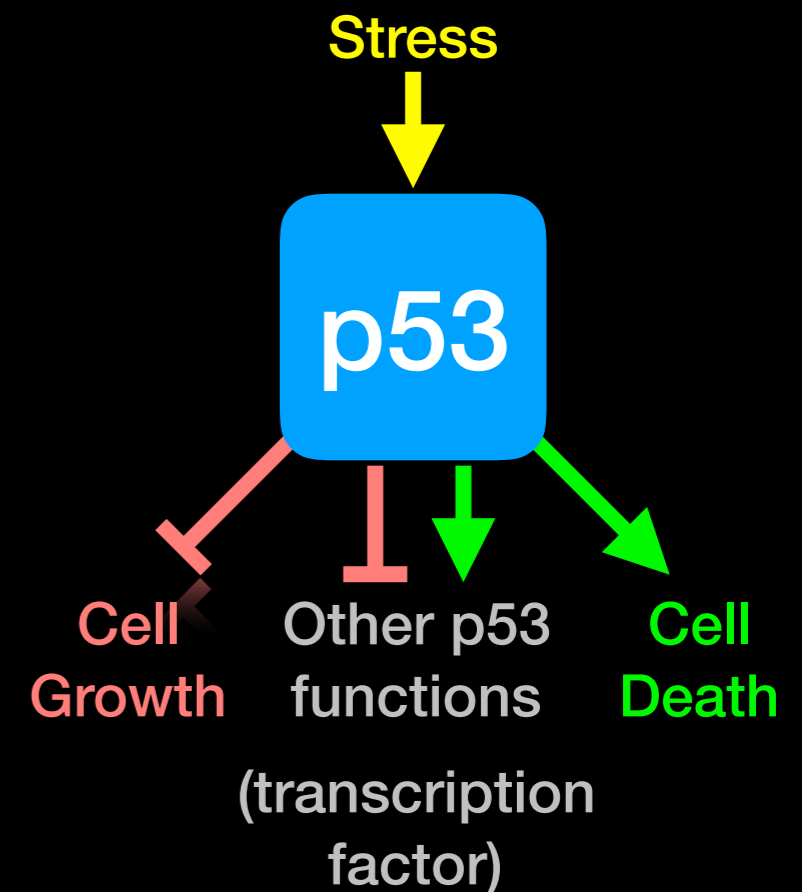
Regulators of Cell Cycle and Cell Death



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.



Do it Yourself!

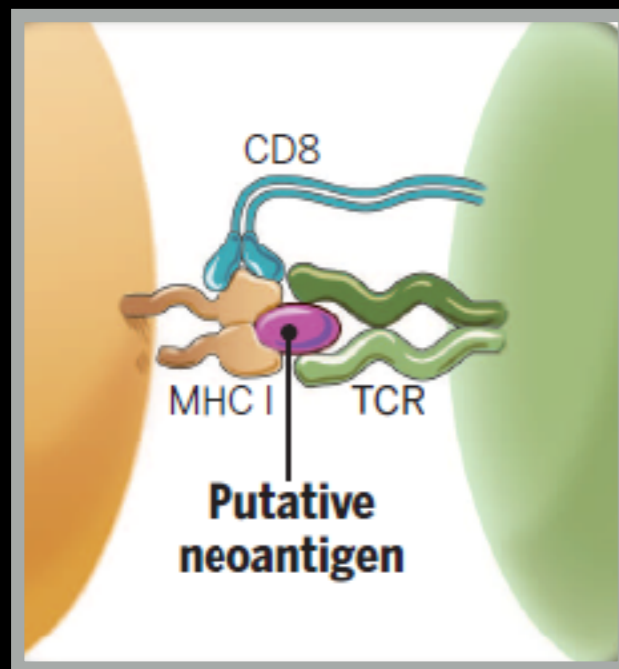
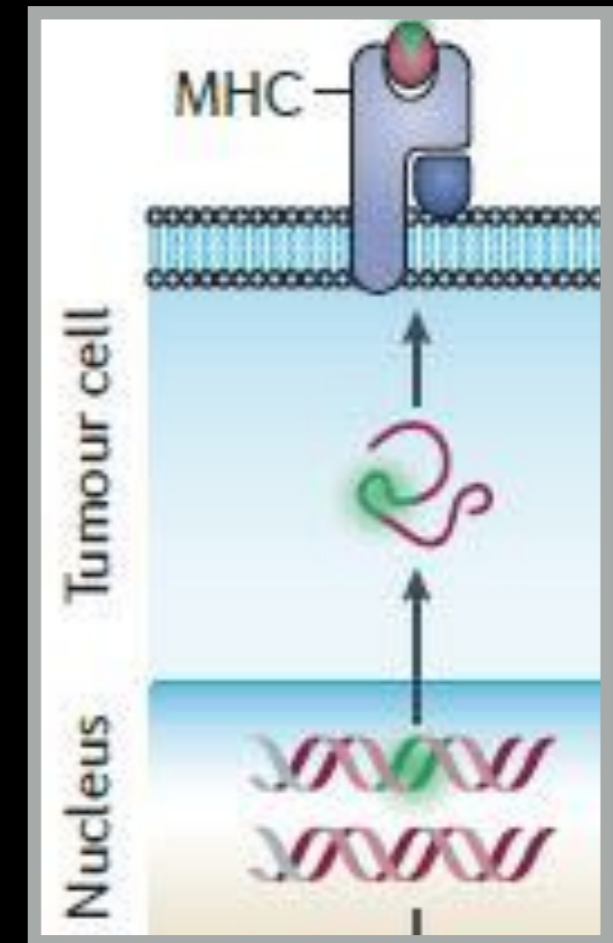
Hands-on time!

https://bioboot.github.io/bimm143_S18/lectures/#18

Part 1 Only Please

Cancer Immunotherapy

- 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!

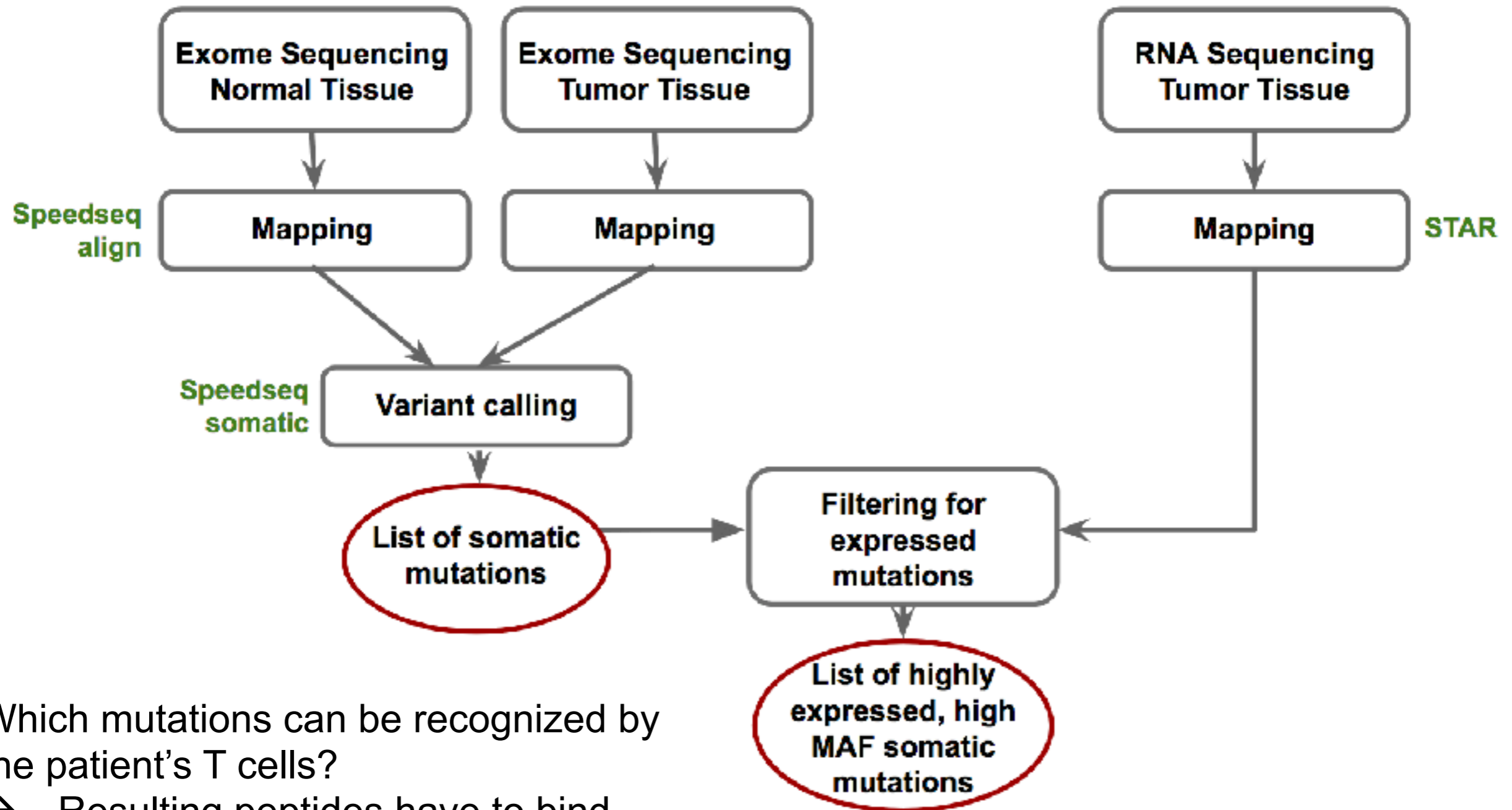
Coulie et al, Nat Rev Cancer. 2014 Feb;14(2):135-46

Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74

- **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 the 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.

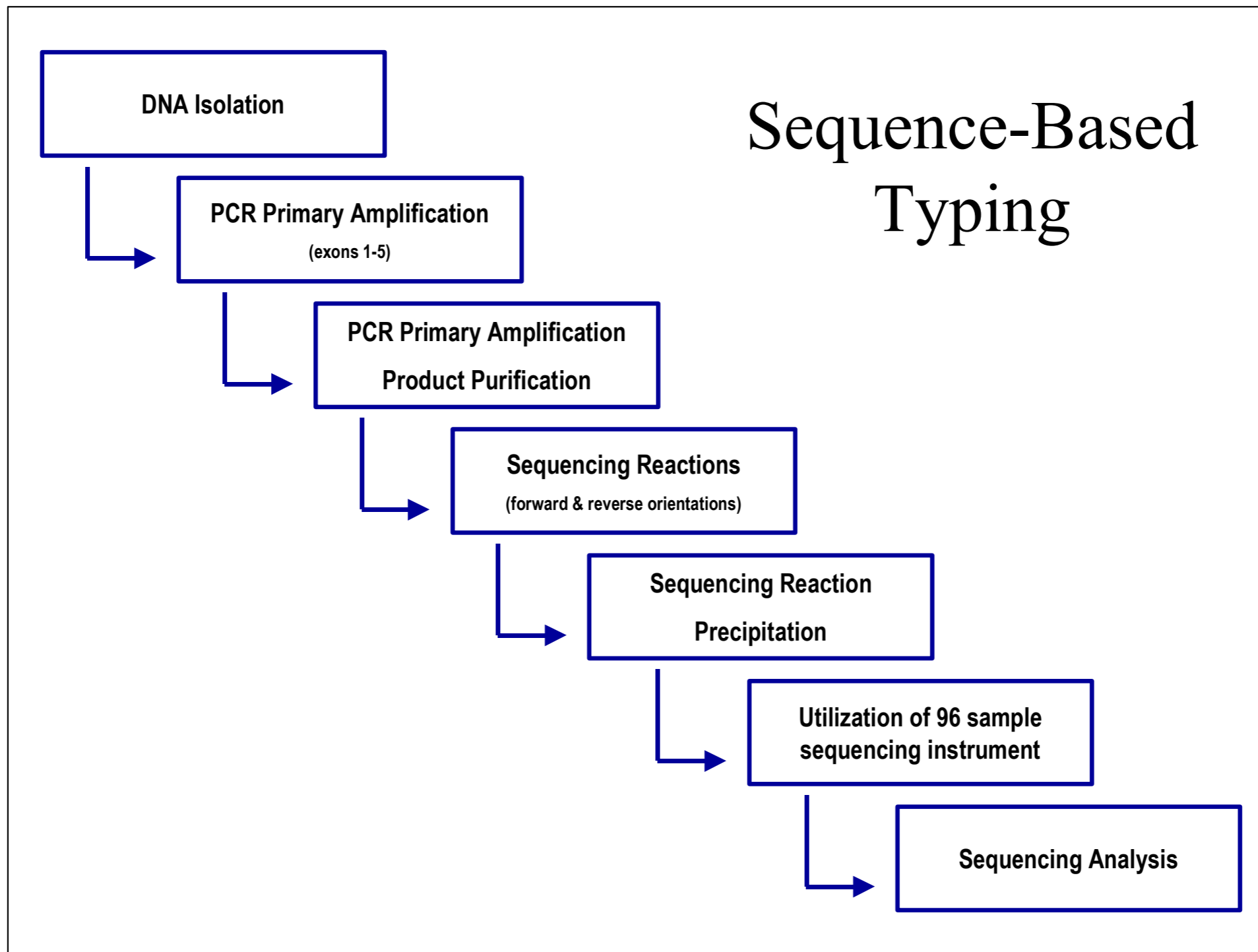
Q. How can such a vaccine be designed?

DNA and RNA sequencing identifies tumor specific somatic mutations

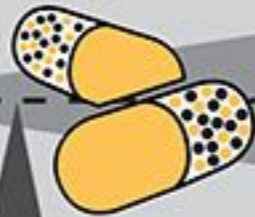


Which mutations can be recognized by the patient's T cells?
→ Resulting peptides have to bind HLA molecules of the patient

HLA Typing: Targeted sequencing of HLA locus



TRADITIONAL CANCER THERAPIES



DRUGS OR RADIATION

Kills **Cancerous Cells**

Kills **Healthy Cells**



CANCER IMMUNOTHERAPIES



IMMUNOTHERAPY

Unleash



Patient's Immune System

Selectively Kills
Cancerous Cells

Healthy Cells



Do it Yourself!

Hands-on time!

https://bioboot.github.io/bimm143_S18/lectures/#18

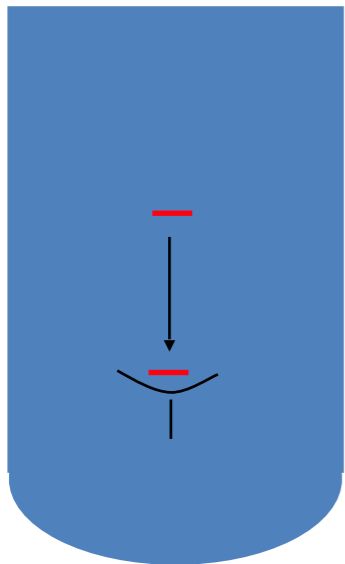
Part 2: Designing a personalized cancer vaccine

Bonus Slides
(For Reference)

Measuring and predicting MHC:peptide binding

Experimental Basis: MHC Binding Assay

List of peptides with allele specific binding affinity



Sequence	IC ₅₀
QIVTMFEAL	3.6
LKGPDIIYKG	308
NFCNLTSAF	50,000
AQSQCRTFR	38,000
CTYAGPFGM	143
CFGNTAVAK	50,000
...	

$\log(\text{IC}_{50}) \sim \text{Binding free Energy}$

low IC₅₀ → high affinity

Impossible to measure all peptides

→ Predict binding peptides using machine learning

Find function F_i in F_1, F_2, F_3, \dots
 $F_i(\text{Sequence}) \approx \text{Affinity}$

Many different approaches (ANN, SVM, HMM, LP, ...)

T cell epitope mapping

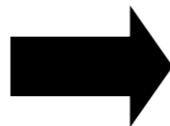
ORF 1	M G Q I V T M F E A L P H I I D E V I N I V I I V L I V I T G I K A V Y N ...
ORF 2	M G L K G P D I Y K G V Y Q F K S V E F D M S H L N L T M P N A C S A N N ...
ORF 3	M H N F C N L T S A F N K K T F D H T L M S I V S S L H L S I D G N S N Y ...
ORF 4	M S A Q S Q C R T F R G R V L D M F R T A F G G K Y M R S G W G W T G S D ...
ORF 5	M H C T Y A G P F G M S R I L L S Q E K T K F F T R R L A G T F T W T L S ...
ORF 6	M K C F G N T A V A K C N V N H D A E F C D M L R L I D Y N K A A L S K F ...
ORF 7	M L M R N H L L D L M G V P Y C N Y S K F W Y L E H A K T G E T S V P K C ...

Calculate scoring matrix from affinities

Machine learning PSSM = Minimize the difference between predicted and measured binding affinities by varying the matrix values

N peptides with measured binding affinities

log (IC50)	Peptide
0.50	FQPQNGSFI
0.72	ISVANKIYM
2.37	RVYEALYYV
3.42	FQPQSGQFI
3.46	LYEKVKSQL
4.07	FKSVEFDMS
4.18	FQPQNGQFH
4.24	VLMLPVWFL
4.39	YMTLGQVVF
4.40	EDVKNAVG
4.90	VFYEQMKRF
...	

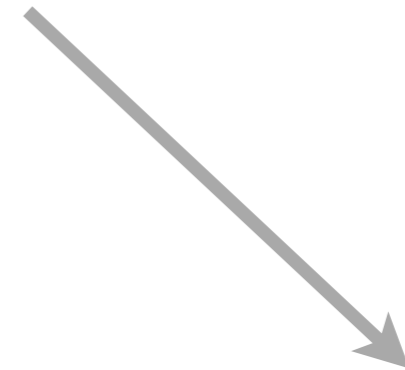
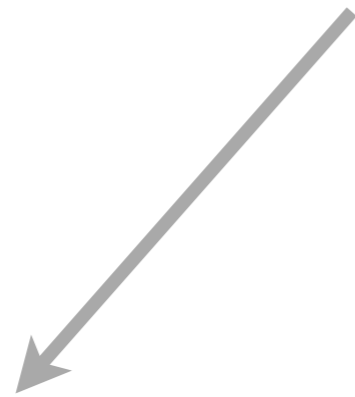
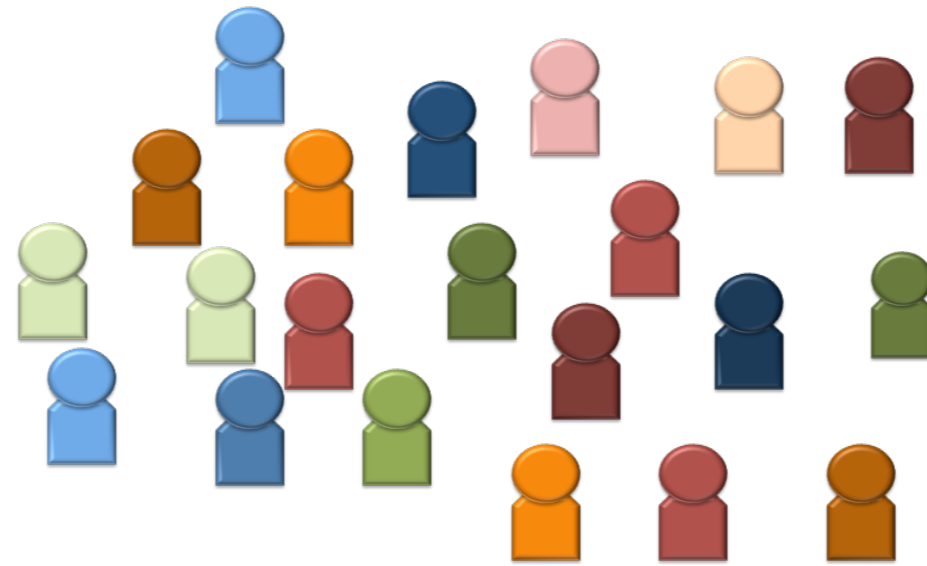


	HLA A*0201								
	1	2	3	4	5	6	7	8	9
A	-0.3	0.8	-0.3	-0.3	-0.2	-0.3	0.0	0.0	-0.9
C	0.2	0.9	0.0	0.3	-0.5	-0.1	0.1	0.2	0.4
D	0.8	0.9	-0.4	-0.3	0.3	0.2	0.4	0.3	0.6
E	0.6	-0.4	0.7	-0.2	0.1	-0.4	-0.2	-0.2	-0.5
F	-1.3	0.5	-0.5	0.1	-0.1	0.0	-0.3	-0.4	-0.8
G	-0.2	0.1	0.3	-0.1	0.0	0.4	0.3	-0.1	0.2
H	1.1	0.9	-0.1	0.4	0.1	0.2	0.0	0.2	0.8
I	-0.4	-0.7	-0.4	0.1	-0.1	-0.4	-0.5	0.5	-1.4
K	-0.3	0.0	1.1	0.1	0.1	0.6	0.9	0.2	0.9
L	0.0	-1.9	-0.4	-0.2	0.0	-0.2	0.0	-0.1	-1.1
M	-0.7	-1.2	-0.7	0.2	-0.6	0.0	0.0	0.0	-0.8
N	-0.1	0.3	0.1	-0.3	-0.1	-0.3	0.0	0.2	0.7
P	1.2	0.5	0.6	-0.3	0.4	0.0	-0.4	-0.5	0.7
Q	0.4	-1.1	0.0	-0.1	0.4	-0.2	-0.3	0.2	0.7
R	-0.2	0.9	1.0	0.3	0.1	0.4	0.7	0.0	0.9
S	-0.3	0.1	0.1	-0.4	0.1	0.3	-0.2	-0.1	0.2
T	-0.2	-0.5	0.1	0.4	0.1	-0.5	0.2	0.0	-0.1
V	-0.1	-0.9	-0.1	0.2	0.0	-0.3	0.1	0.1	-1.9
W	0.0	0.7	-0.5	-0.2	-0.1	0.2	-0.3	-0.1	0.4
Y	-0.3	0.2	-0.6	0.2	0.0	0.4	-0.4	-0.3	0.8

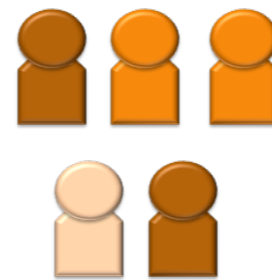
Offset: 4.3

**Genetic and genomic approaches
can identify a cancers molecular
signature to usefully stratify
tumors for treatment**

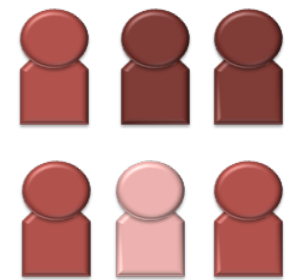
Stratify tumors based on molecular patterns



Good prognosis
Favorable response

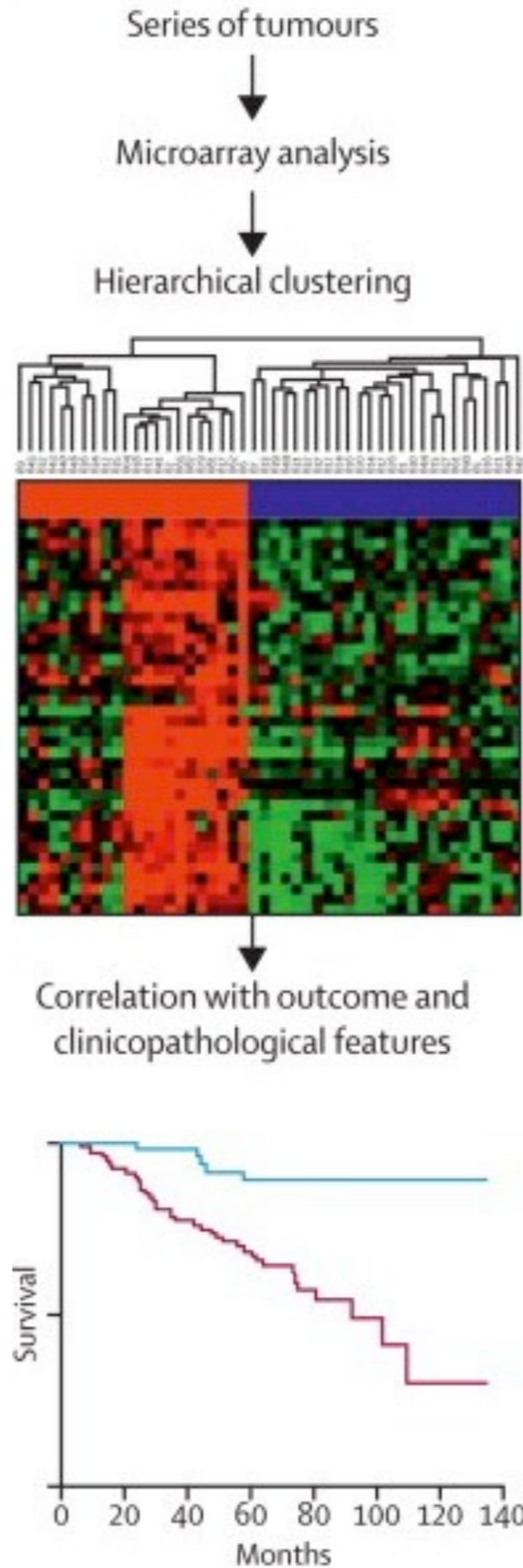


Bad prognosis
Unfavorable response

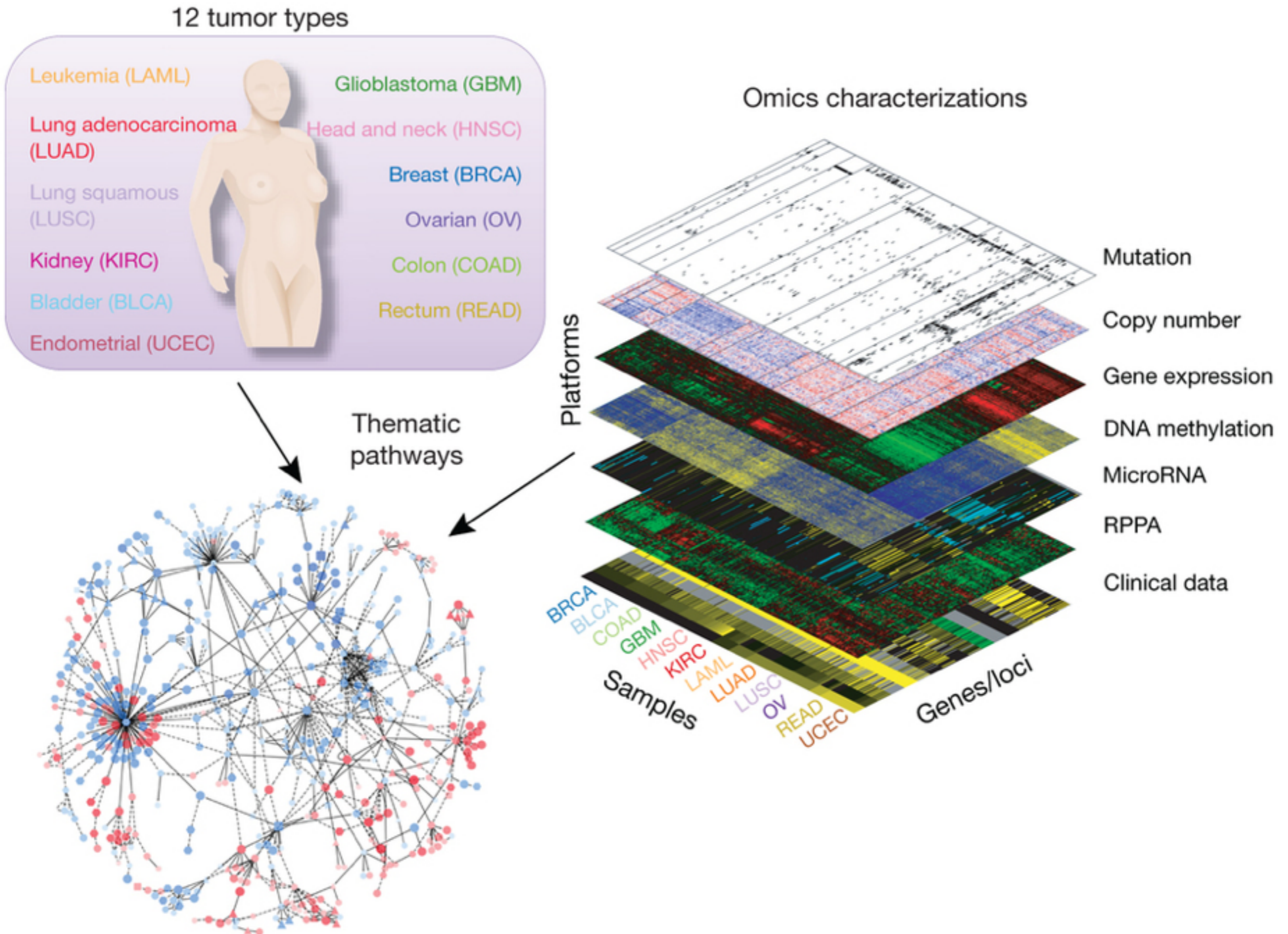


Increased toxicity

Stratify tumors based on molecular patterns



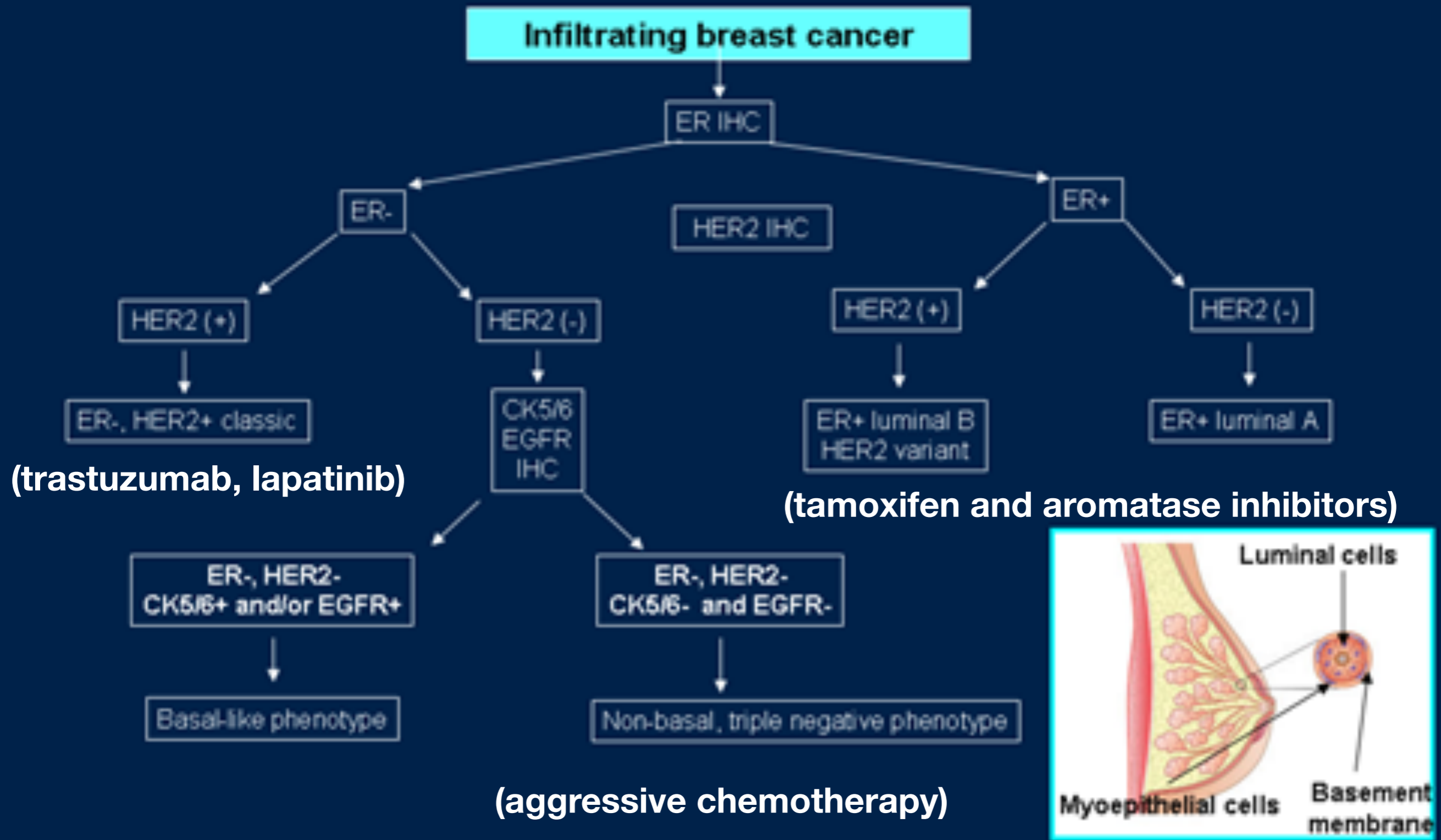
TCGA Pan-Cancer project



For example, breast cancer may be classified into various types based upon which proteins are expressed on the surface of the tumor cells. Breast tumors that express human epidermal growth factor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR), or are triple negative (do not express HER2, ER, or PR) behave differently and have different prognoses. Tumors that are HER2 positive are treated with medications that bind to HER2 (e.g. trastuzumab, lapatinib) and inhibit its activity. ER and PR are hormone receptors, and ER/PR positive tumors are treated with antihormonal therapies (e.g. tamoxifen and aromatase inhibitors). Triple negative tumors have the poorest prognosis and are unlikely to respond to HER2-targeted therapies or antihormonal therapies. Such cancers are usually treated very aggressively with chemotherapy.

As more has been learned about the molecular signature of various cancer subtypes, therapies that are specifically targeted to those signatures have been developed. Conventional chemotherapy acts on all rapidly dividing cells and does not distinguish between cancer cells and normal cells.

Classification of Breast Cancer



Readings to find out more...

Leading Edge
Review

Cell

The Genetic Basis for Cancer Treatment Decisions

Janet E. Dancey,^{1,2} Philippe L. Bedard,^{3,4} Nicole Onetto,¹ and Thomas J. Hudson^{1,5,6,*}

¹Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada

²NCIC-Clinical Trials Group, Queen's University, Kingston, ON K7L 3N6, Canada

³Princess Margaret Hospital, Division of Medical Oncology and Hematology, University Health Network

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⁵Department of Medical Biophysics

⁶Department of Molecular Genetics

University of Toronto, Toronto, ON M5S 1A1, Canada

*Correspondence: tom.hudson@oicr.on.ca

DOI 10.1016/j.cell.2012.01.014

Personalized cancer medicine is based on increased knowledge of the cancer mutation repertoire and availability of agents that target altered genes or pathways. Given advances in cancer genetics, technology, and therapeutics development, the timing is right to develop a clinical trial and research framework to move future clinical decisions from heuristic to evidence-based decisions. Although the challenges of integrating genomic testing into cancer treatment decision making are wide-ranging and complex, there is a scientific and ethical imperative to realize the benefits of personalized cancer medicine, given the overwhelming burden of cancer and the unprecedented opportunities for advancements in outcomes for patients.

Your Turn

Read and share your thoughts on the following class [Readings](#)

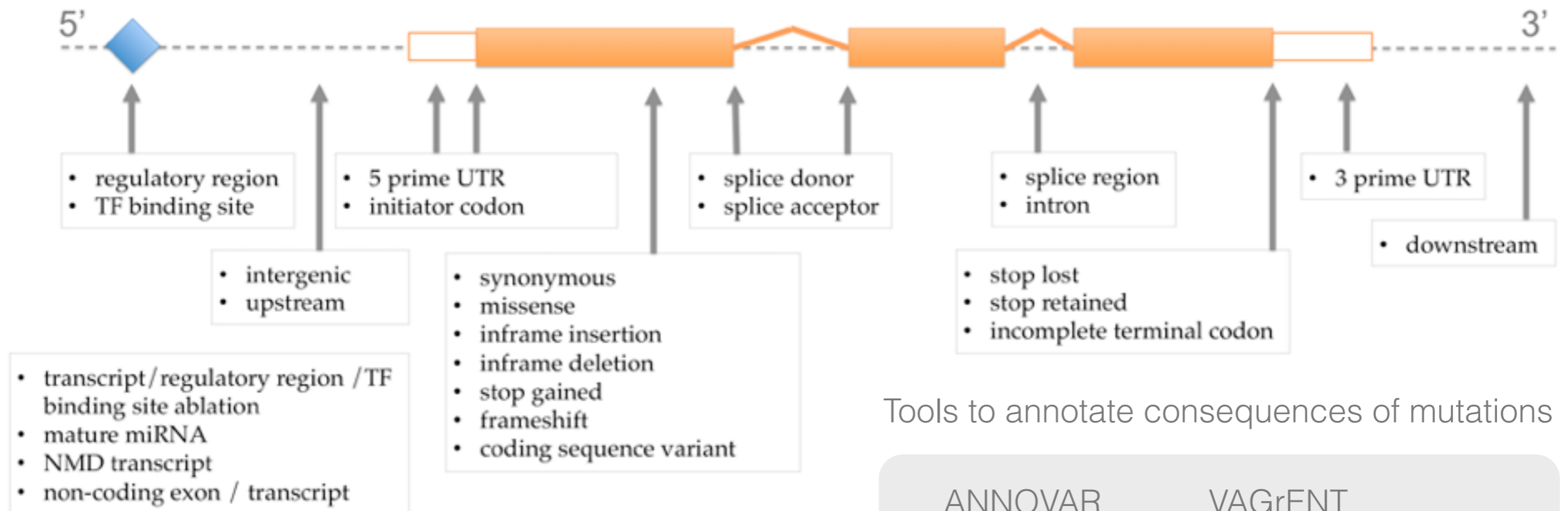
- Calling cancer's bluff with neoantigen vaccines
- Can genomics help detect early cancer and monitor treatment effectiveness?
- The increasing cost of cancer therapies

https://bioboot.github.io/bimm194_W18/readings/

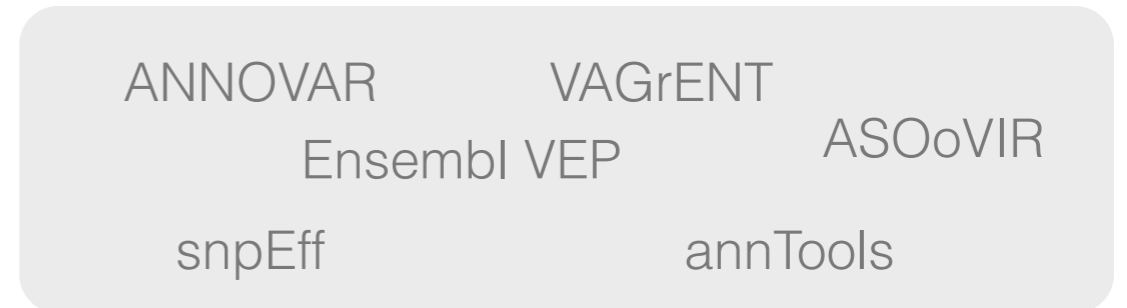
1. Predict consequences of mutations

ACTGCCTACGTCTCACCGTCGACTTCAAATCGCTTAACCCGTACTCCCATGCTACTGCATCTCGGGTAACTC
GACGTTTTTCATGCATGTGTGCACCCCAATATATATGCAACTTTTTGTGCACCTCTGTCACGCGCGAGTTGGCA
CTGTCGCCCCTGTGTGCATGTGCACCTGTCTCTCGCTGCACCTGCCTACGTCTCACCGTCGACTTCAAATCGCTT
AACCCGTACTCCCATGCTACTGCATCTCGGGTAACTCGACGTTTTGCATGCATGTGTGCACCCCAATATATA
TGCAACTTTTTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCTGTGTGCATGTGCACCTGTCTCTCGA

Map mutations into genome annotations to predict its possible effect



Tools to annotate consequences of mutations

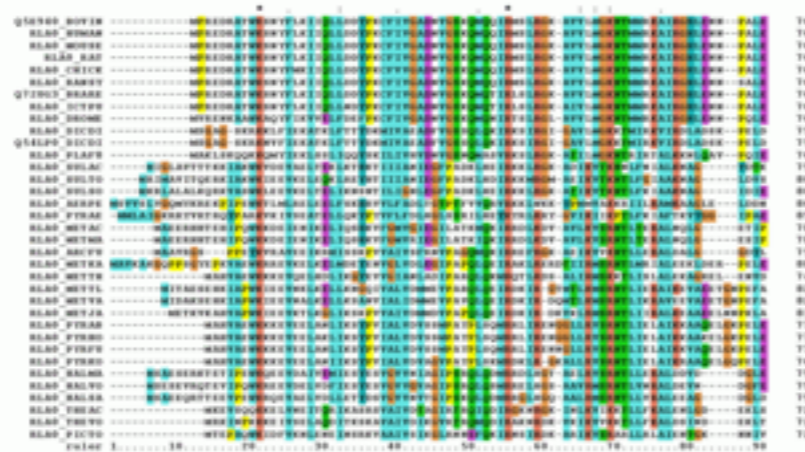


2. Assess the functional impact of nsSNVs

nsSNVs = non-synonymous Single Nucleotide Variant (missense)

ATC GAA GCA CGT
Met Glu Ala Gly

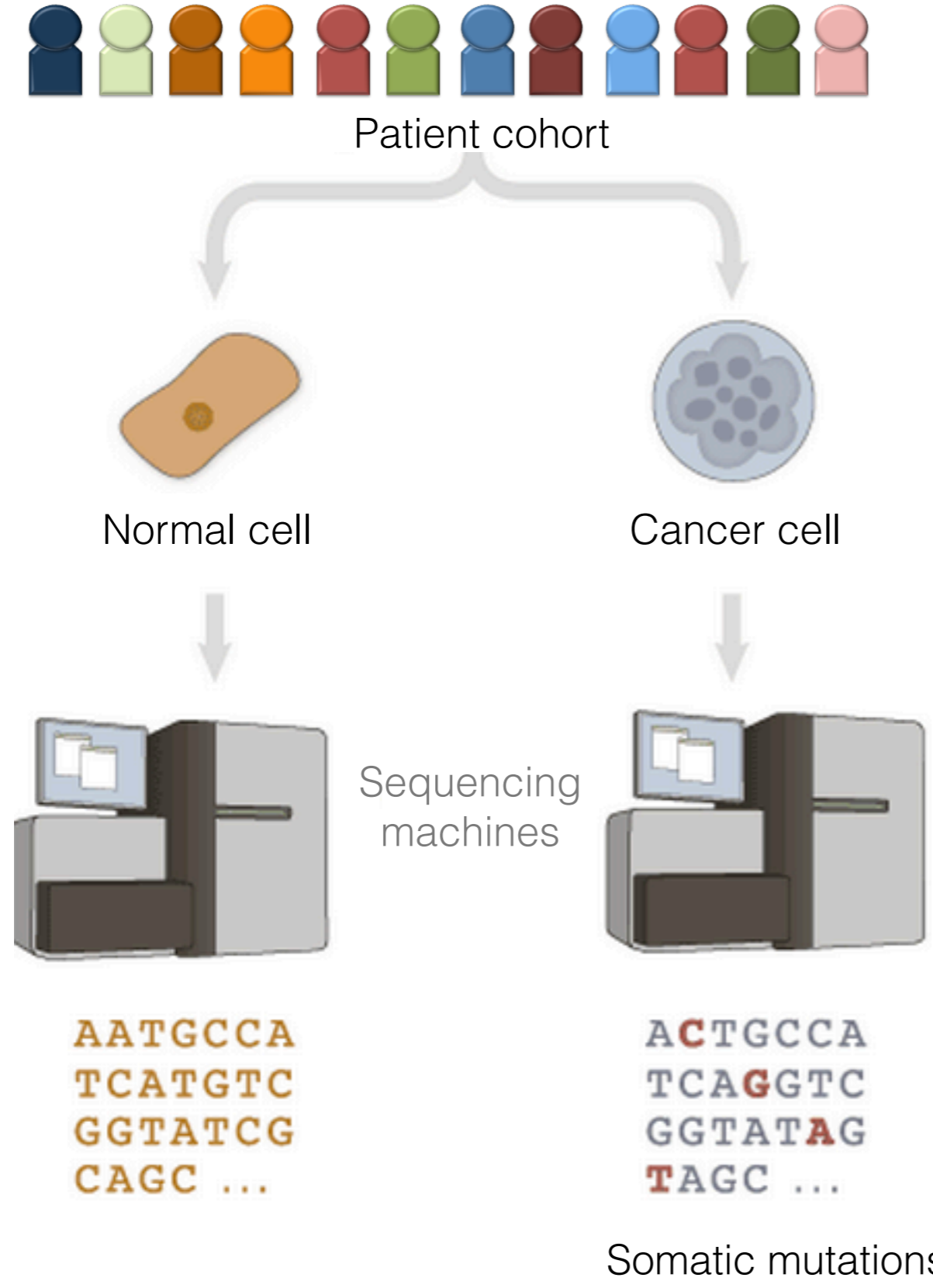
ATC **GAC** GCA CGT
Met **Asp** Ala Gly



Computational methods to assess the functional impact of nsSNVs

MutationTaster LogRe MutPred SNPs&GO
CanPredict PolyPhen2 CHASM SNPeffect
SIFT MutationAssessor PMut transFIC

3. Identify cancer drivers from somatic mutations

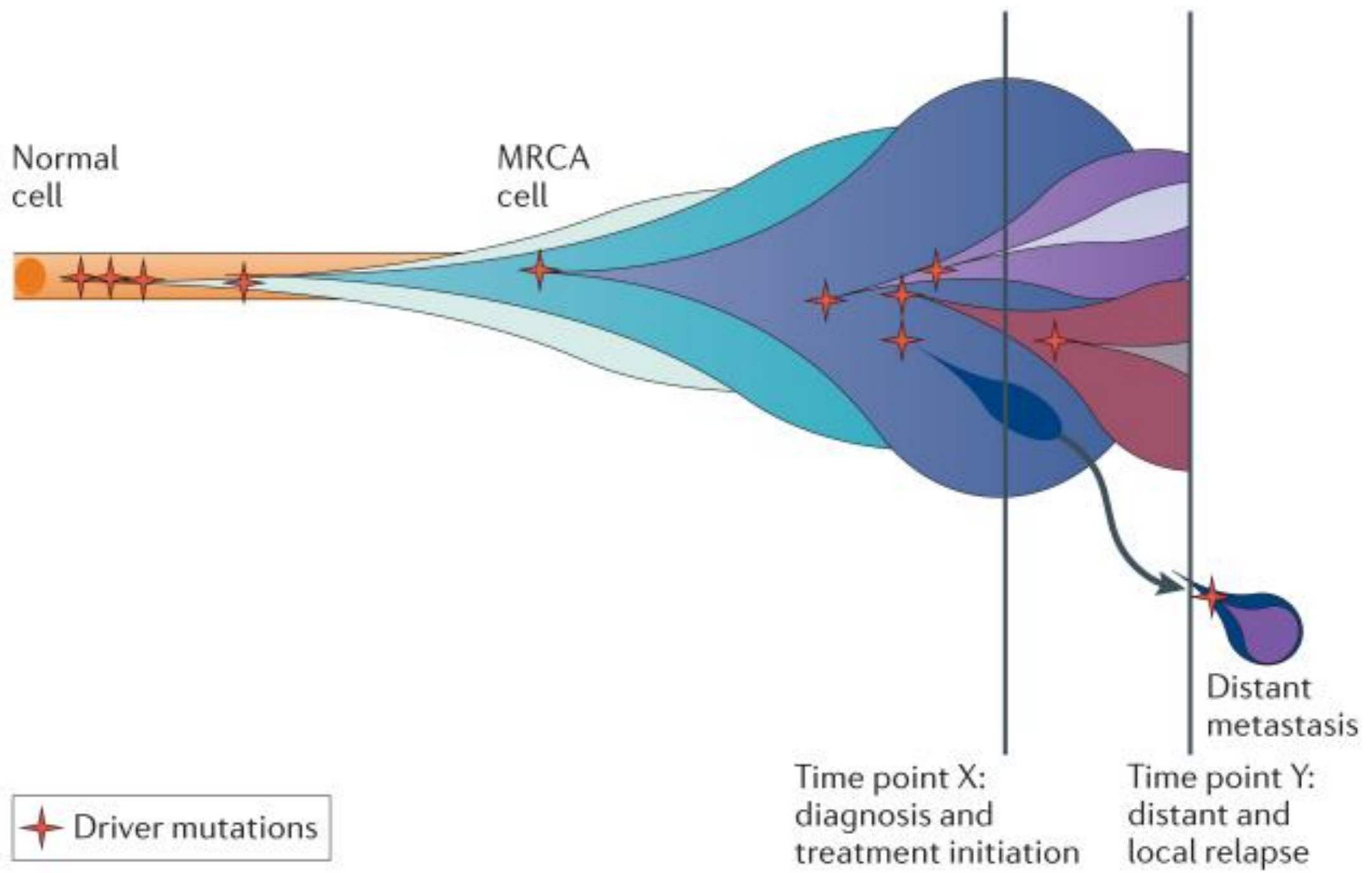


Which mutations are cancer drivers?



Find signals of selection across tumors

Cancer is an evolutionary process



How to differentiate drivers from passengers?

ACTG**C**CTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATGCTACTGC
ATCTCGGGTTAACTCGACGTTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTT
TTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCCTGTGTGCATGTGCACCTGT
CTC**T**CGCTGCACTGCCTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCC
ATGCTACTGCATCTCGGGTTAACTCGACGTTTT**G**CATGCATGTGTGCACCCCAATATA
TATGCA**A**CTTTTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCCTGTGTGCA
TGTGCACTGTCTC**T**CGAGTTTT**G**CATGCATGTGTGCACCTGTGCACCTCTGTTACGTCT

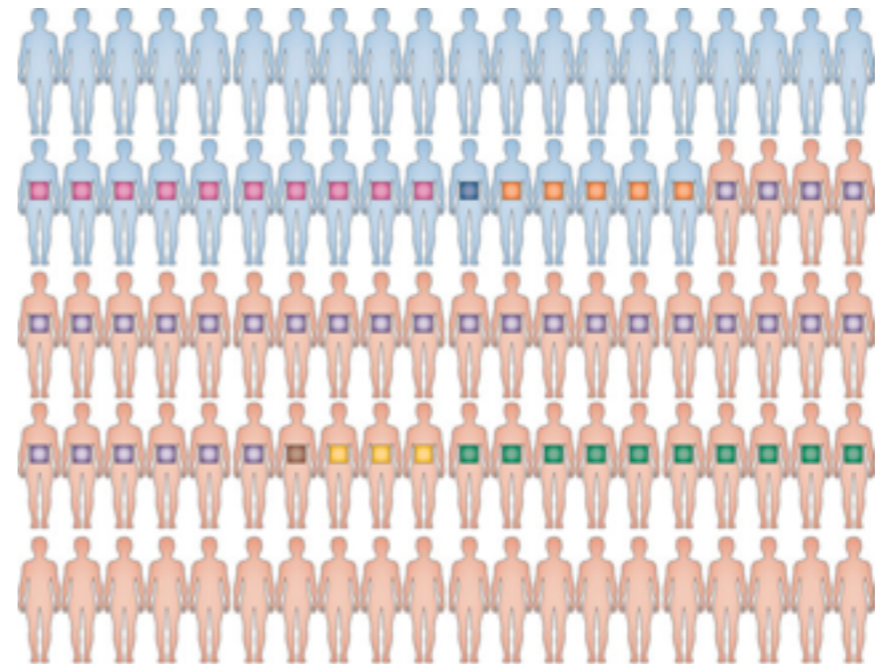


How to differentiate drivers from passengers?

ACTG**C**CTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCCATGCTACTGC
ATCTCGGGTTAACTCGACGTTTT**T**CATGCATGTGTGCACCCCAATATATATGCA**A**CTT
TTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCCTGTGTGCATGTGC**A**CTGT
CTC**T**CGCTGCACTGCCTACGTCTCACCGTCGACTTCAAATCG**C**TTAACCCGTACTCCC
ATGCTACTGCATCTCGGGTTAACTCGACGTTTT**G**CATGCATGTGTGCACCCCAATATA
TATGCA**A**CTTTTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCCTGTGTGCA
TGTGCACTGTCTC**T**CGAGTTTT**G**CATGCATGTGTGCACCTCTGTTACGTCT



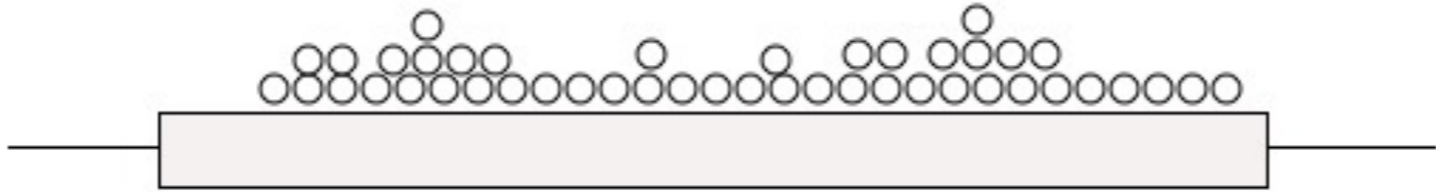
Find signals of positive selection across tumour re-sequenced genomes



Signals of positive selection

Recurrence

MuSiC-SMG / MutSigCV

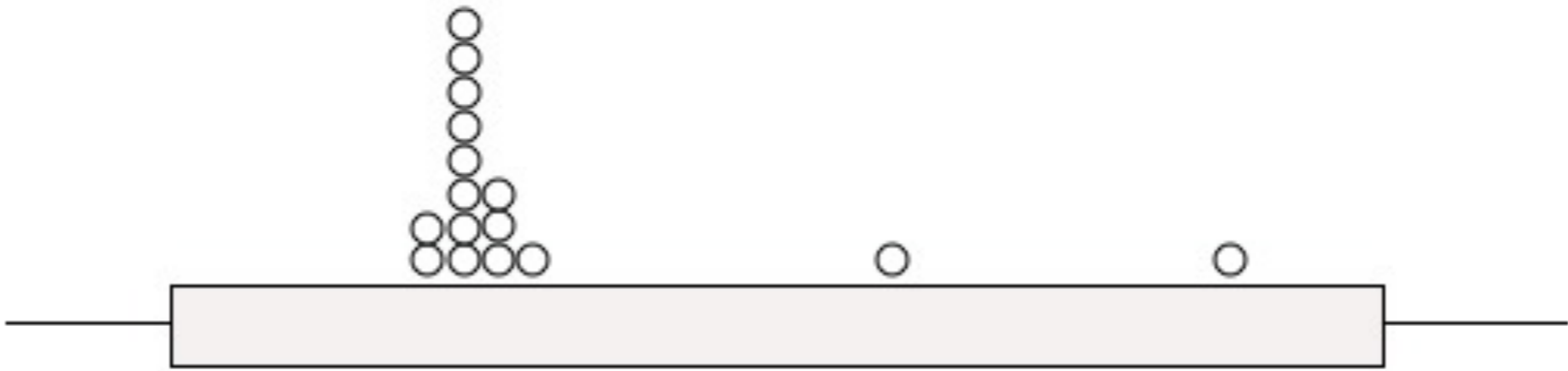


○ Mutation

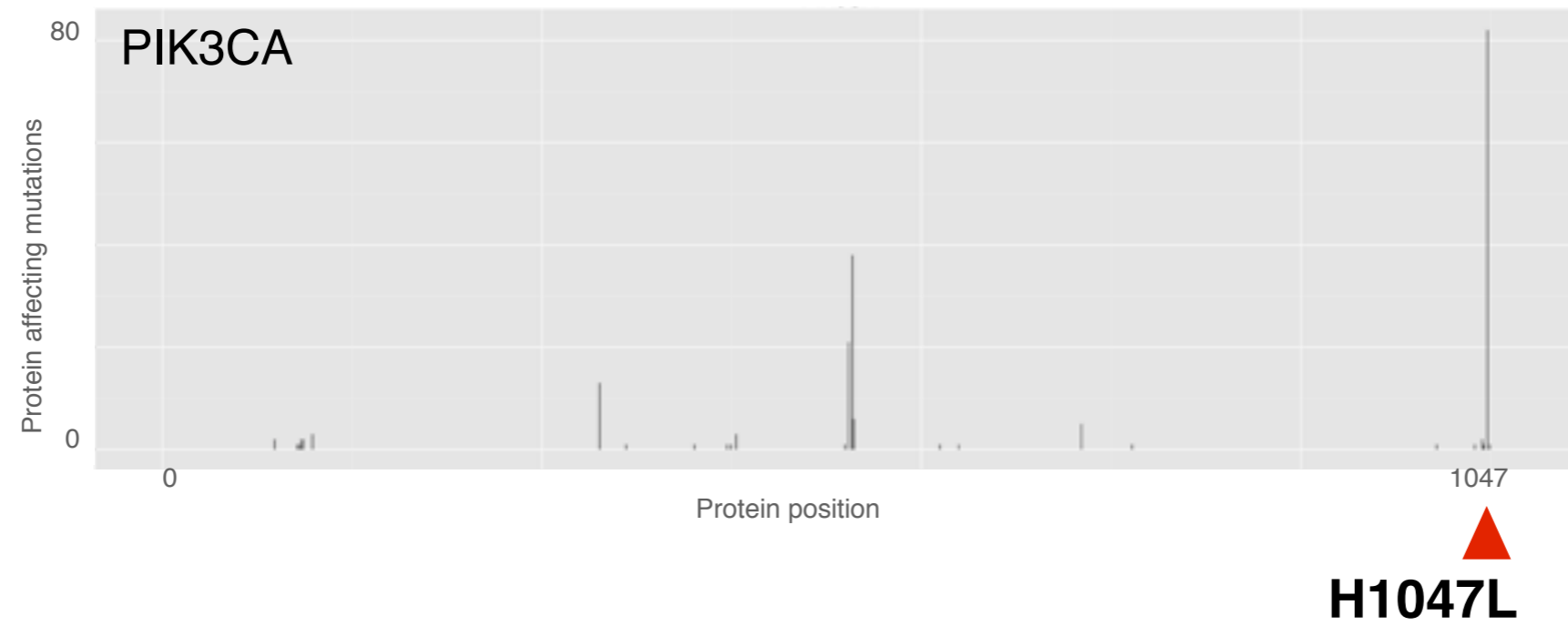
Identify genes mutated more frequently than background mutation rate

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