



# BIMM 143

## Cancer Genomics & Immunoinformatics

Lecture 18

Barry Grant  
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

## 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?

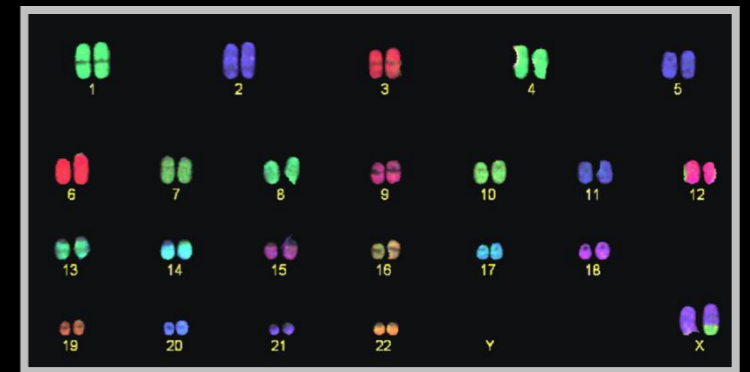
“Cancer is a name given to a collection of related diseases, where some of the body’s cells begin to divide without stopping and spread into surrounding tissue”

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**



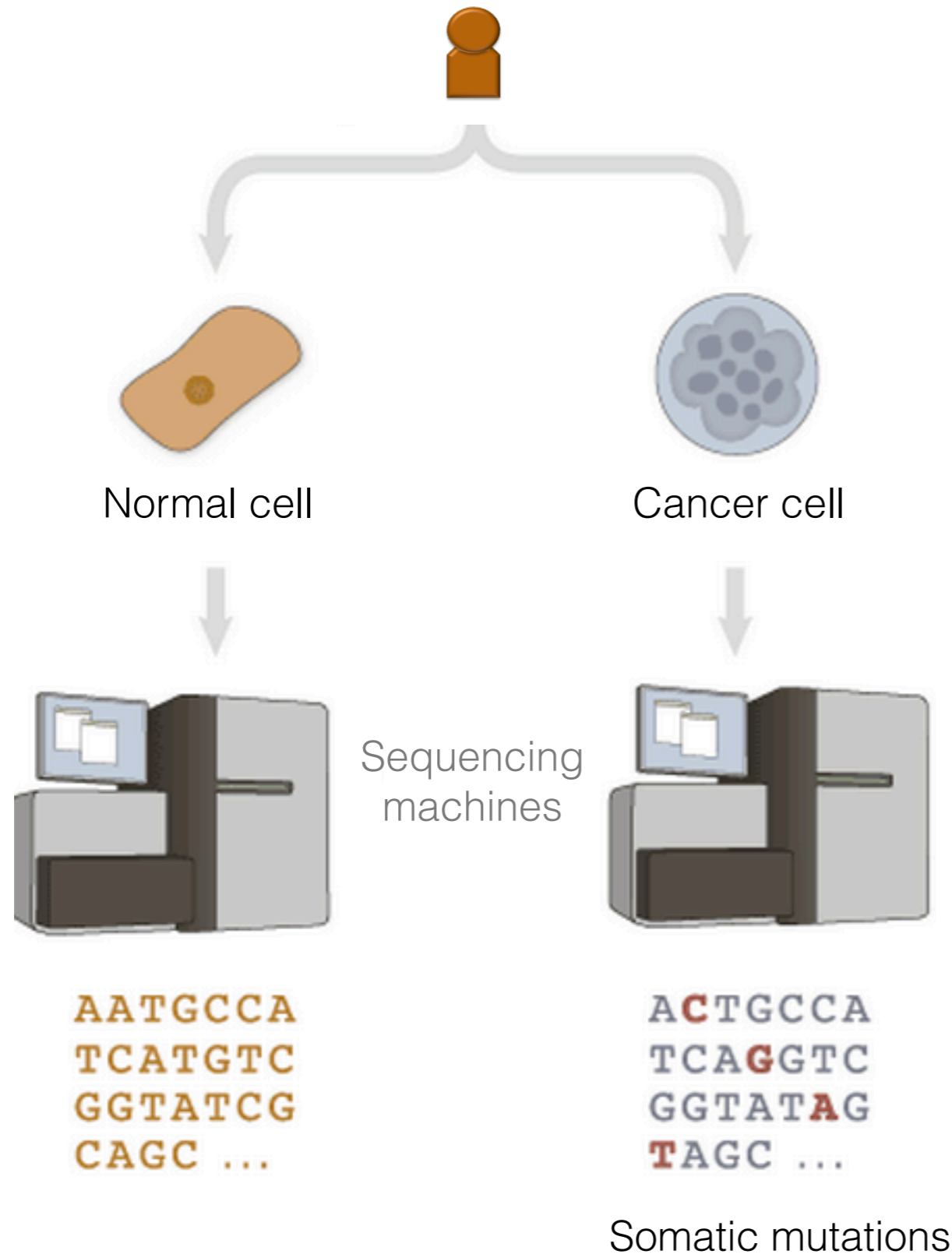
**Example cancer 59  
chromosomes**

# 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 Associated Mutations



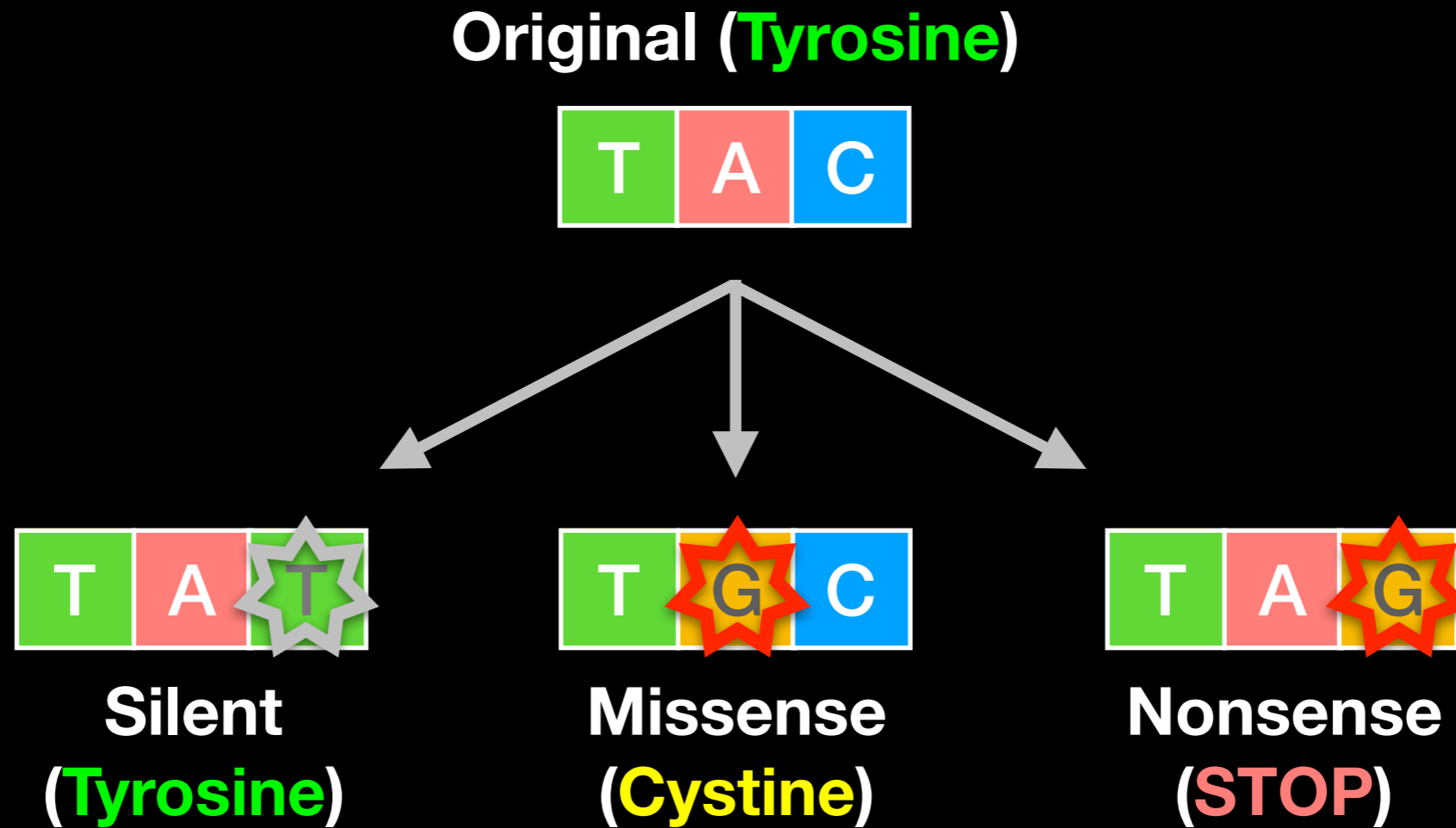
Identify all mutations specific to tumor cells



Filter out silent mutations



# Mutations detected: Point mutations



# Mutations detected: Indels

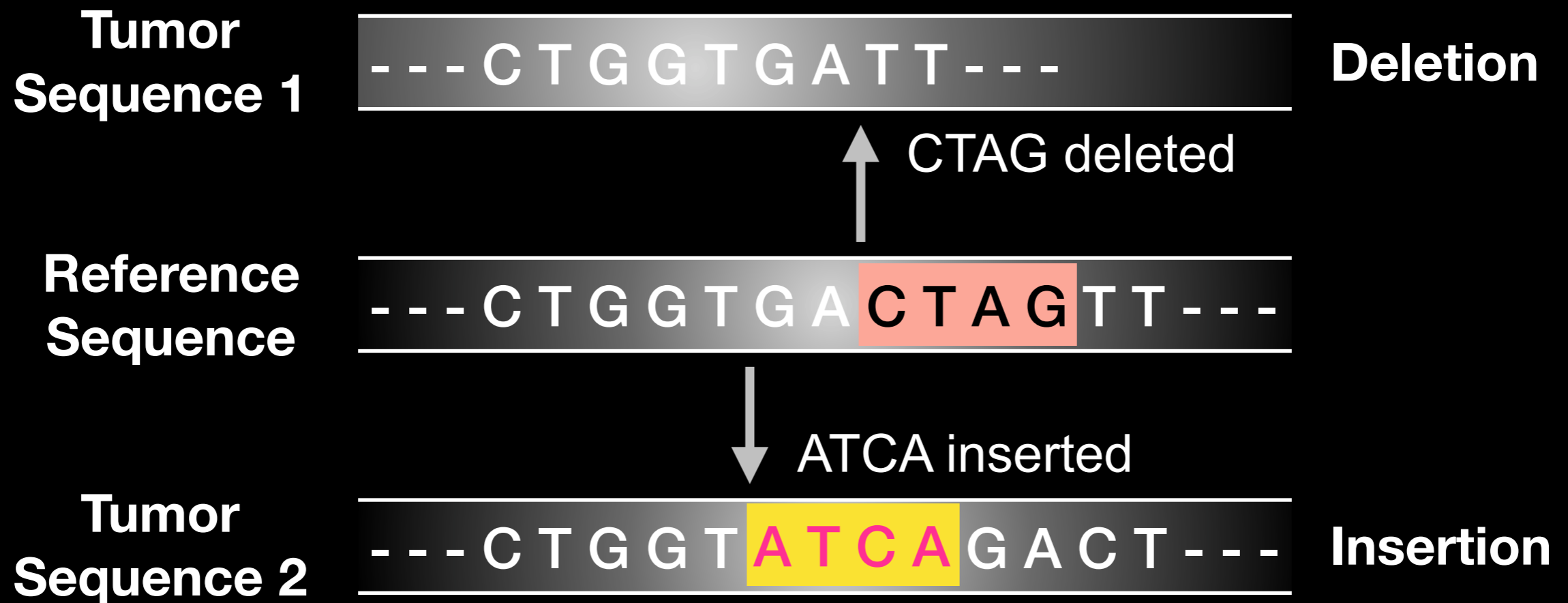
Reference  
Sequence

---CTGGTGACTAGTT---

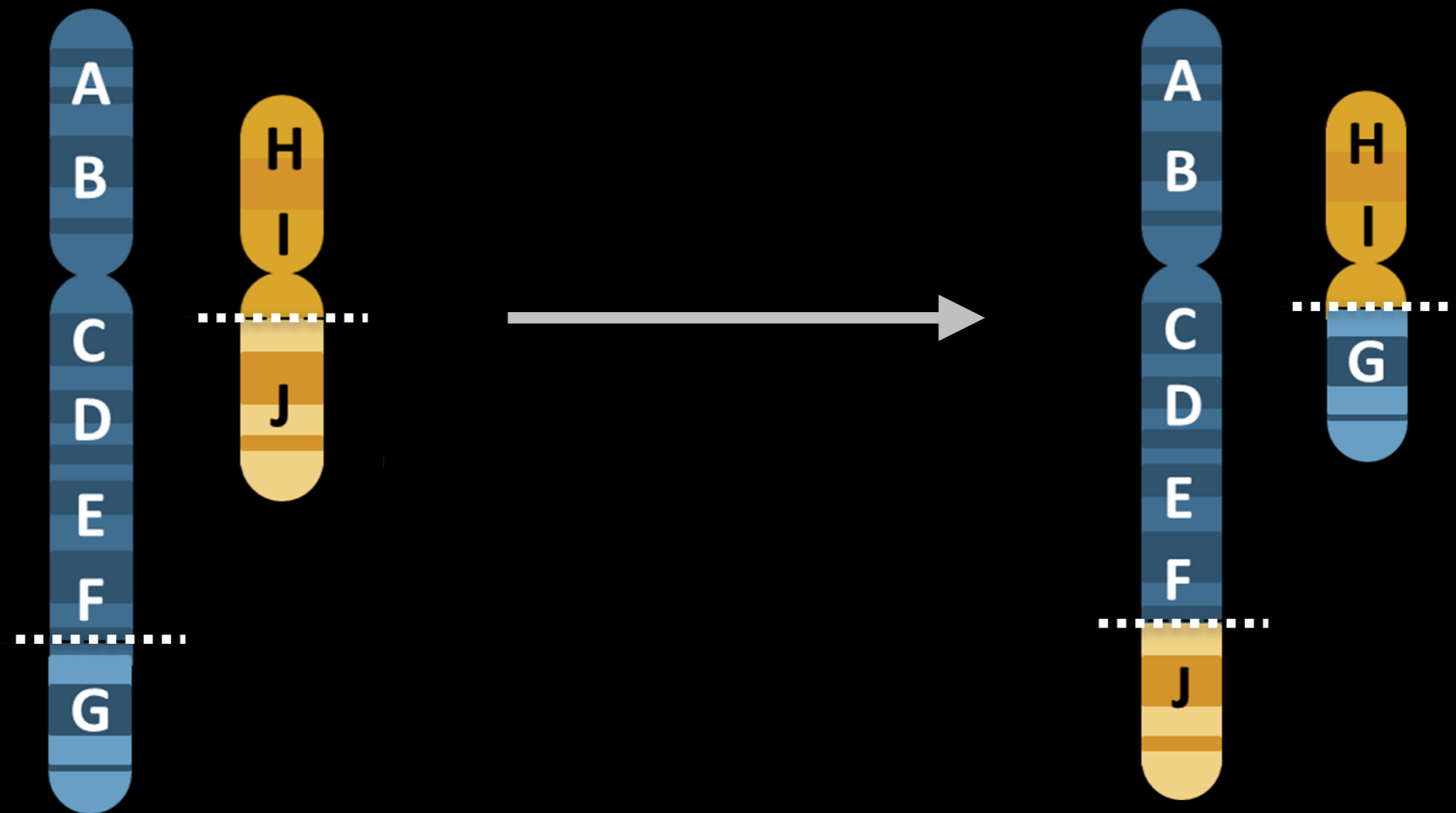




# Mutations detected: Indels



# Mutations detected: Translocations



# What can go wrong in cancer genomes?

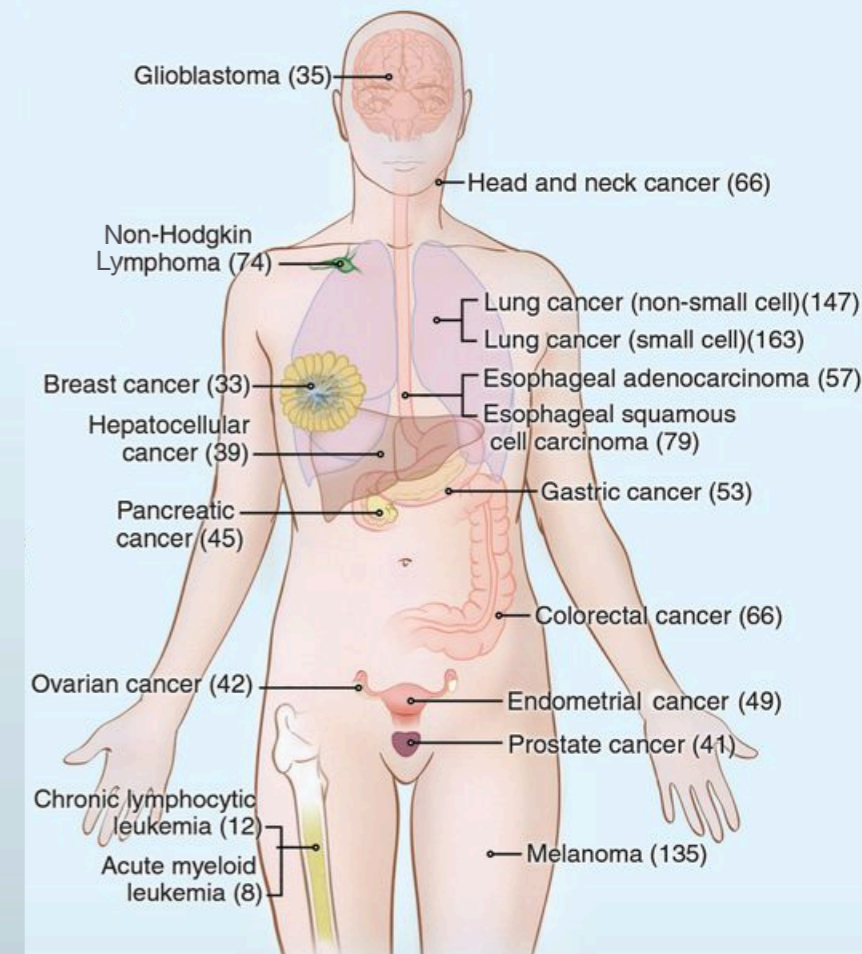
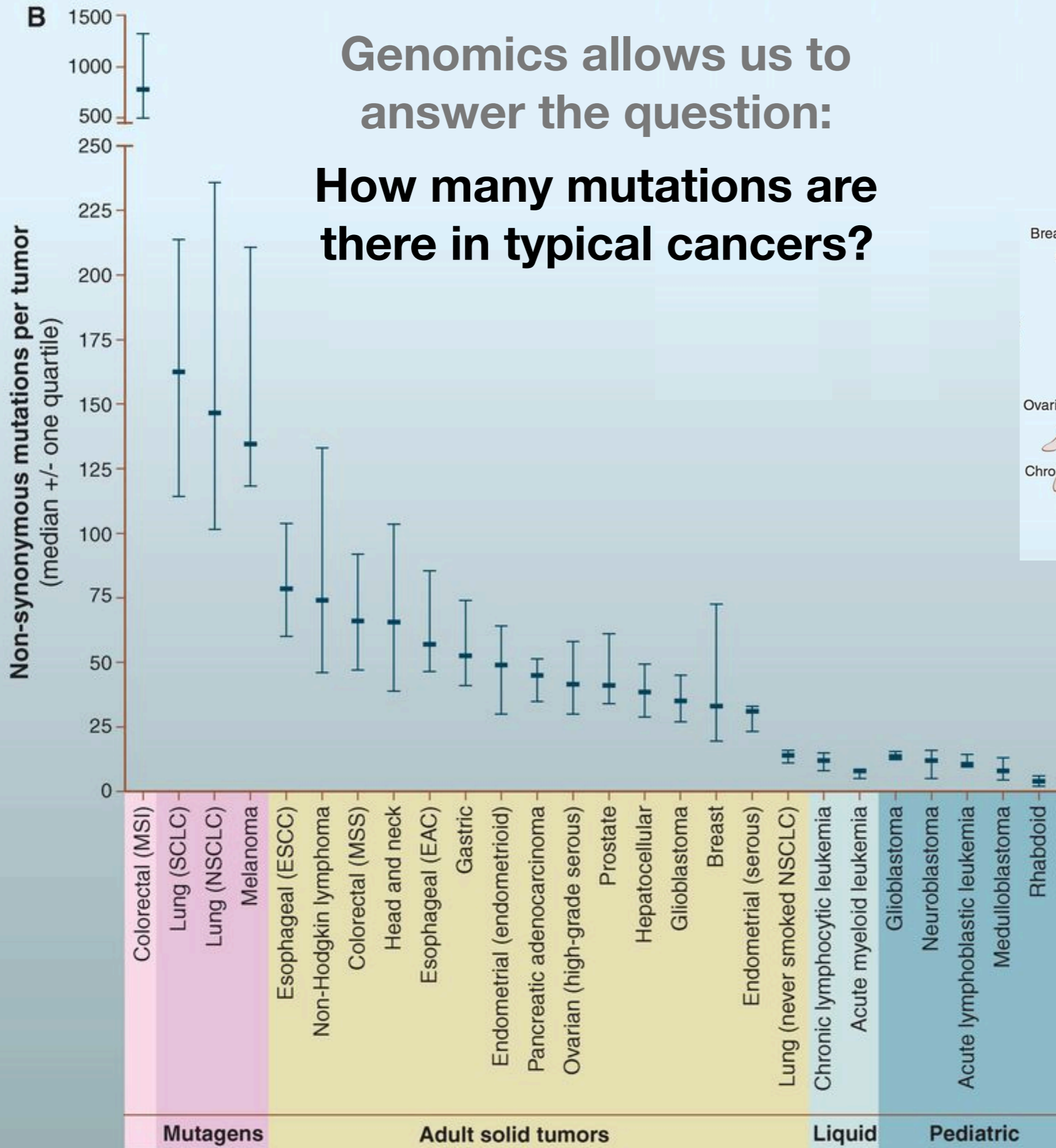
Type of change	Some common technology to study changes
DNA mutations	WGS, WXS
DNA structural variations	WGS
Copy number variation (CNV)	CGH array, SNP array, WGS
DNA methylation	Methylation array, RRBS, WGBS
mRNA expression changes	mRNA expression array, RNA-seq
miRNA expression changes	miRNA expression 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

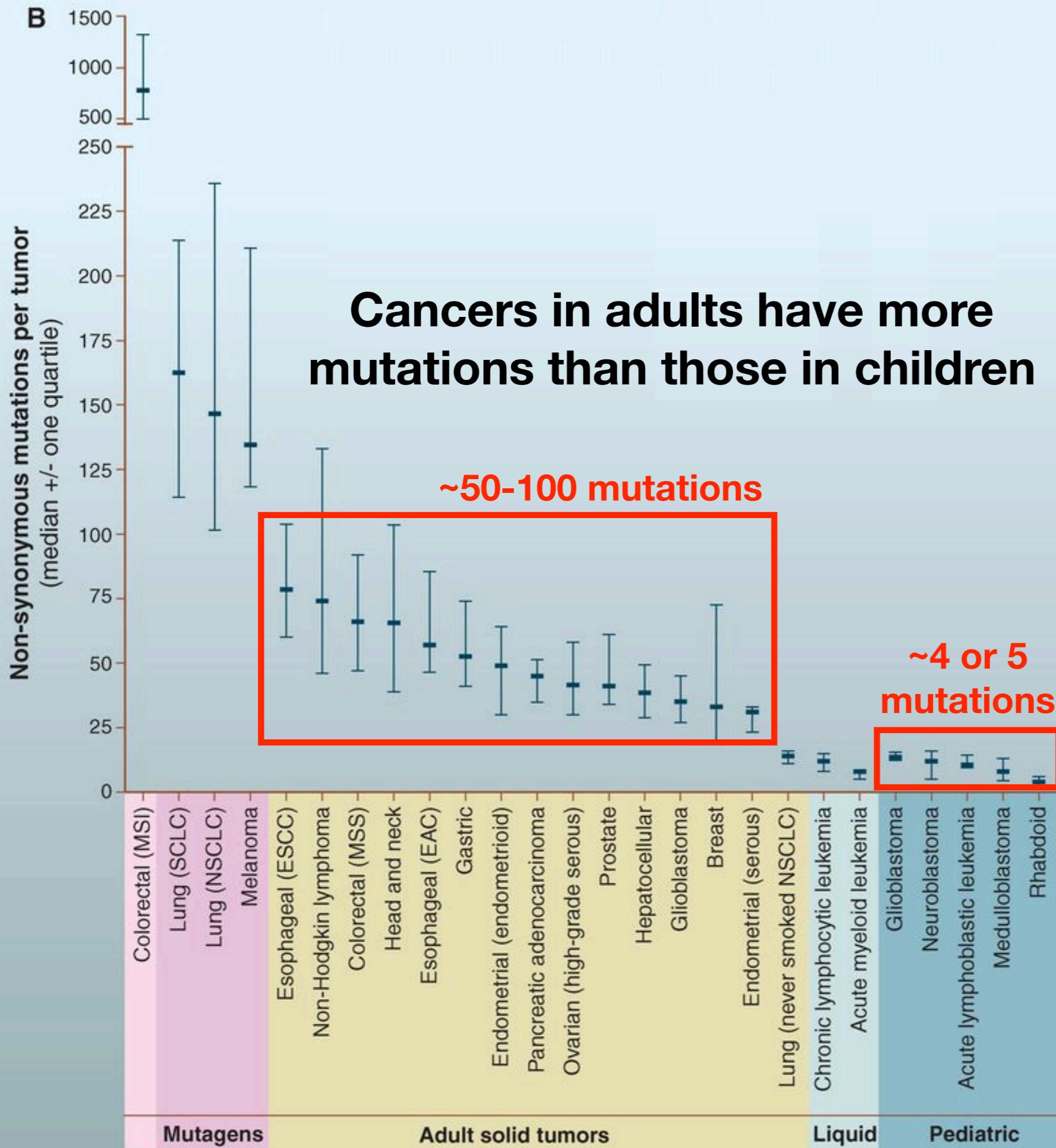


# Genomics allows us to answer the question: How many mutations are there in typical cancers?



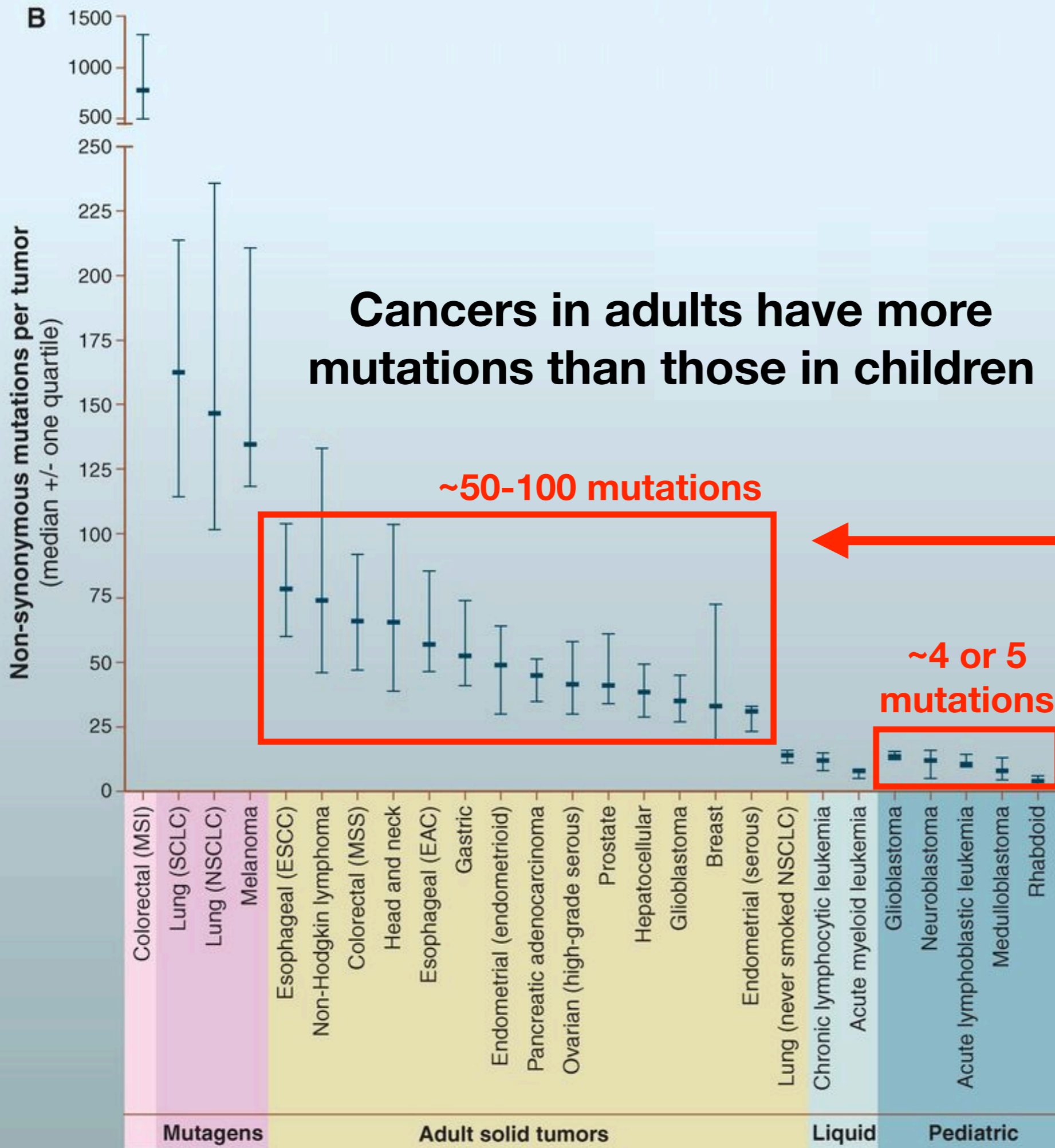
Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

Vogelstein et al. Science (2013)

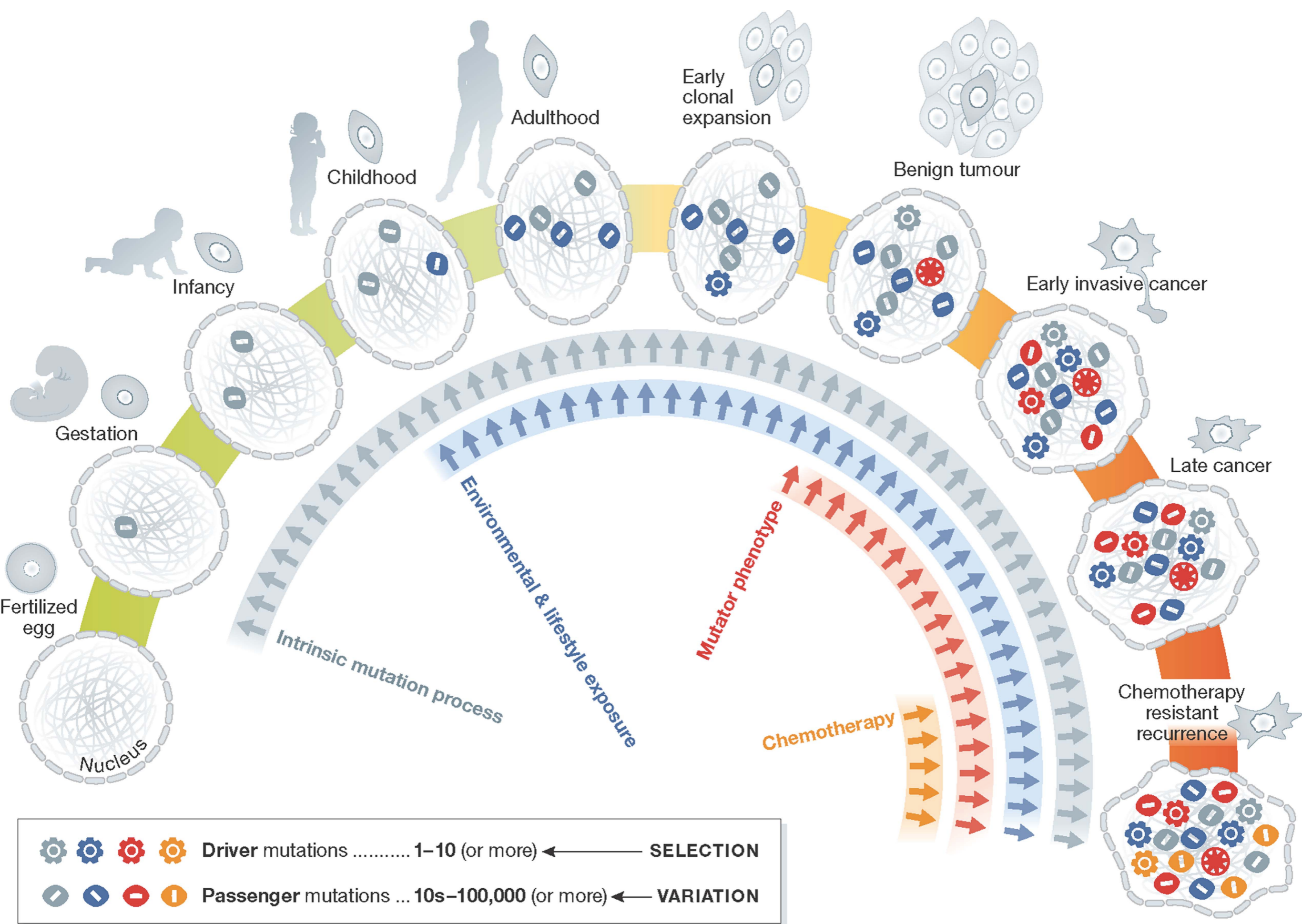


**Vogelstein et al.  
Science (2013)**

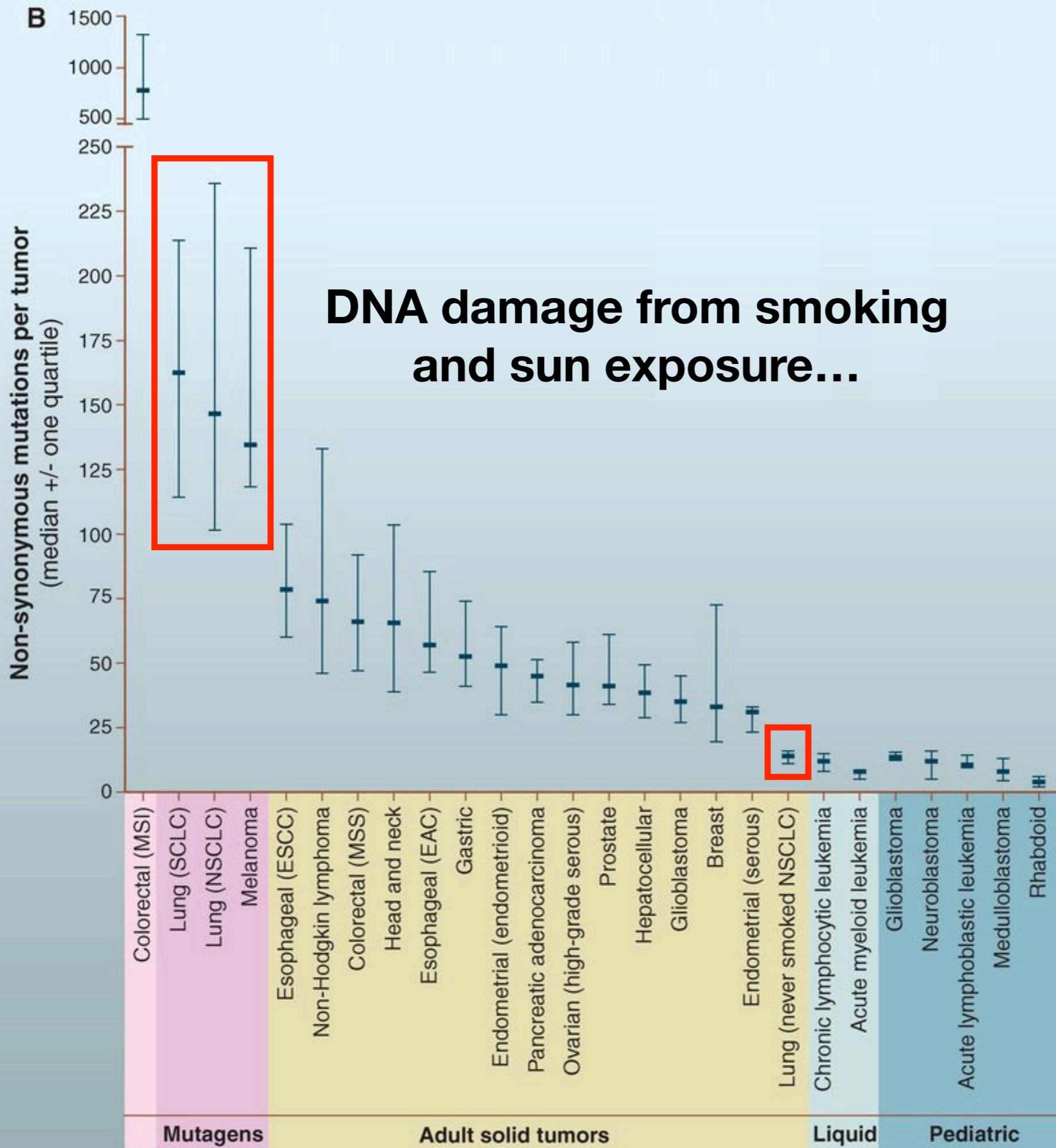




**Vogelstein et al.  
Science (2013)**

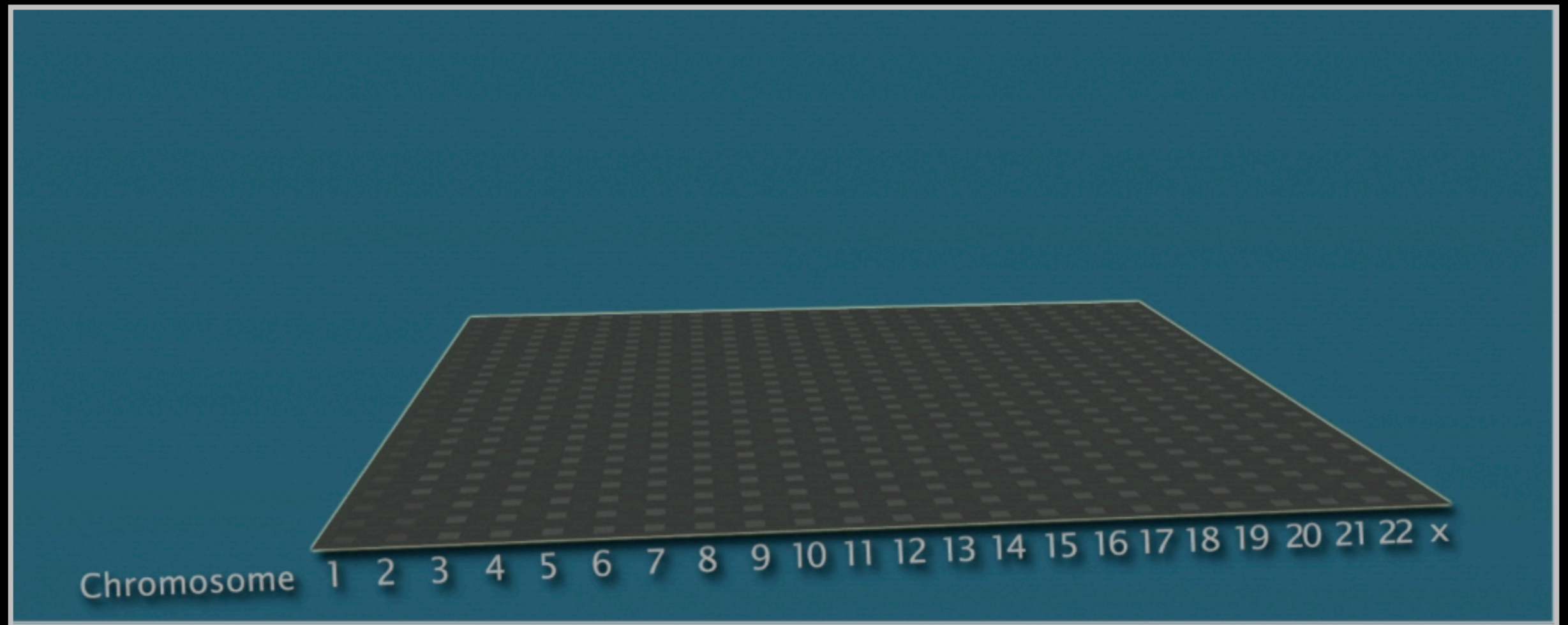






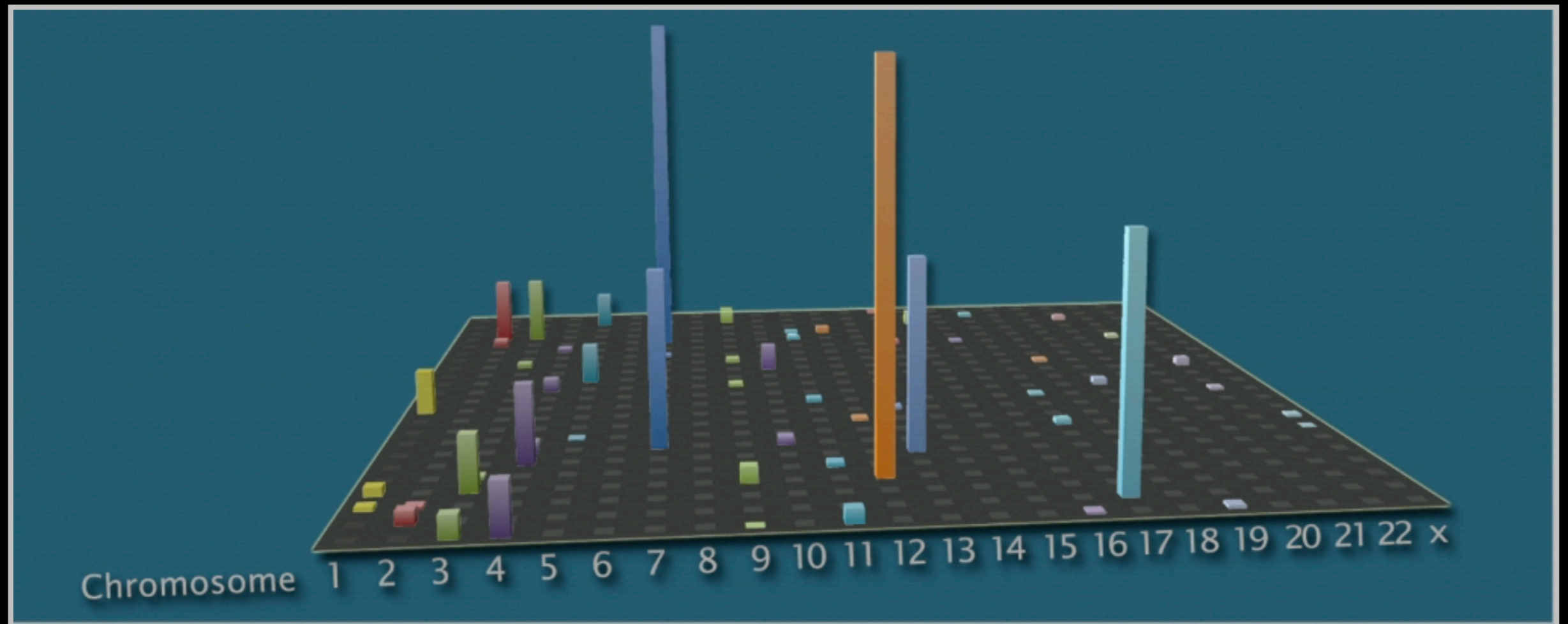
**Vogelstein et al.  
Science (2013)**

# Genomic approaches can identify the genes most commonly mutated in cancer



**Arrange all genes in a matrix, ordered by chromosomes**

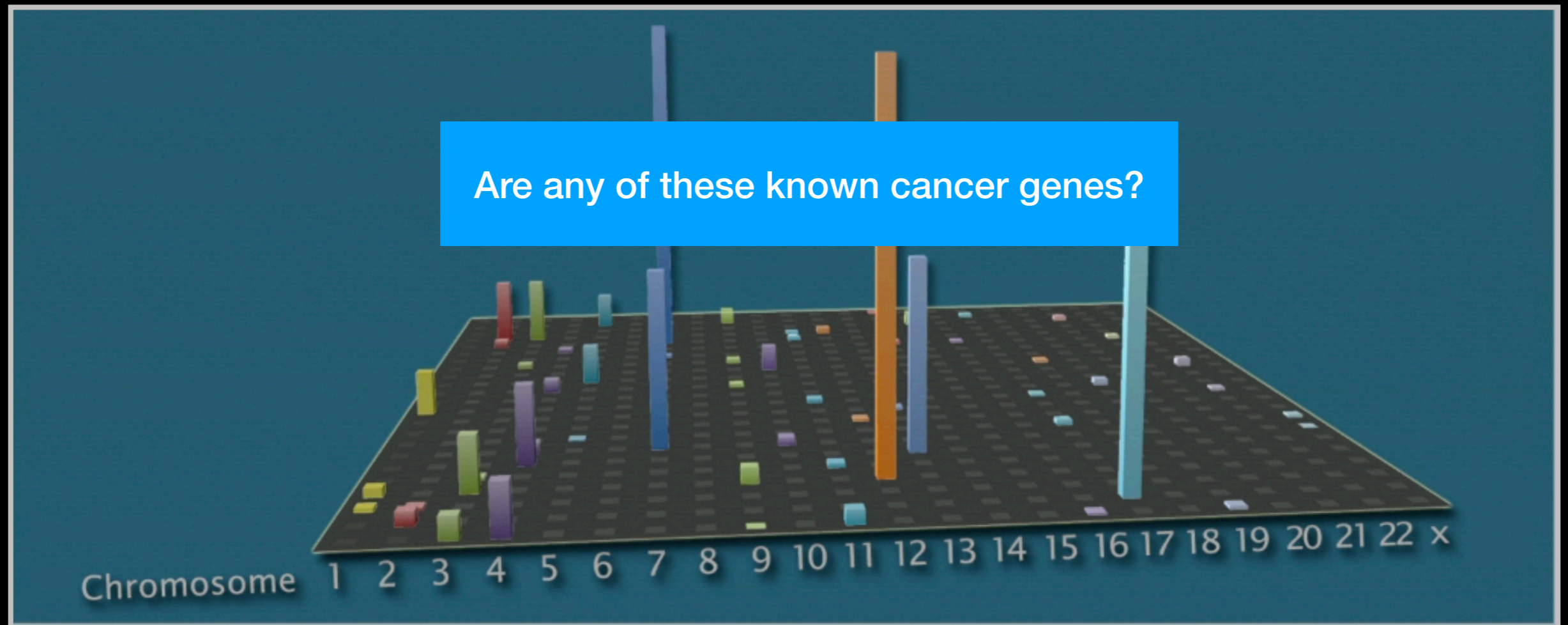
# Identifying genes most commonly mutated in cancer



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

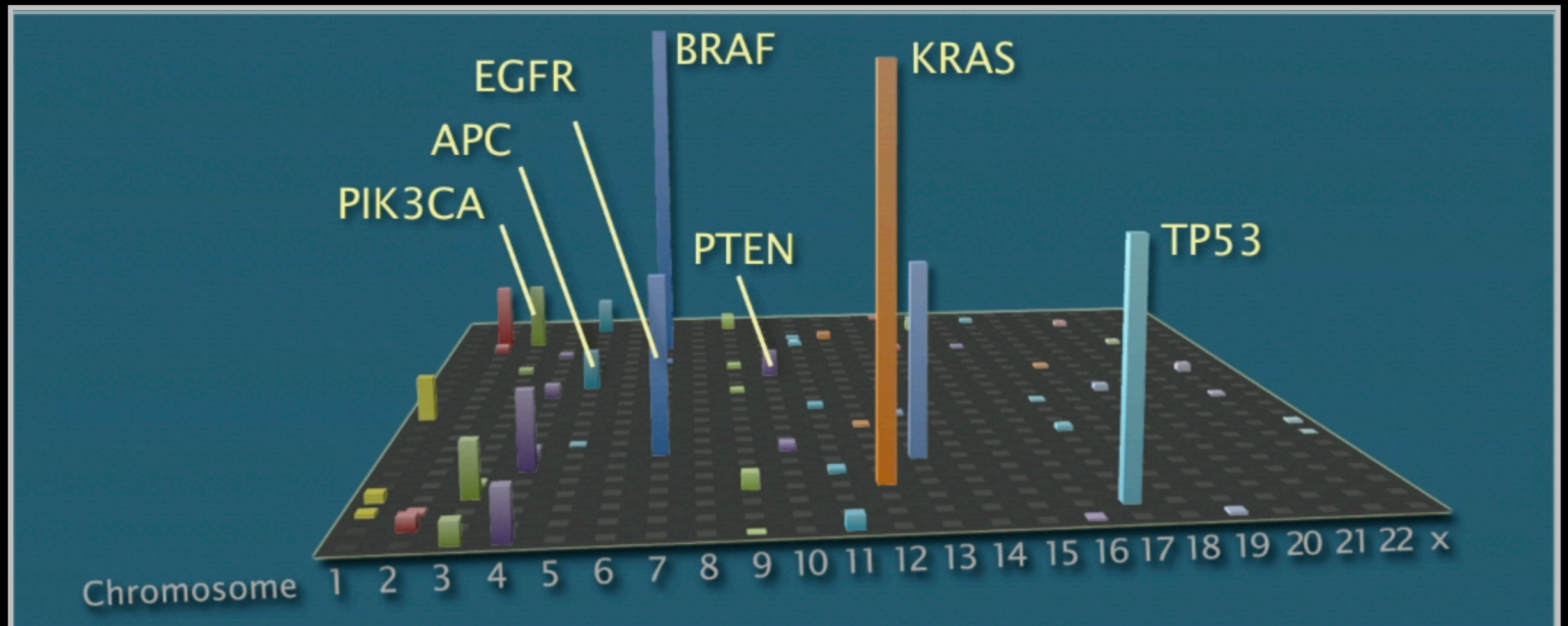


# Identifying genes most commonly mutated in cancer



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

# Identifying genes most commonly mutated in cancer



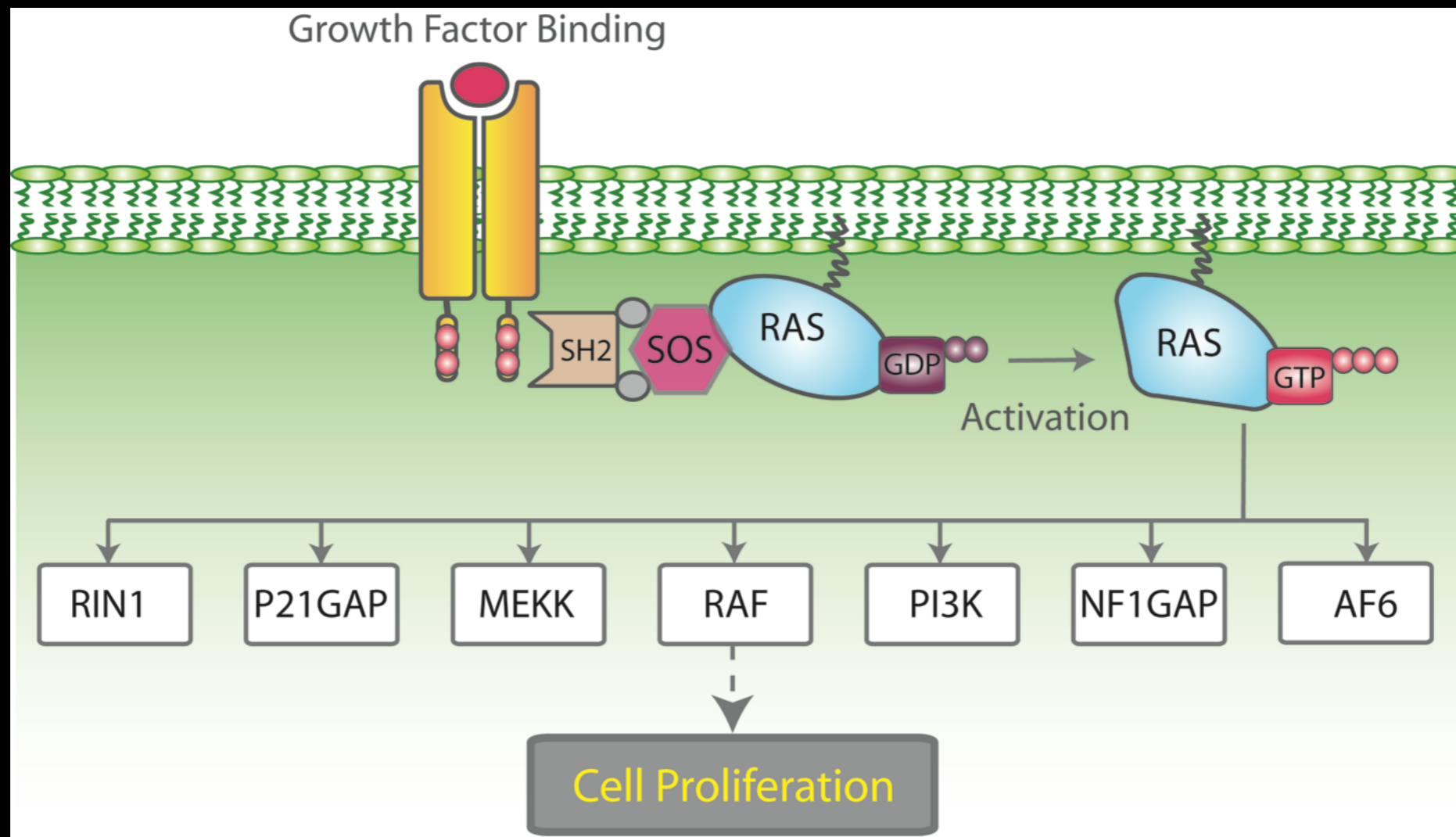
**Many are famous proto-oncogenes, many others are new cancer genes!**

# 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

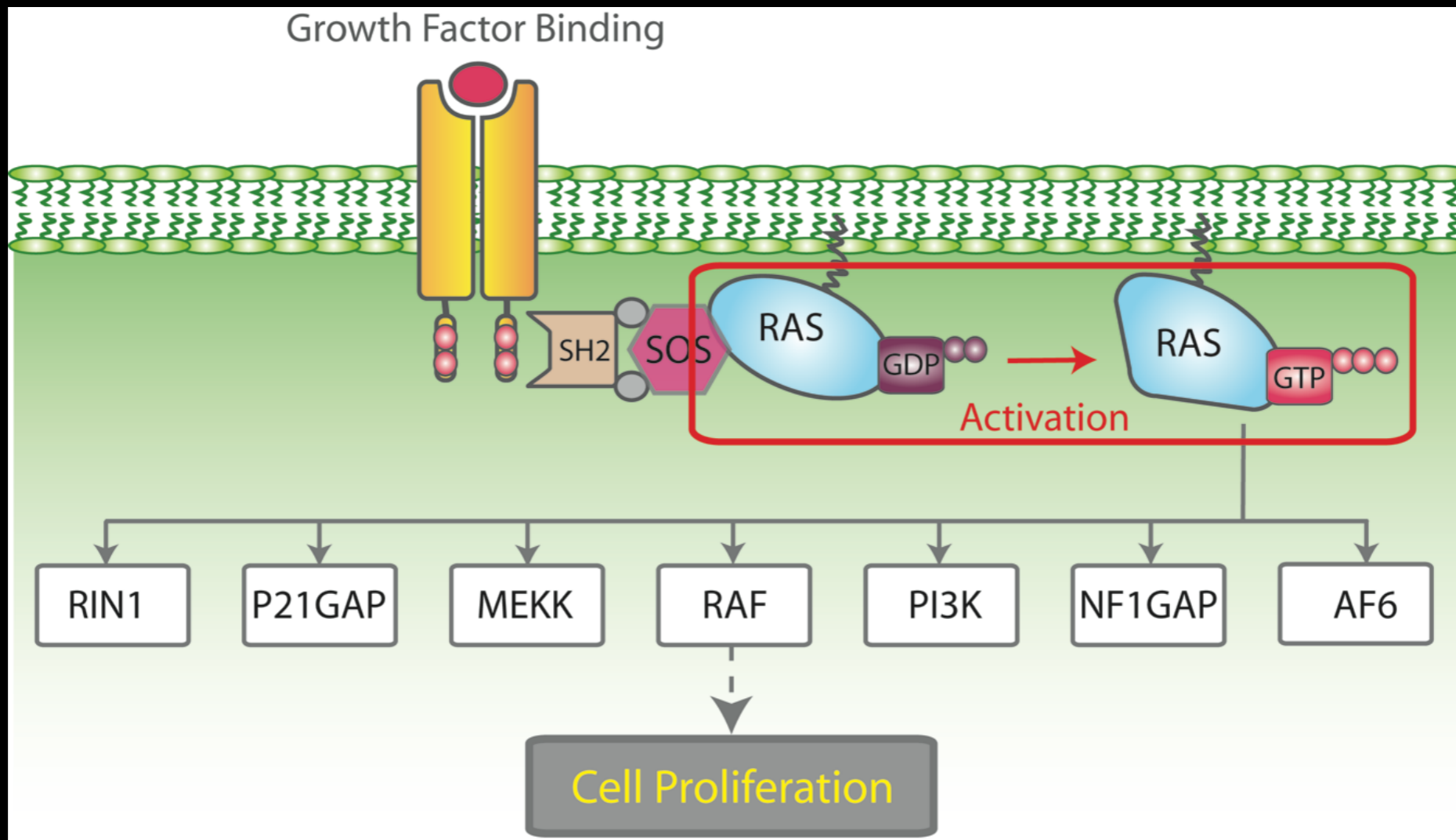
Many participate in signaling pathways that promote cell proliferation  
(E.G. EGFR, Ras, BRAF, MEK etc.)



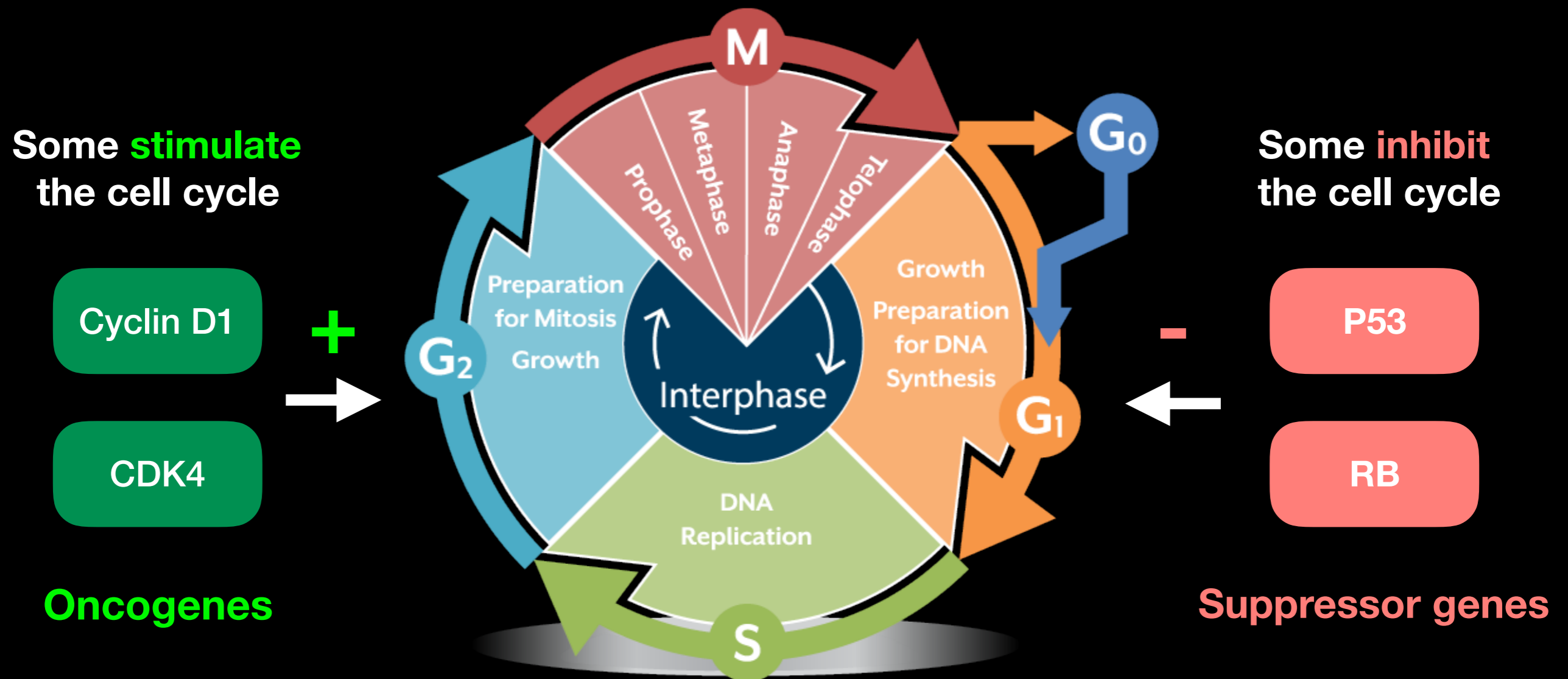


# Cell growth and survival genes

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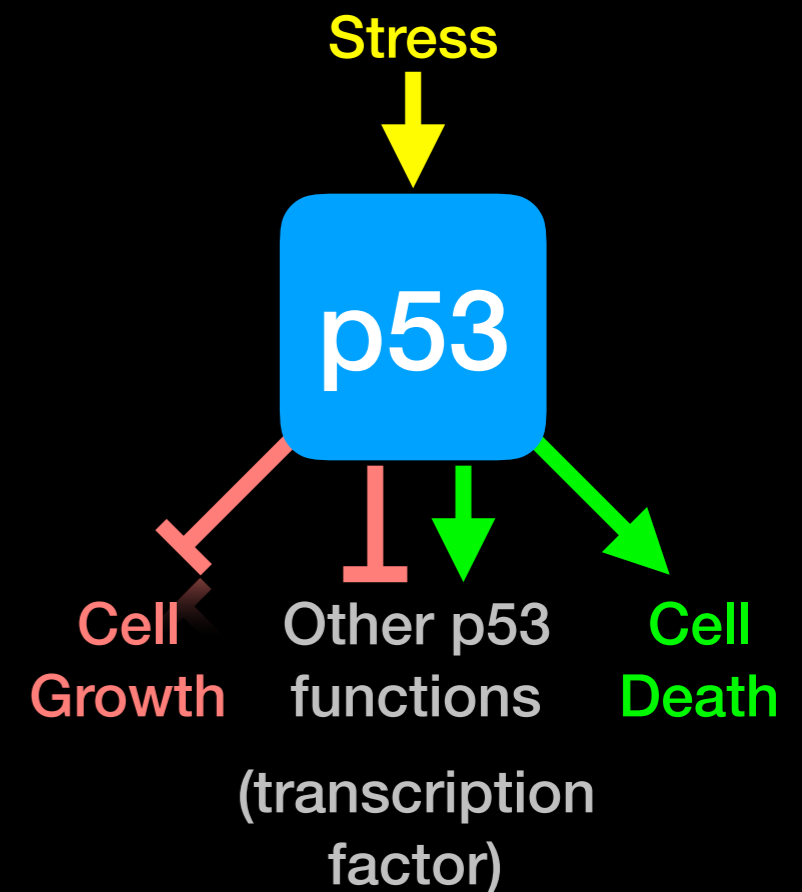
# Regulators of Cell Cycle and Cell Death



# 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!

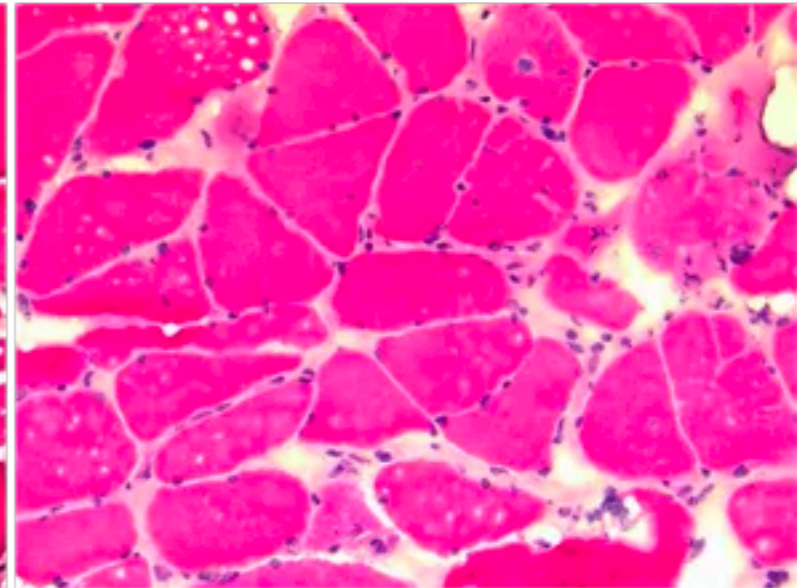
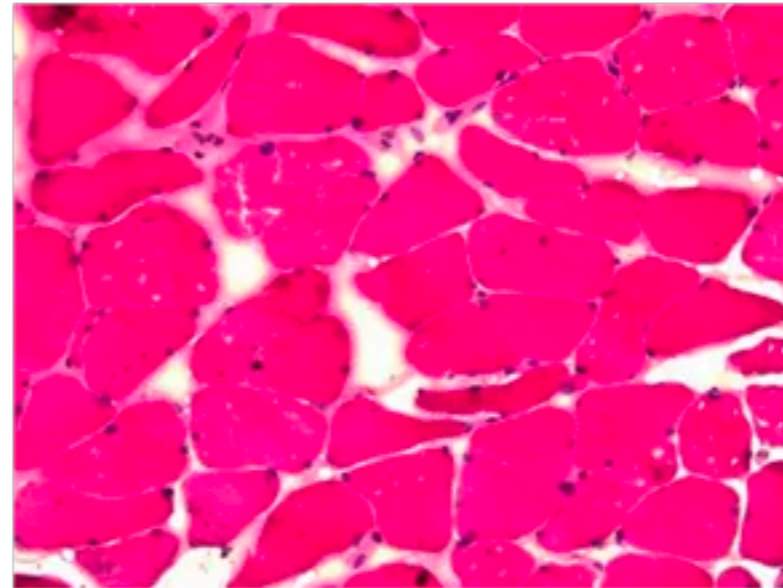
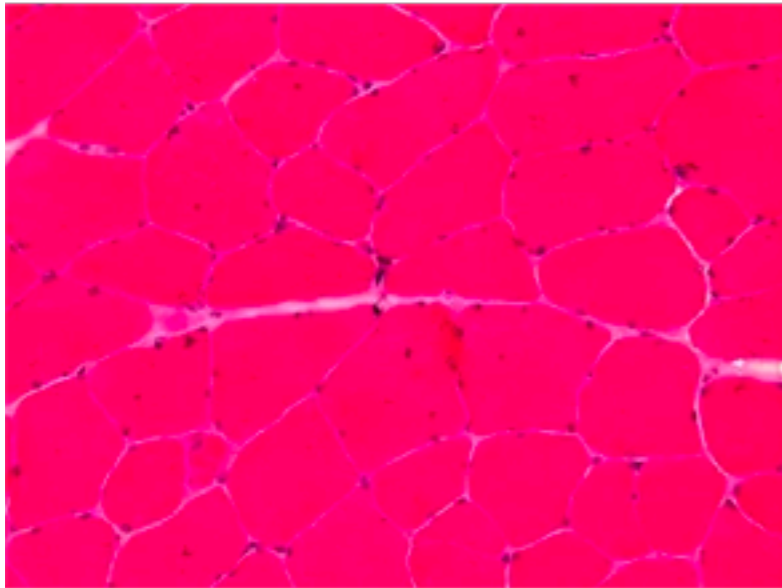
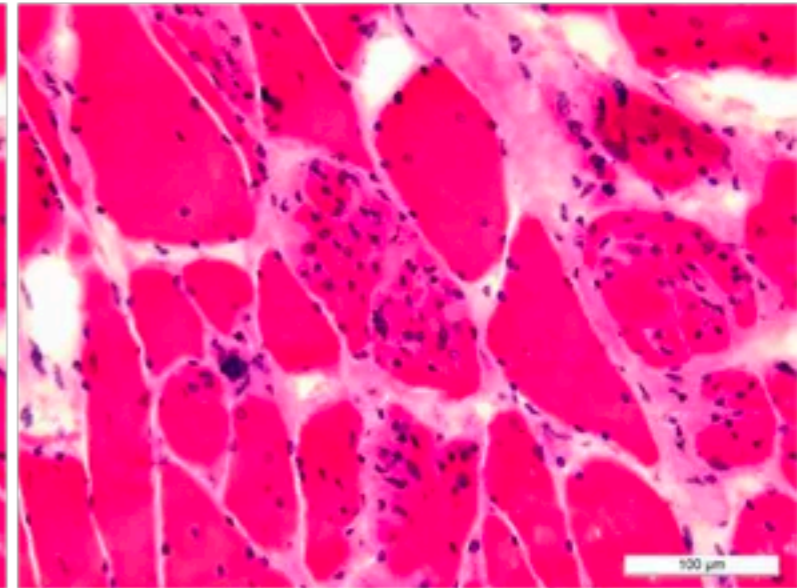
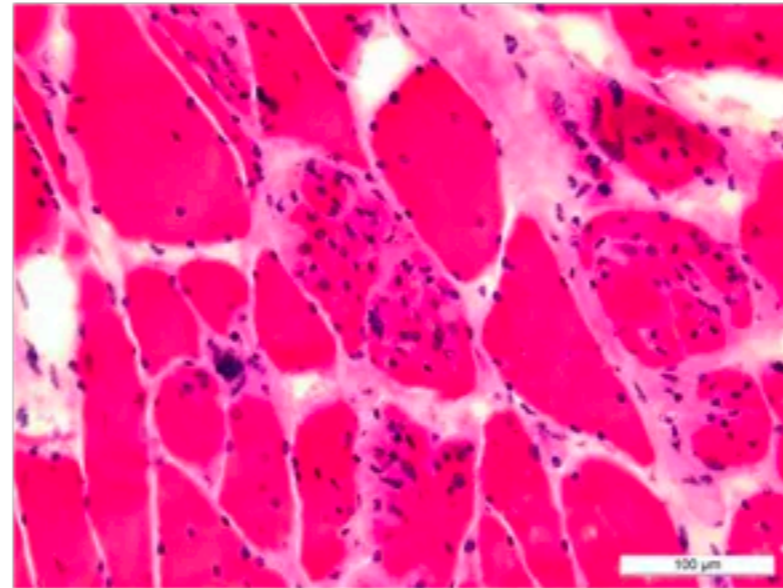
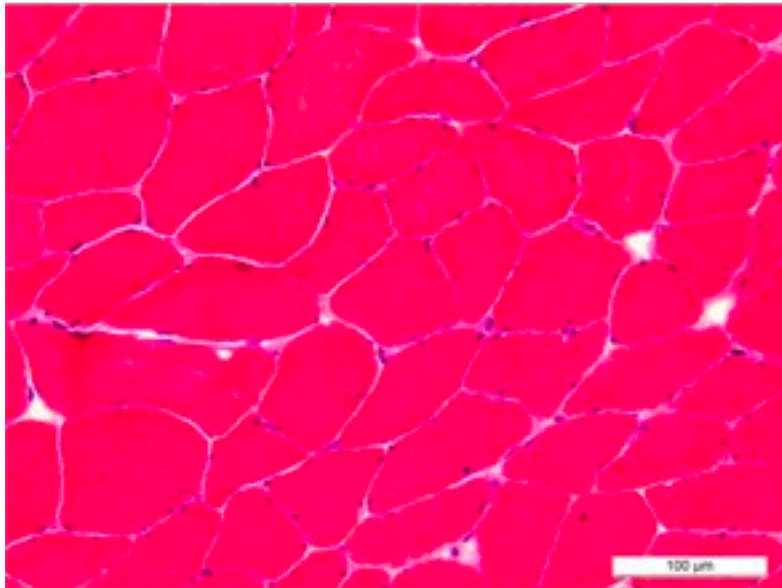
# Hands-on time!

[https://bioboot.github.io/bimm143\\_W19/lectures/#17](https://bioboot.github.io/bimm143_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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## Towards personalized cancer treatments

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mutations that can be recognized by T cells

## Cancer Immunoinformatics

**Hands-on analysis** to design personalized  
cancer vaccines

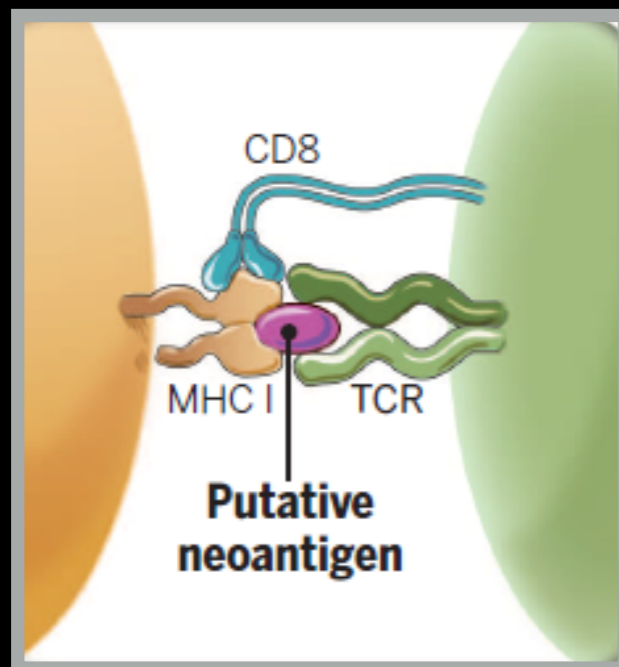
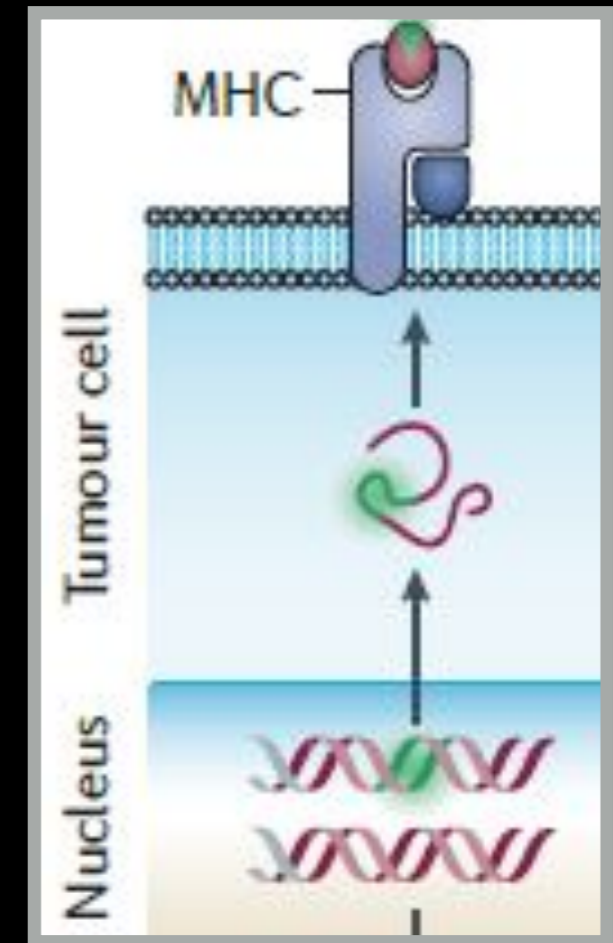
Next Up:

**Next Up:**

**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

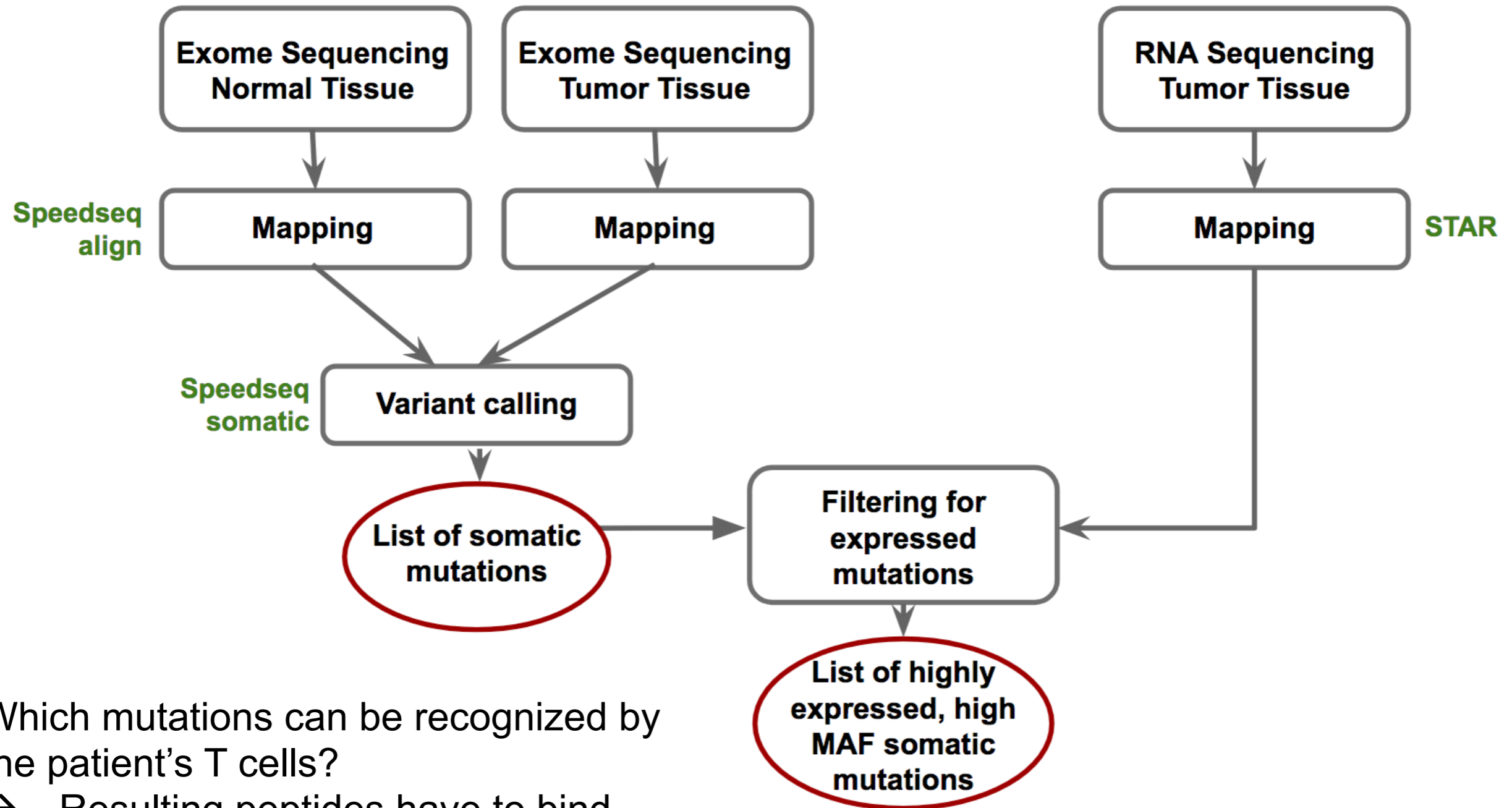
Schumacher & Schreiber, Science. 2015 Apr 3;348(6230):69-74



- **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?

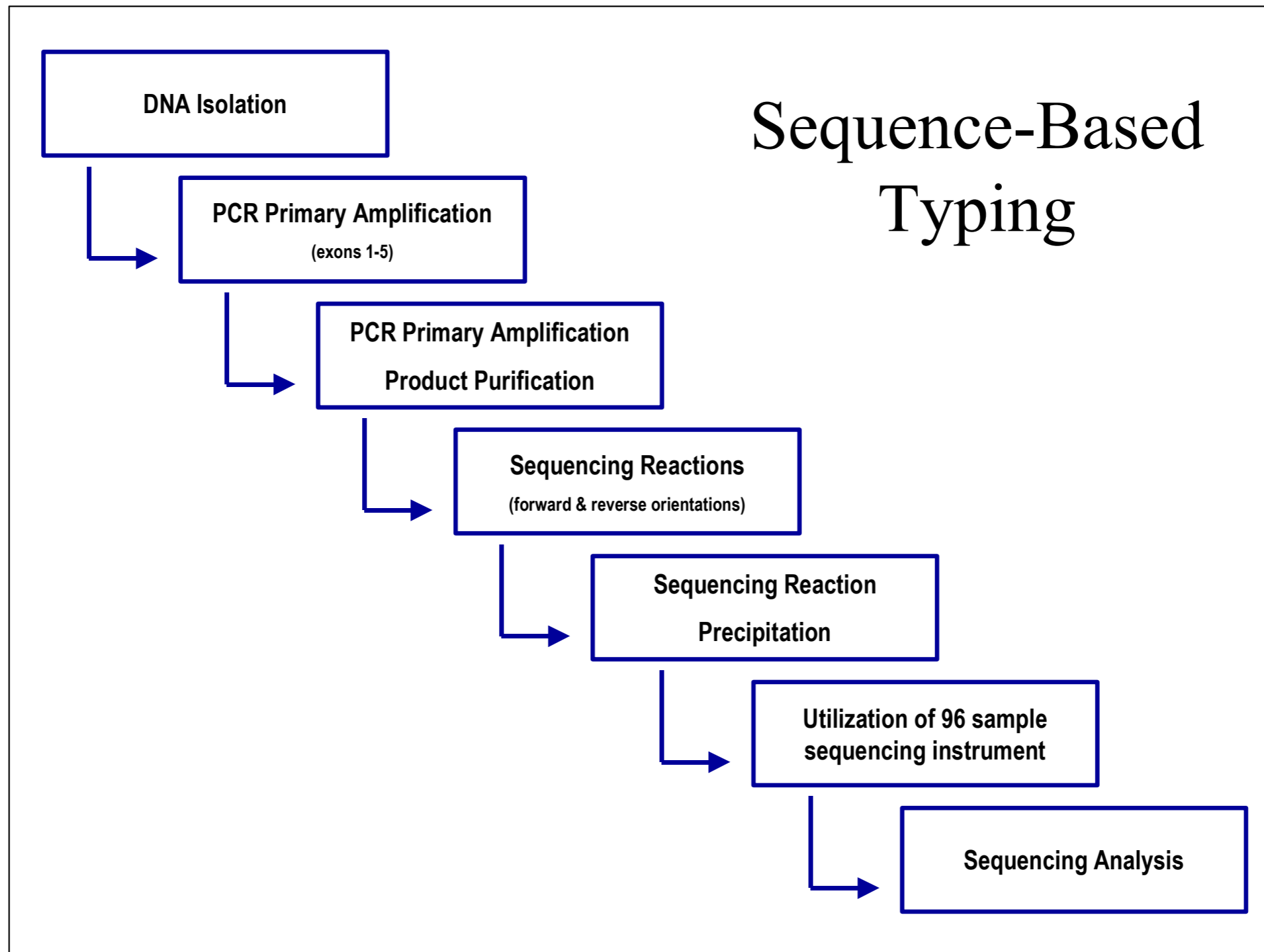
# DNA and RNA sequencing identifies tumor specific somatic mutations



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



•[http://www.ashi-hla.org/publicationfiles/ASHI\\_Quarterly/25\\_2\\_2001/highthrusbt3.htm](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



**IMMUNOTHERAPY**

Unleash



Patient's Immune System

Selectively Kills  
**Cancerous Cells**

**Healthy Cells**



Do it Yourself!

# Hands-on time!

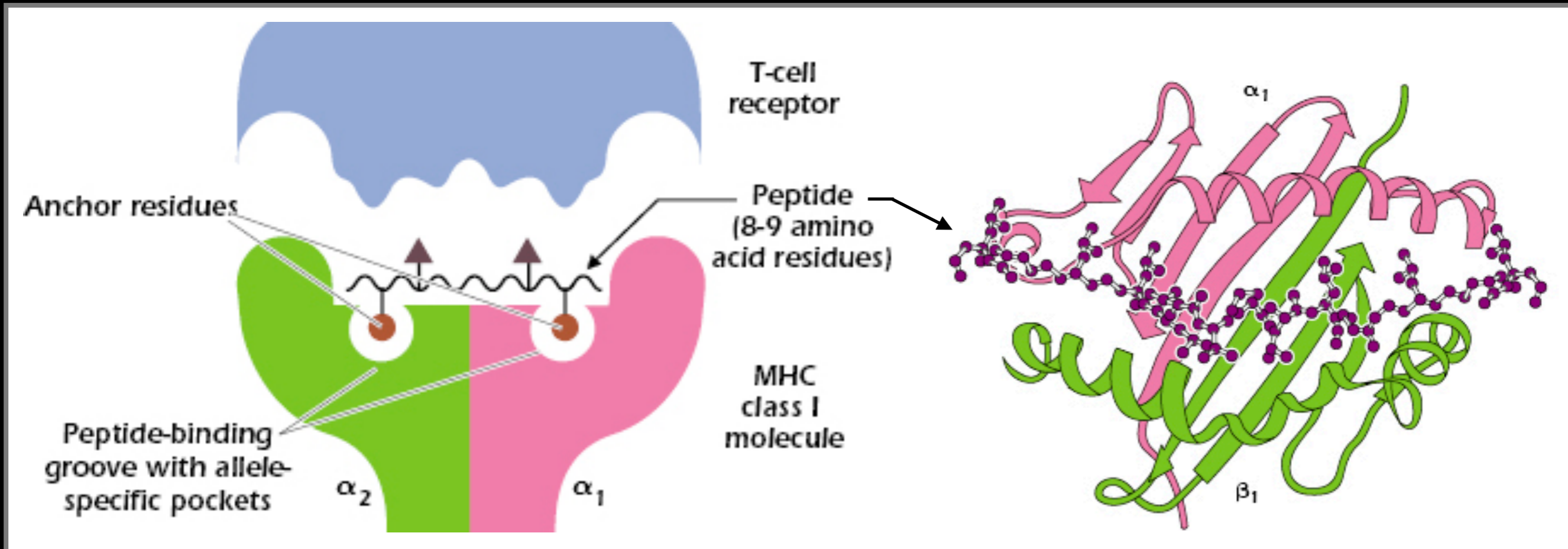
[https://bioboot.github.io/bimm143\\_F18/lectures/#17](https://bioboot.github.io/bimm143_F18/lectures/#17)

**Part 2: Designing a personalized cancer vaccine**

# Workflow:

- **Step 1:** Identify sequence regions that contain all **9-mer** peptides that are only found in the tumor
- **Step 2:** Run HLA binding prediction to identify 9-mer peptides in the sequence regions unique to the tumor to select peptides that can be **presented to T cells** in this patient
- **Step 3:** Determine if the identified peptides are specific for the tumor (i.e. are they found anywhere else?)
- **Final question:** Which peptide would you choose?

# Depictions of the peptide bound MHC and T-cell receptor



## Note:

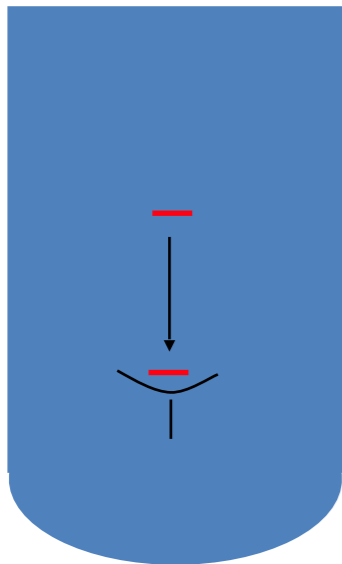
- Anchor residues in the peptide bind to the allele-specific pockets of the MHC molecule.
- Certain MHC molecules (alleles) preferentially bind peptides with specific anchor residues in the 8- or 9-amino-acid peptide sequence.
- We want our tumor specific residues to be within 8 to 9-mer sequences bound by a patient HLA alleles!

**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 <sub>50</sub>
QIVTMFEAL	3.6
LKGPDIYKG	308
NFCNLTSAF	50,000
AQSQCRTFR	38,000
CTYAGPFGM	143
CFGNTAVAK	50,000
...	

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

low IC<sub>50</sub> → 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 ...

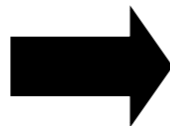


# Calculate scoring matrix from affinities

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
...	

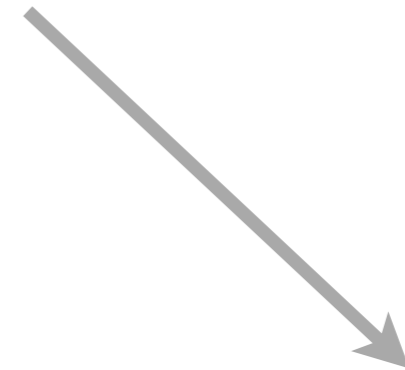
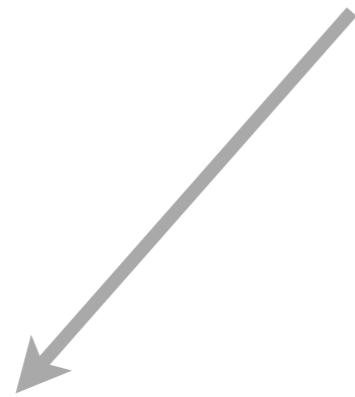
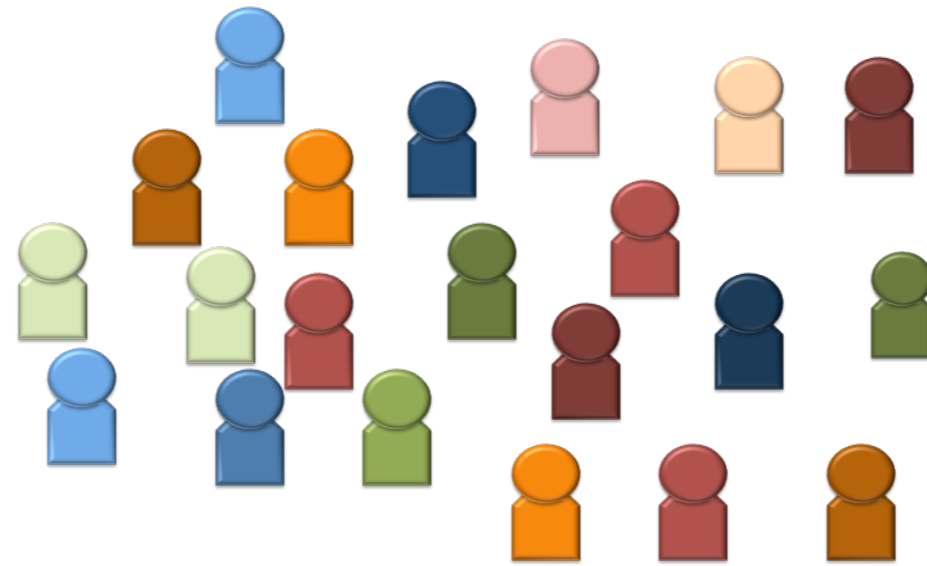


	HLA A*0201								
	1	2	3	4	5	6	7	8	9
A	-0.3	0.8	-0.3	-0.3	-0.2	-0.3	0.0	0.0	-0.9
C	0.2	0.9	0.0	0.3	-0.5	-0.1	0.1	0.2	0.4
D	0.8	0.9	-0.4	-0.3	0.3	0.2	0.4	0.3	0.6
E	0.6	-0.4	0.7	-0.2	0.1	-0.4	-0.2	-0.2	-0.5
F	-1.3	0.5	-0.5	0.1	-0.1	0.0	-0.3	-0.4	-0.8
G	-0.2	0.1	0.3	-0.1	0.0	0.4	0.3	-0.1	0.2
H	1.1	0.9	-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

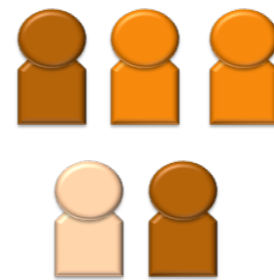
Offset: 4.3

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

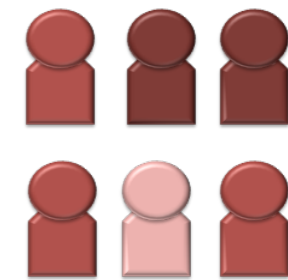
# Stratify tumors based on molecular patterns



Good prognosis  
Favorable response

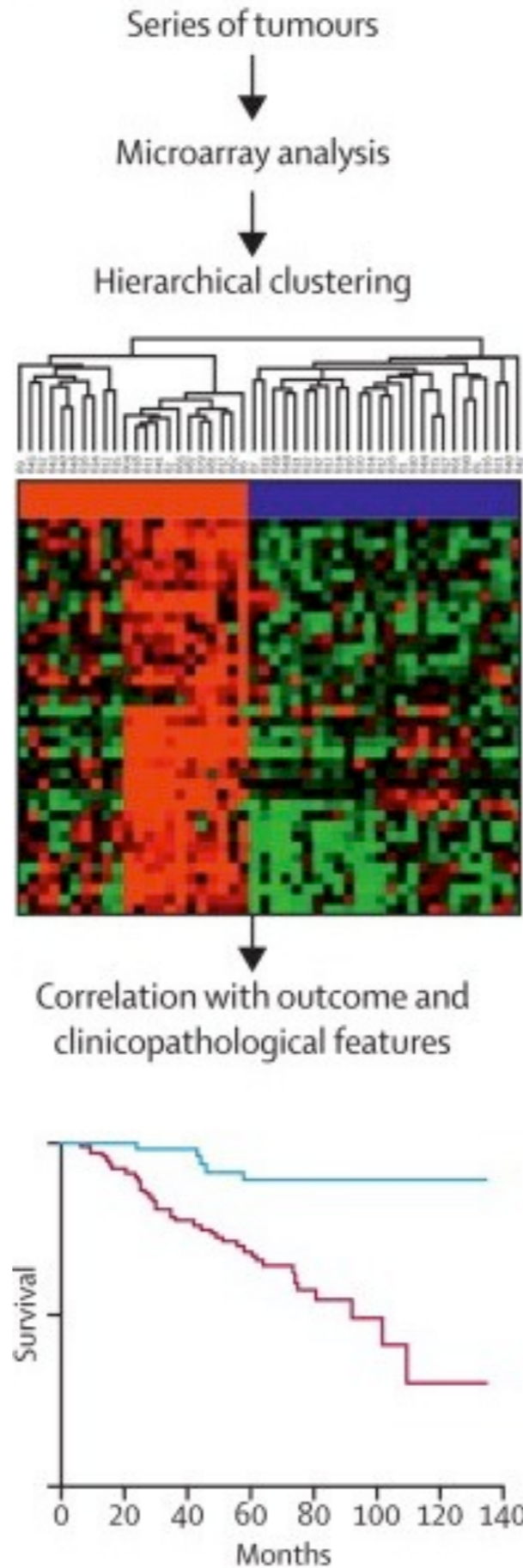


Bad prognosis  
Unfavorable response



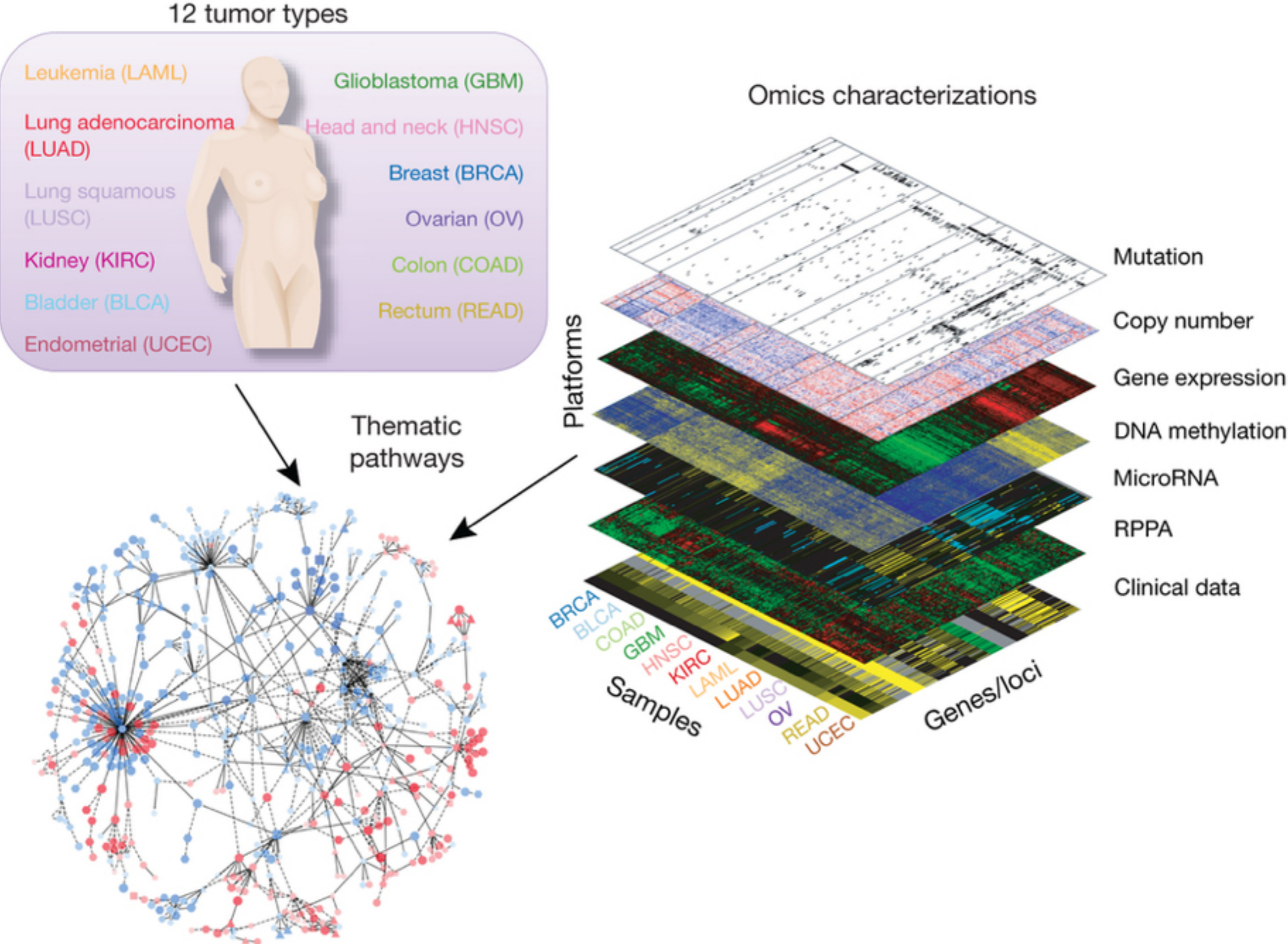
Increased toxicity

# Stratify tumors based on molecular patterns





# TCGA Pan-Cancer project

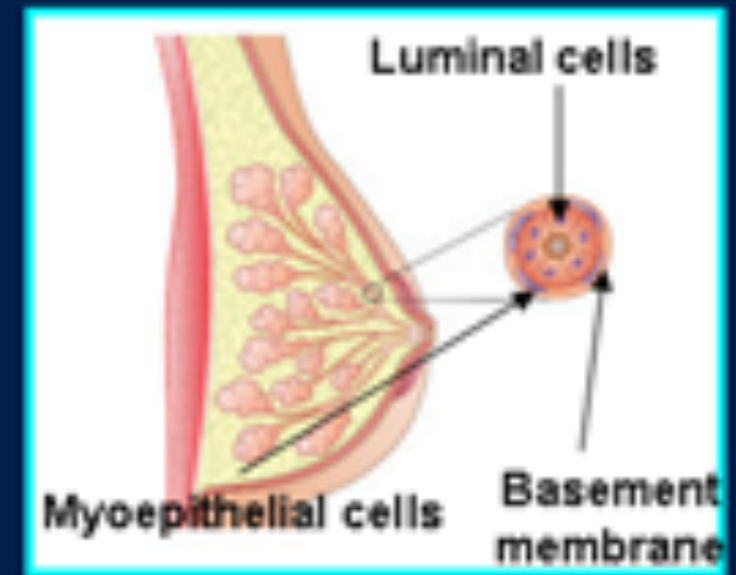
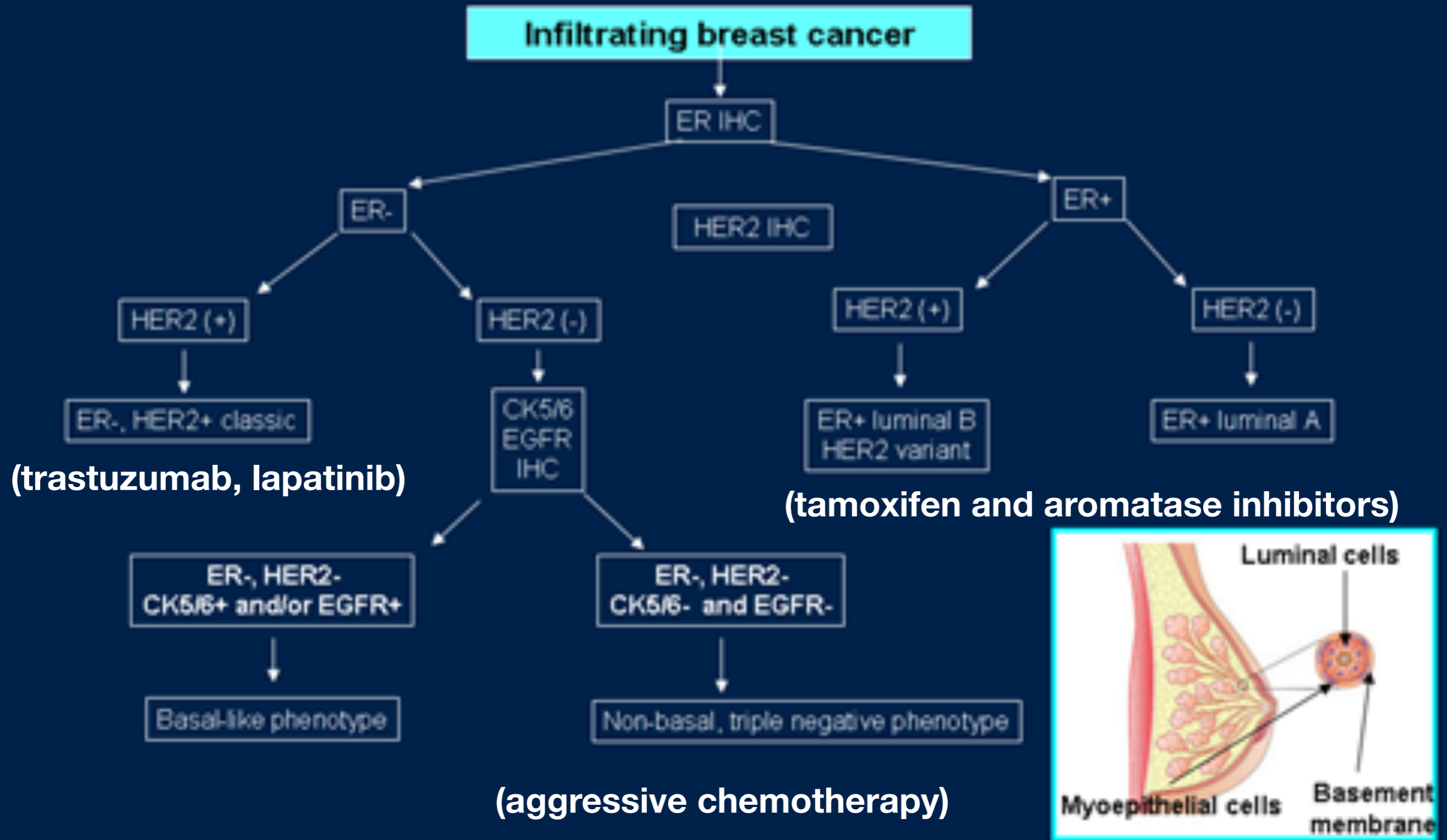




**For example, breast cancer may be classified into various types based upon which proteins are expressed on the surface of the tumor cells. Breast tumors that express human epidermal growth factor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR), or are triple negative (do not express 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,<sup>1,2</sup> Philippe L. Bedard,<sup>3,4</sup> Nicole Onetto,<sup>1</sup> and Thomas J. Hudson<sup>1,5,6,\*</sup>

<sup>1</sup>Ontario Institute for Cancer Research, Toronto, ON M5G 0A3, Canada

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

<sup>3</sup>Princess Margaret Hospital, Division of Medical Oncology and Hematology, University Health Network

<sup>4</sup>Department of Medicine

<sup>5</sup>Department of Medical Biophysics

<sup>6</sup>Department of Molecular Genetics

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

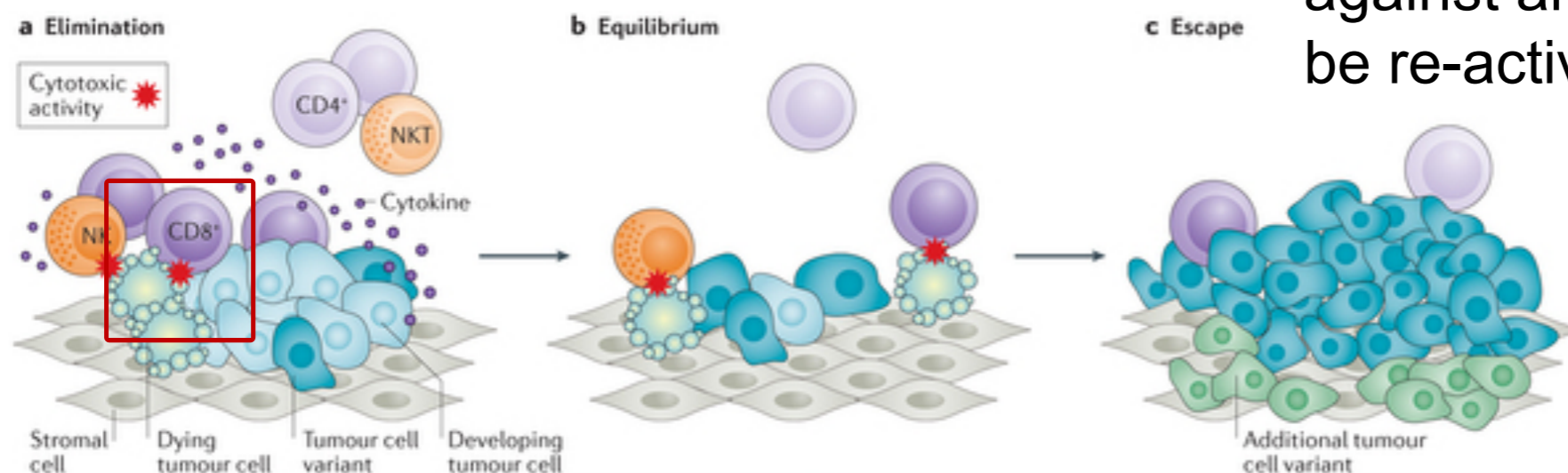
\*Correspondence: [tom.hudson@oicr.on.ca](mailto:tom.hudson@oicr.on.ca)

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.

# Cancer immune surveillance and escape

- Mutations in cells occur frequently
- The immune system has the capacity to detect and eliminate such mutated cells, and will do so on a regular basis
- Only when mutated cells find ways to hide from- or suppress an attack by the immune system, they can grow and spread unhindered leading to clinically apparent tumors



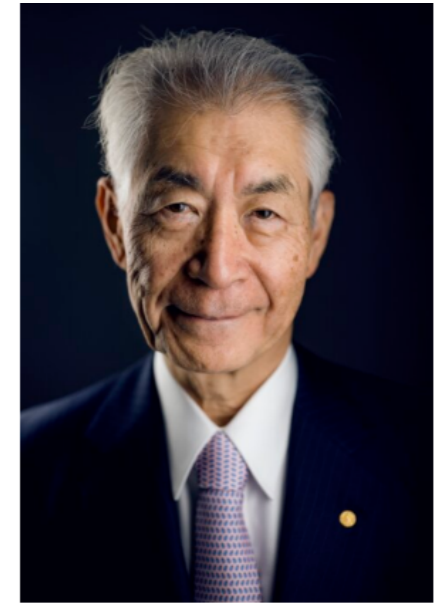
Can the immune response against an 'escaped' cancer be re-activated?

# Nobel Prize 2018 in Medicine

- Identification of the molecules PD-1 and CTLA-4 that function as 'T cell brakes' (immune checkpoints)
- Blockade of PD-1 and CTLA-4 results in activation of T cells which has *"fundamentally changed the outcome for certain groups of patients with advanced cancer"*
- *"Similar to other cancer therapies, adverse side effects are seen, which can be serious and even life threatening. They are caused by an overactive immune response leading to autoimmune reactions [...]"*



© Nobel Media AB. Photo: A. Mahmoud  
James P. Allison



© Nobel Media AB. Photo: A. Mahmoud  
Tasuku Honjo

*"for their discovery of cancer therapy by inhibition of negative immune regulation"*



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### Is the Next Big Step in Cancer Therapy Personalized Vaccines?

*UC San Diego Health and La Jolla Institute launch clinical trial harnessing an individual's immune system in a syringe*

October 12, 2018 | Yadira Galindo



Ezra Cohen, MD, UC San Diego Health physician scientist, administered the first-of-its-kind personalized cancer vaccine to Tamara Strauss, while Aaron Miller, MD, PhD, UC San Diego Health physician scientist, Tamara's mother, Iris Strauss, and Stephen Schoenberger, PhD, La Jolla Institute for Allergy and Immunology professor of immunology, look on.

neoantigens that generated the strongest T cell response from Tamara's tissue samples. These neoantigens were then presented to Tamara's own T cells and cultured over a two-week period using 50 milliliters of her blood to develop a personalized vaccine.

After sequencing Tamara's tumor and normal tissue, the team identified mutations expressed solely by cancer cells in her body. Schoenberger and LJI's Bjoern Peters, PhD, developed a novel algorithm to select mutations that are recognized by the immune system. This algorithm was deployed to recognize the

Several trials for personalized cancer vaccines are currently ongoing

# Personalized Cancer Immunotherapy



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# Your Turn

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

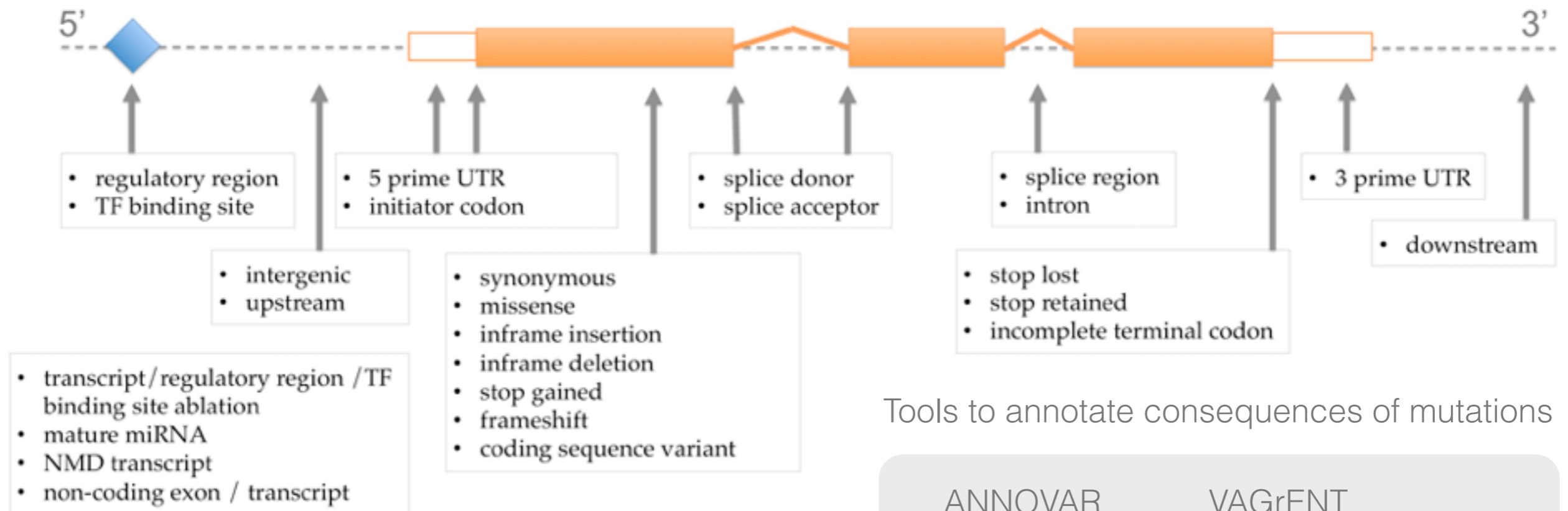
- Calling cancer's bluff with neoantigen vaccines
- Can genomics help detect early cancer and monitor treatment effectiveness?
- The increasing cost of cancer therapies

[https://bioboot.github.io/bimm194\\_W18/readings/](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

ANNOVAR

VAGrENT

Ensembl VEP

ASOoVIR

snpEff

annTools

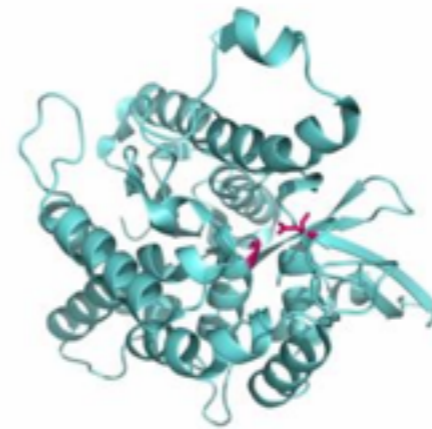
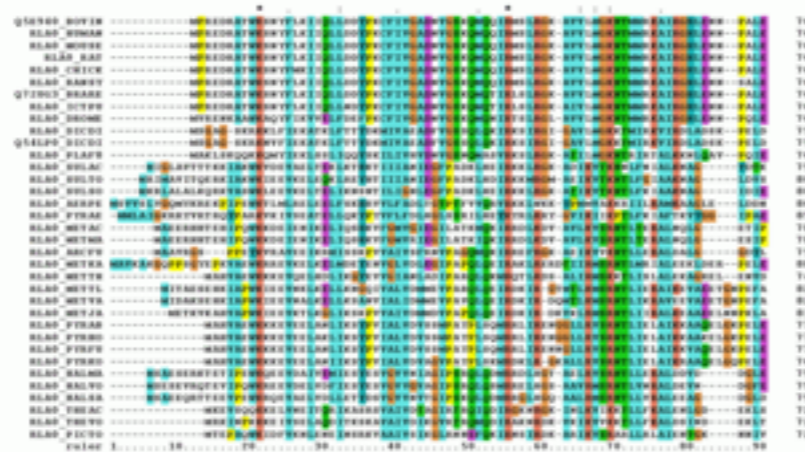


# 2. Assess the functional impact of nsSNVs

nsSNVs = non-synonymous Single Nucleotide Variant (missense)

ATC GAA GCA CGT  
Met Glu Ala Gly

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

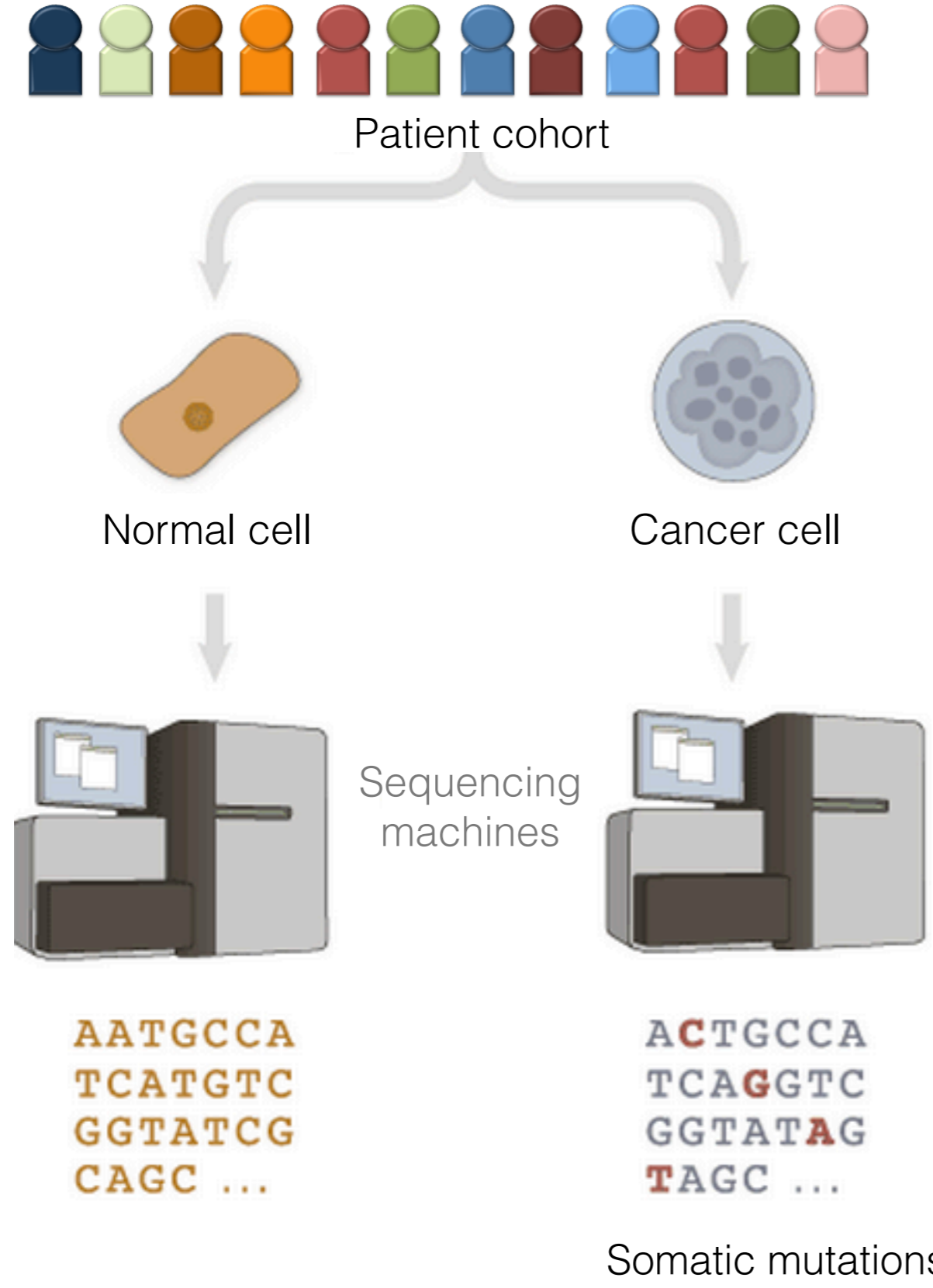


Computational methods to assess the functional impact of nsSNVs

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



# 3. Identify cancer drivers from somatic mutations

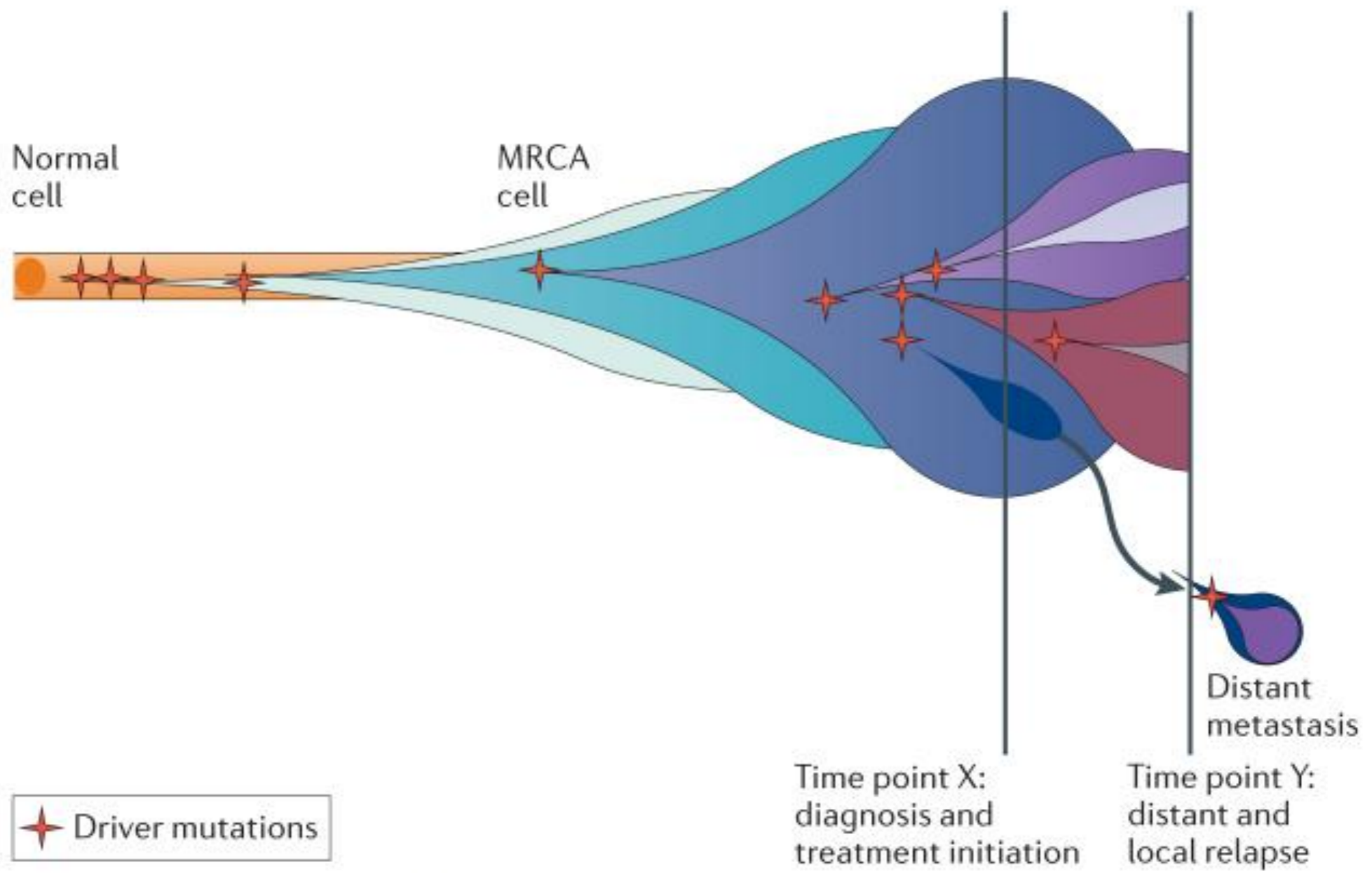


Which mutations are cancer drivers?



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

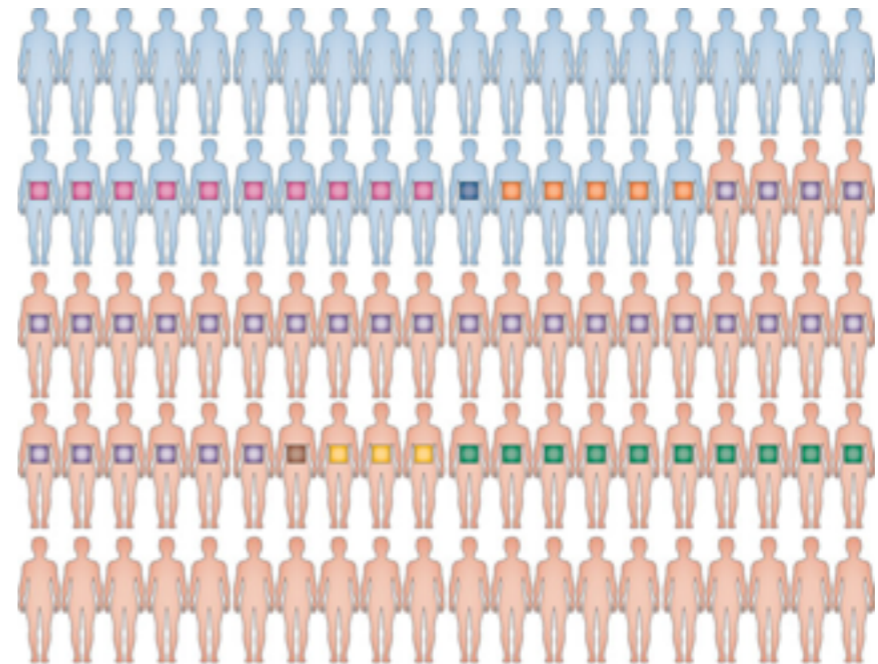


# How to differentiate drivers from passengers?

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



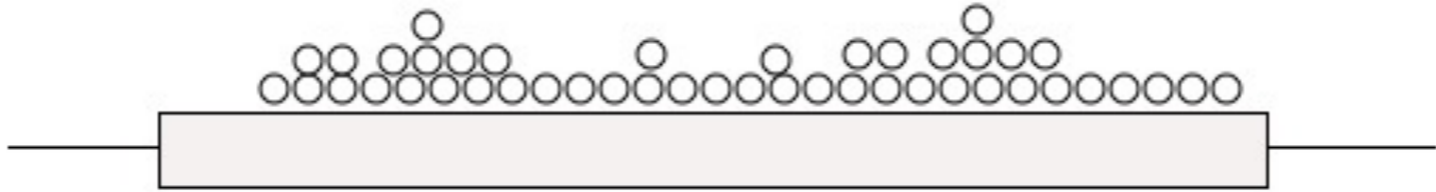
Find signals of positive selection across tumour re-sequenced genomes



# Signals of positive selection

Recurrence

**MuSiC-SMG / MutSigCV**

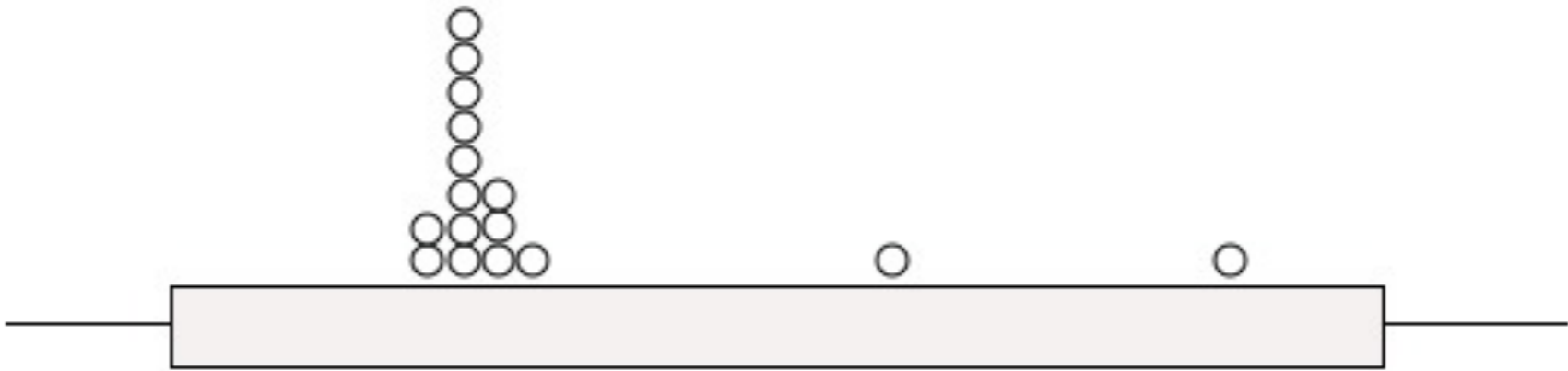


○ Mutation

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](#)