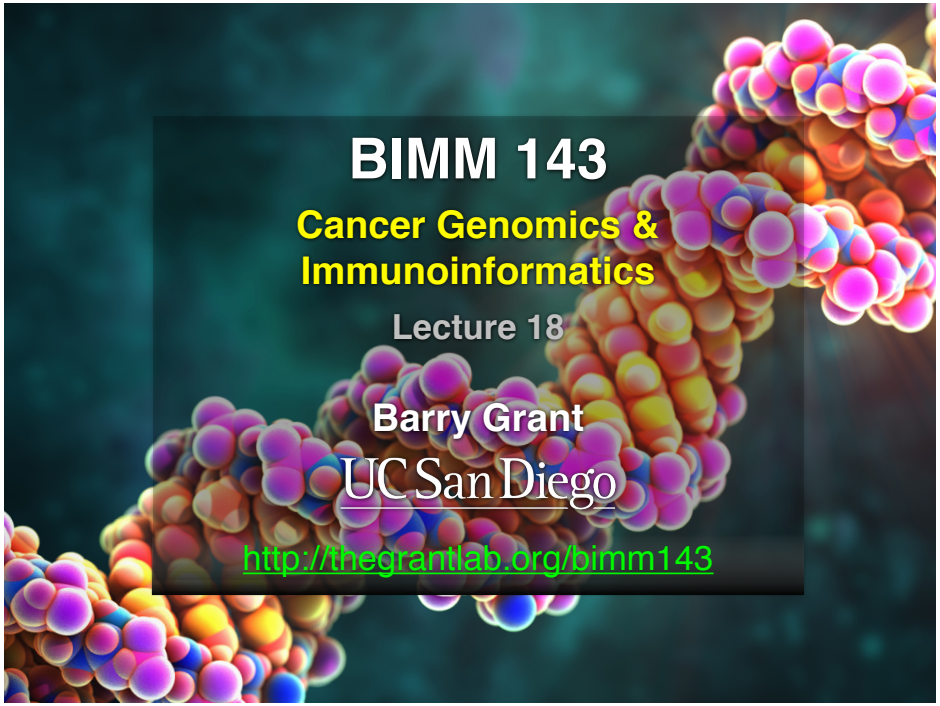


# Today's Menu

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| **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 |
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| **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.

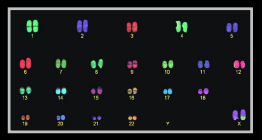

# What is Cancer?

"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"

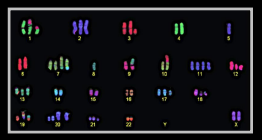
**Source:** https://www.cancer.gov

# 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**



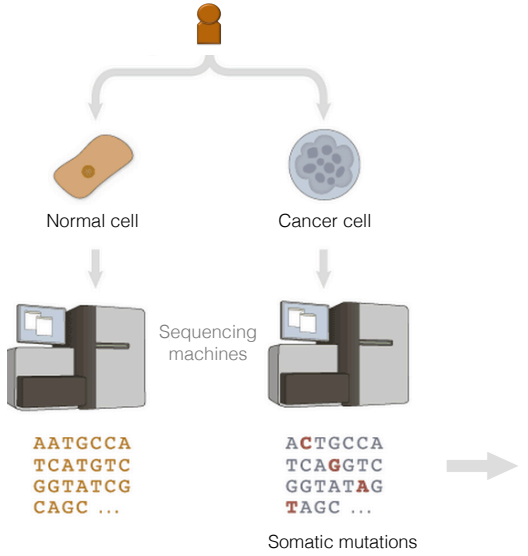
**Example cancer 59 chromosomes**

# Goals of Cancer Genome Research

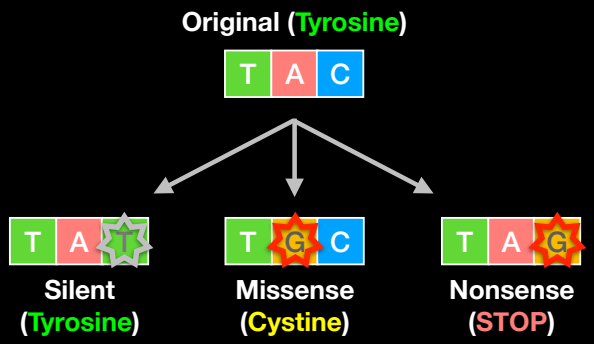
- Identify changes in the genomes of tumors that drive cancer progression
- Identify new targets for therapy
- Select drugs based on the genomics of the tumor
- Provide early cancer detection and treatment response monitoring
- Utilize cancer specific mutations to derive neoantigen immunotherapy approaches

## Finding Cancer Drivers

## Finding Cancer Associated Mutations



# Mutations detected: Point mutations




# Mutations detected: Indels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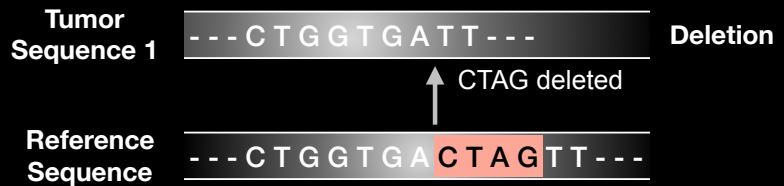
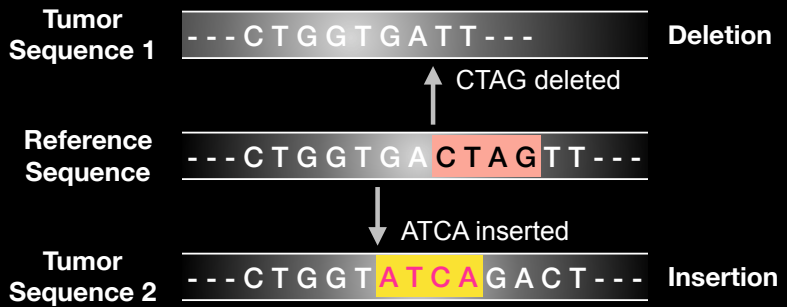
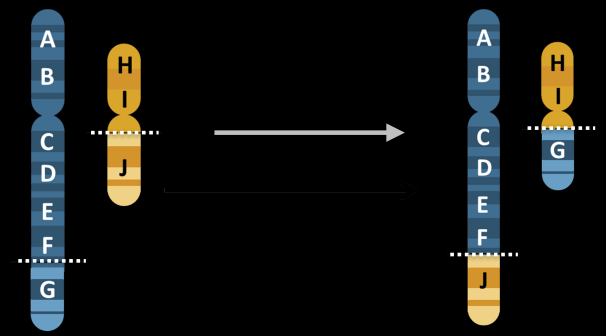



# Mutations detected: Indels



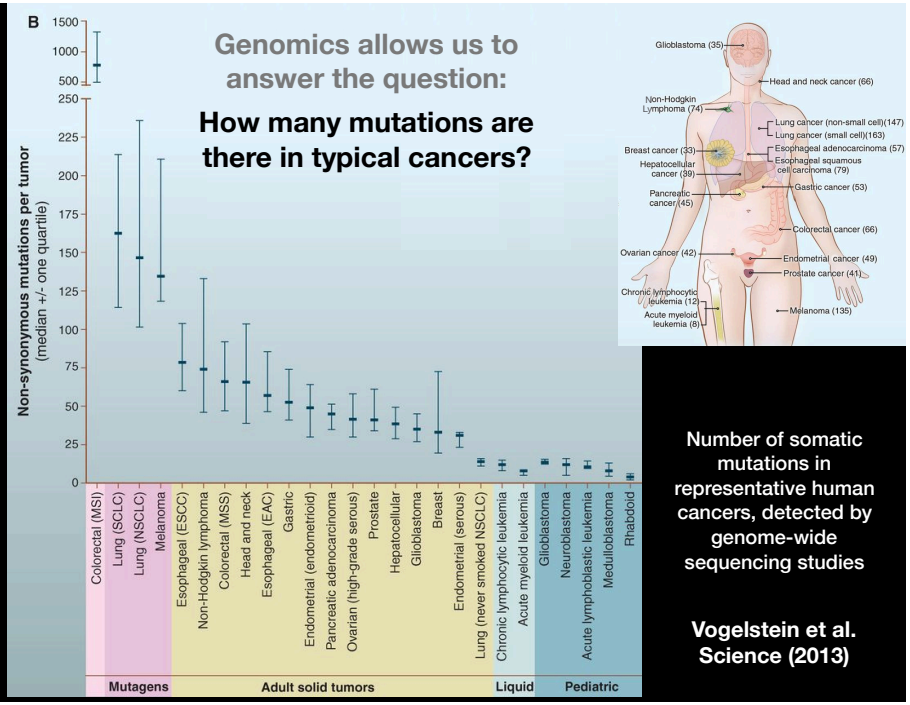
# Mutations detected: Translocations




# What can go wrong in cancer genomes?

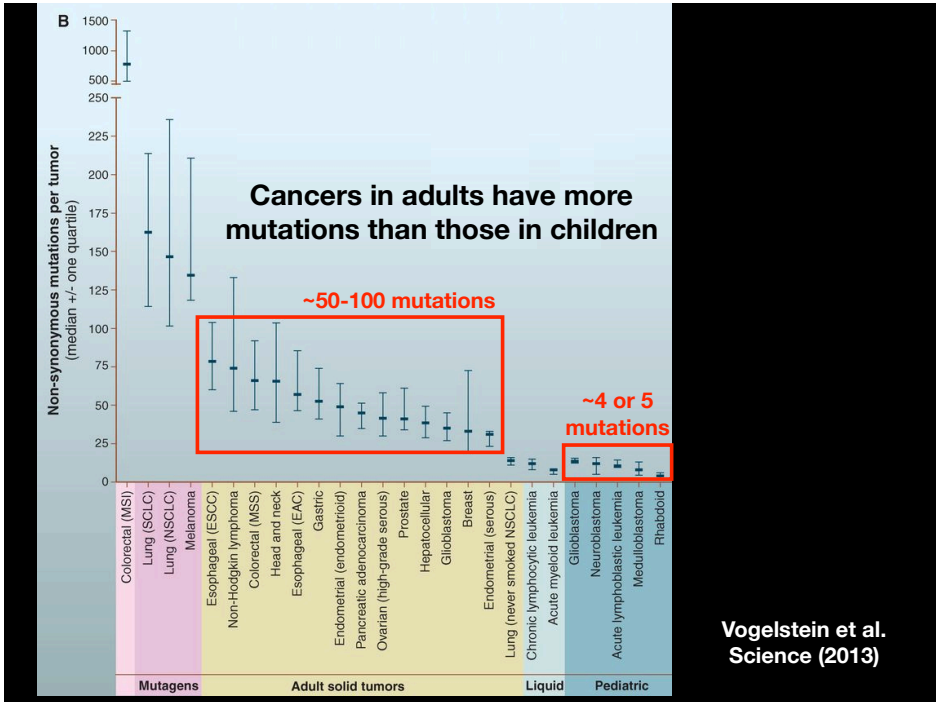
| Type of change | Some common technology to study changes |
|---|---|
| DNA mutations | WGS, WXS |
| DNA structural variations | WGS |
| Copy number variation (CNV) | CGH array, SNP array, WGS |
| DNA methylation | Methylation array, RRBS, WGBS |
| mRNA expression changes | mRNA expression array, RNA-seq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

WGS = whole genome sequencing, WXS = whole exome sequencing
RRBS = reduced representation bisulfite sequencing, WGBS = whole genome bisulfite sequencing

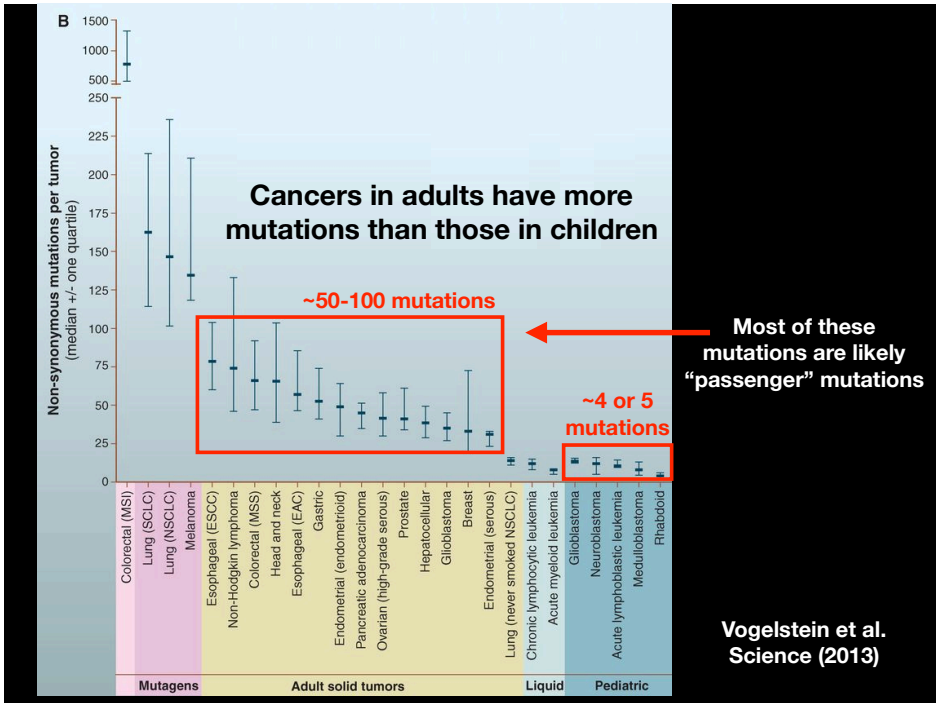



Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies

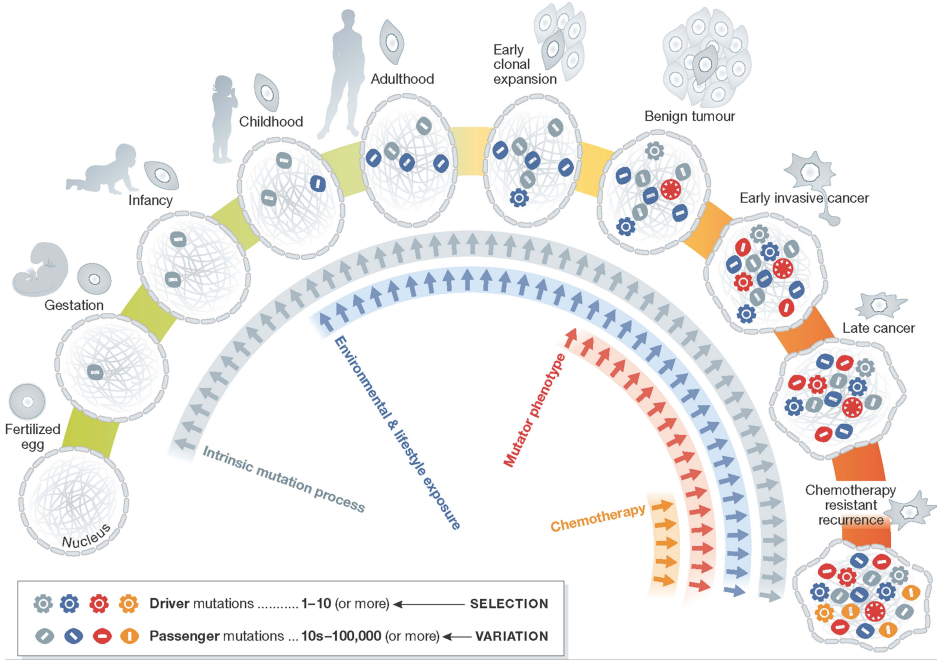
Vogelstein et al. Science (2013)



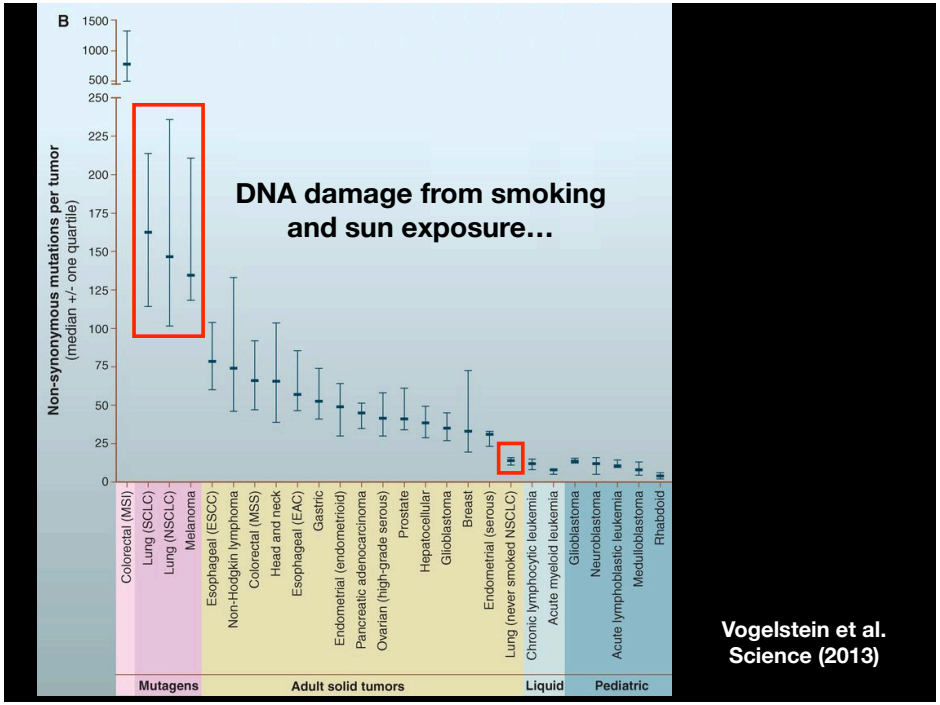

Vogelstein et al. Science (2013)




Vogelstein et al. Science (2013)

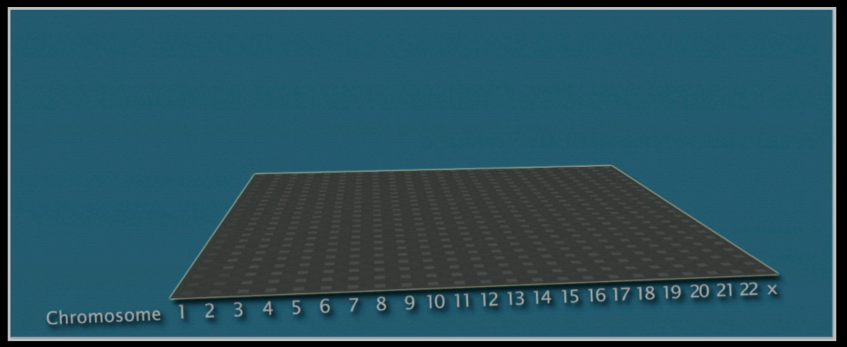



Mike Stratton. EMBO Molecular Medicine (2013)



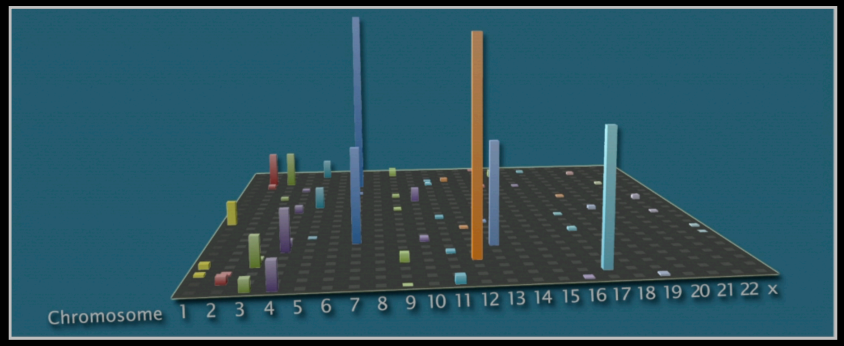

Vogelstein et al. Science (2013)

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



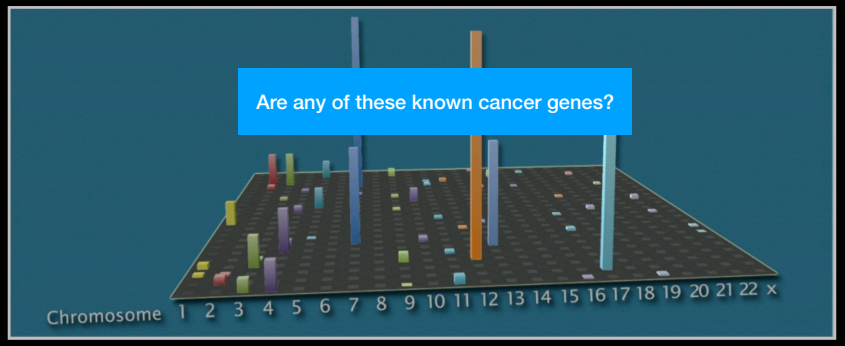

Arrange all genes in a matrix, ordered by chromosomes

# 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

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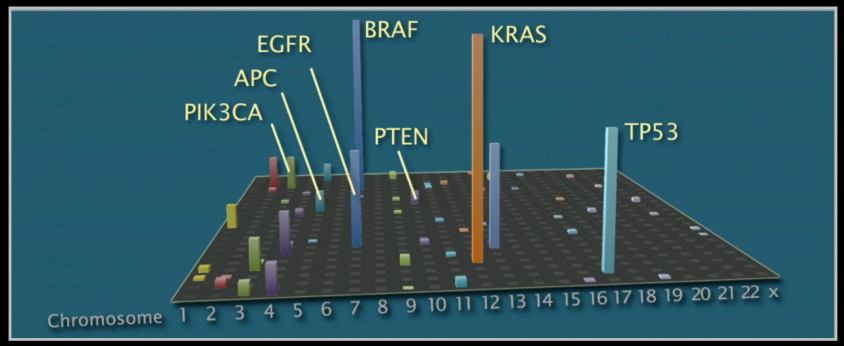
# Identifying genes most commonly mutated in cancer



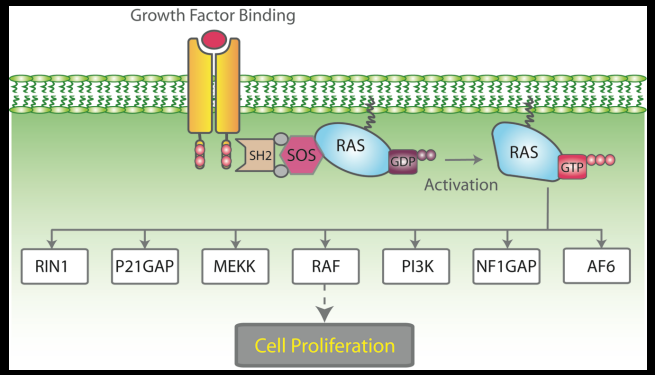

**Many are famous porto-oncogenes, many others are new cancer genes!**

# 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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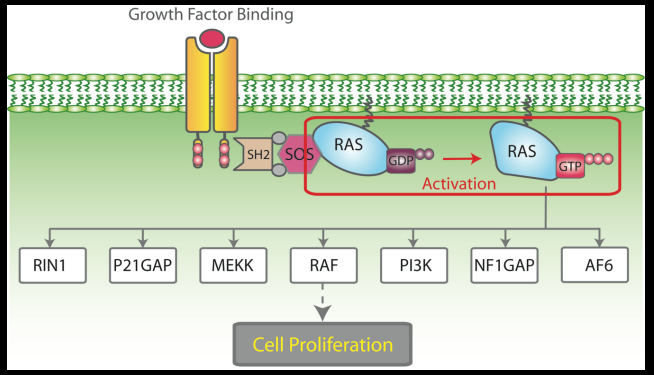


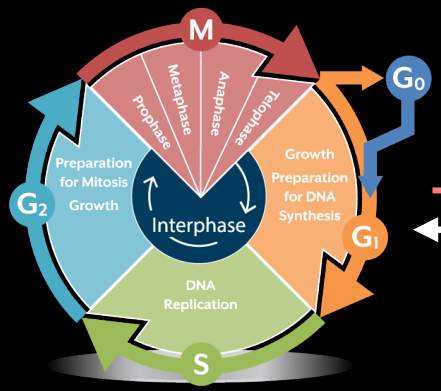

# Regulators of Cell Cycle and Cell Death

Some **stimulate** the cell cycle

Cyclin D1 +

CDK4

**Oncogenes**




Some **inhibit** the cell cycle

P53 -

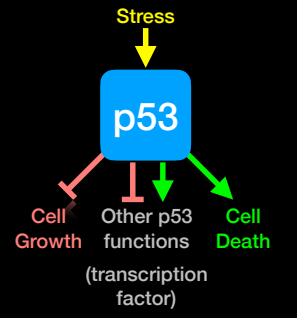
RB

**Suppressor genes**

# 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.

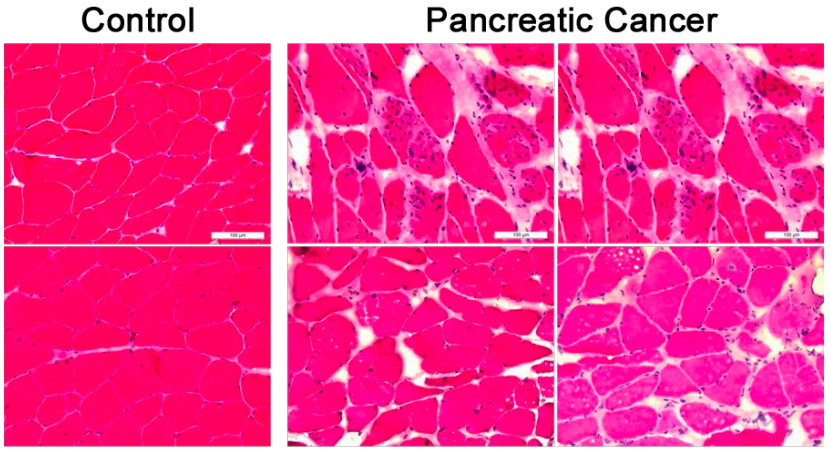


Do it Yourself!

# Hands-on time!

https://bioboot.github.io/bimm143_W19/lectures/#17

**Part 1 Only Please**




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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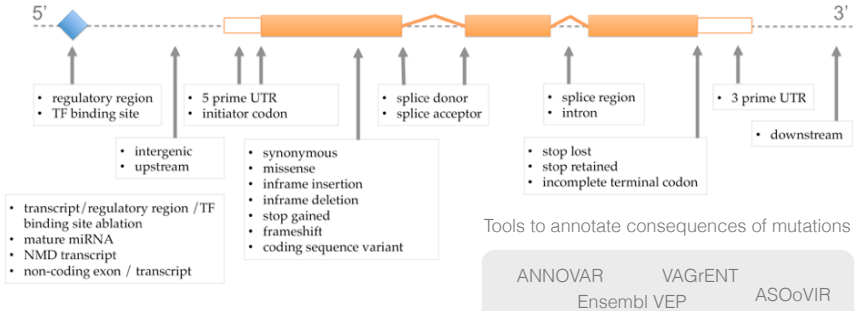
## 1. Predict consequences of mutations

```
ACTGCCTACGTCTCACCGTCGACTTCAAATCGCTTAACCCGTACTCCCATGCTACTGCATCTCGGGTTAACTC
GACGTTTTTCATGCATGTGTGCACCCCAATATATATGCAACTTTTGTGCACCTCTGTCACGCGCGAGTTGGCA
CTGTCGCCCCTGTGTGCATGTGCACTGTCTCTCGCTGCACTGCCTACGTCTCACCGTCGACTTCAAATCGCTT
AACCCGTACTCCCATGCTACTGCATCTCGGGTTAACTCGACGTTTTGCATGCATGTGTGCACCCCAATATATA
TGCAACTTTTGTGCACCTCTGTCACGCGCGAGTTGGCACTGTCGCCCCTGTGTGCATGTGCACTGTCTCTCGA
```

Map mutations into genome annotations to predict its possible effect




Tools to annotate consequences of mutations

ANNOVAR VAGrENT Ensembl VEP ASOoVIR snpEff annTools