## Science Enrichment Program (SEP)

# Introduction to Cancer Biology

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Memorial Sloan Kettering Cancer Center

# What two things do these people have in common?

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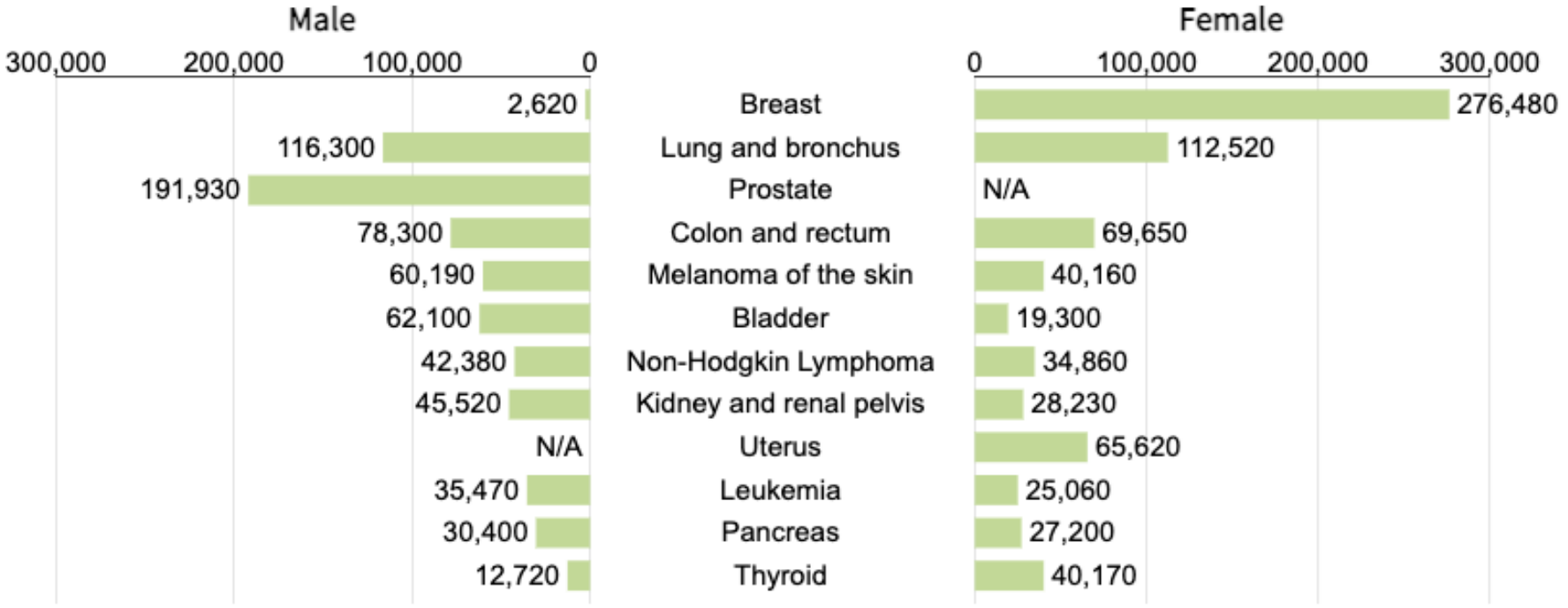
# 1 in 2 men and 1 in 3 women are at lifetime risk for developing cancer in their lifetime

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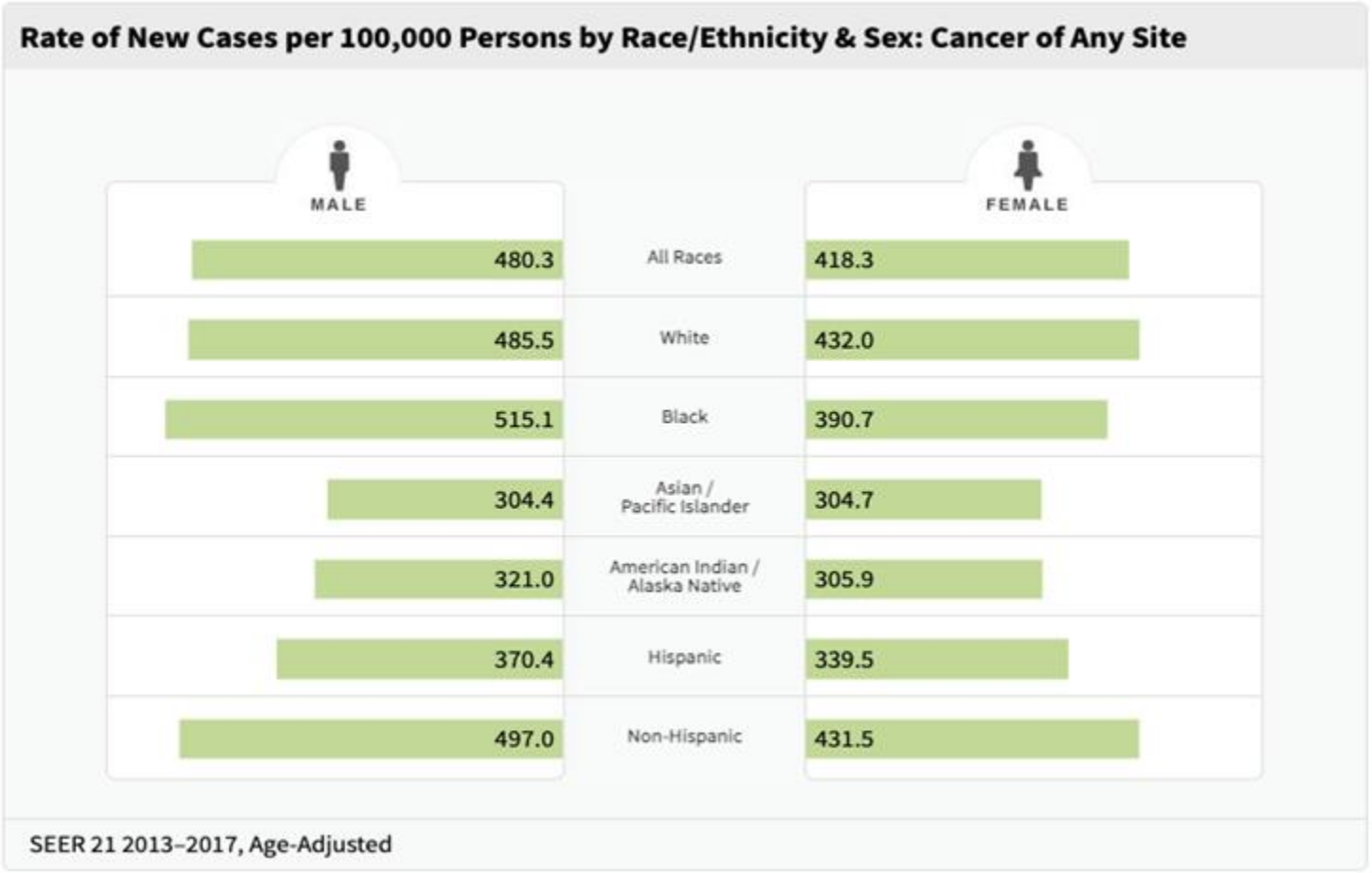
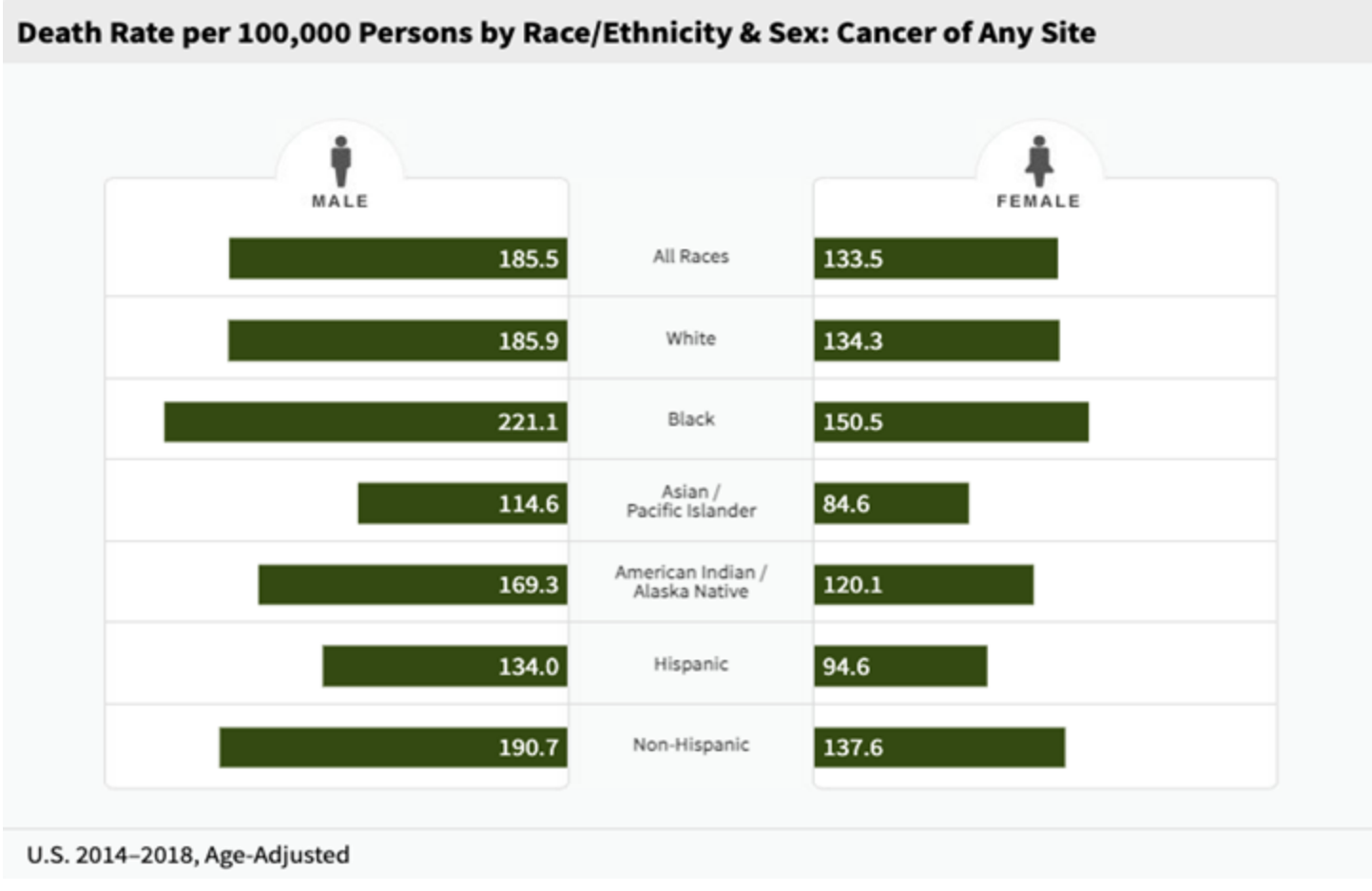
Source: Cancer Facts & Figures 2020, American Cancer Society (ACS), Atlanta, Georgia, 2020.

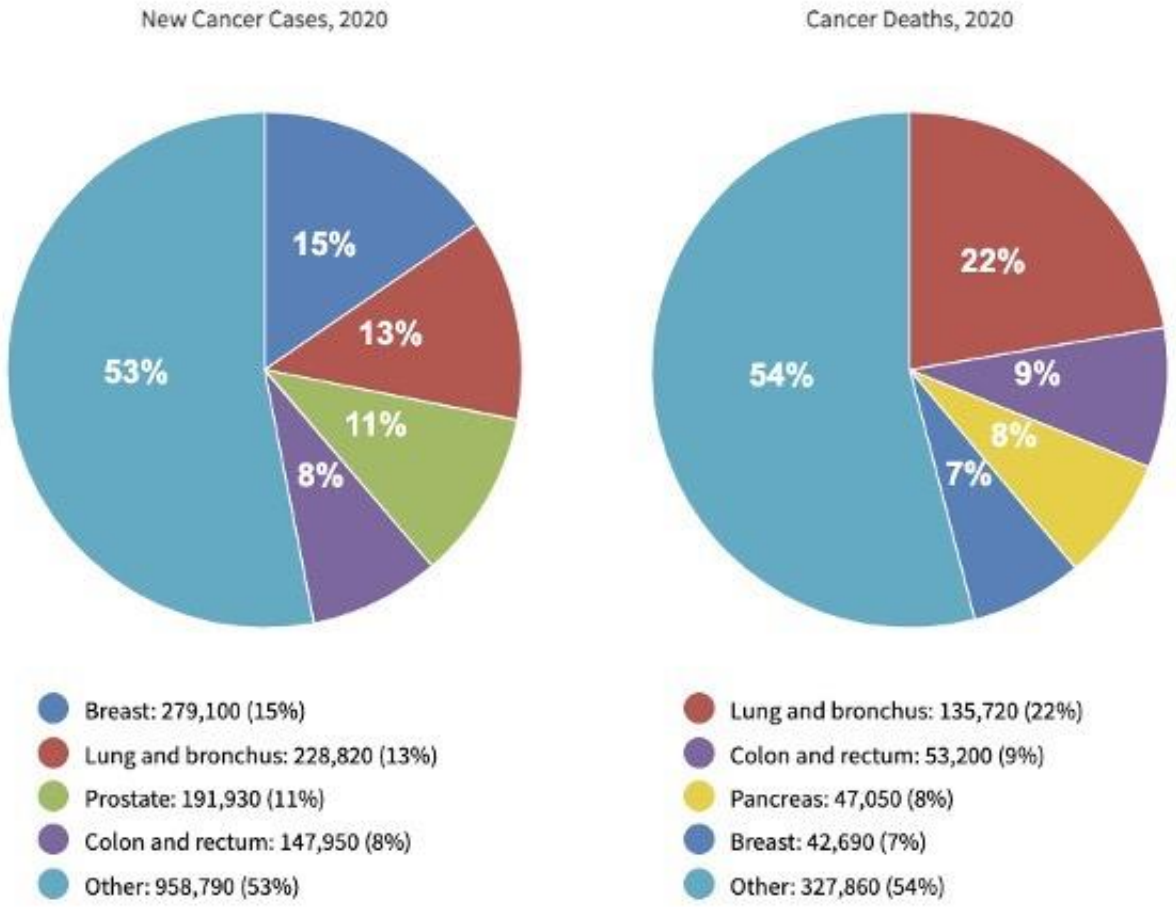
# Who gets cancer?



# Who dies from cancer?



# What are the most common cancers?



# What are the most common cancers?

In 2014, among men, Black/African American men had the highest lung cancer incidence and mortality rates in the United States.

- Smoking rates alone do not explain disparities in the development of the disease

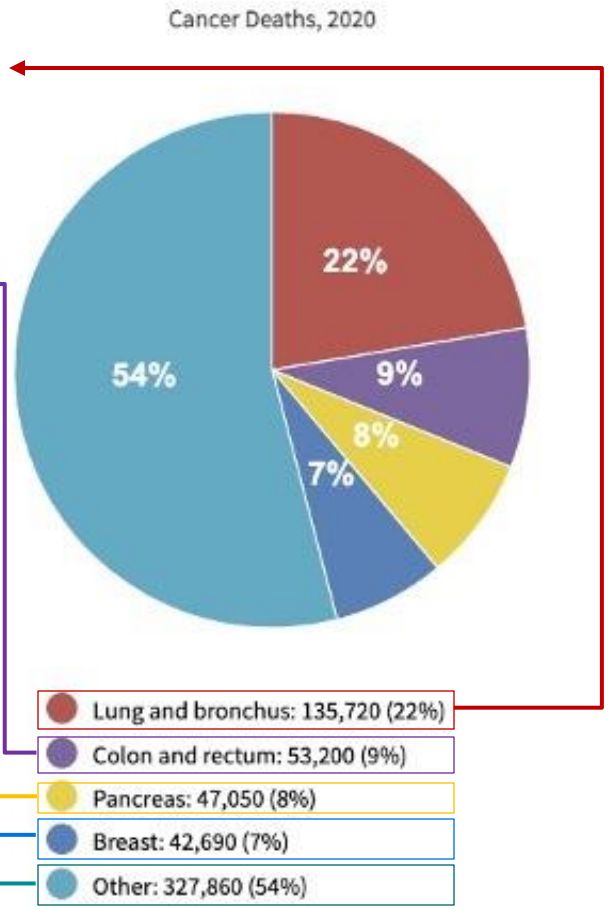
Native Hawaiian people lung cancer rates surpass those of White people b/c of historically high smoking prevalence

- 28% difference in incidence in the diagnosis of distant stage CRC between Black/African American and non-Hispanic whites.
- This difference accounted for more than 60% of the total mortality disparity from CRC.
- In addition, AA have an earlier median age at CRC diagnosis when compared to nHw

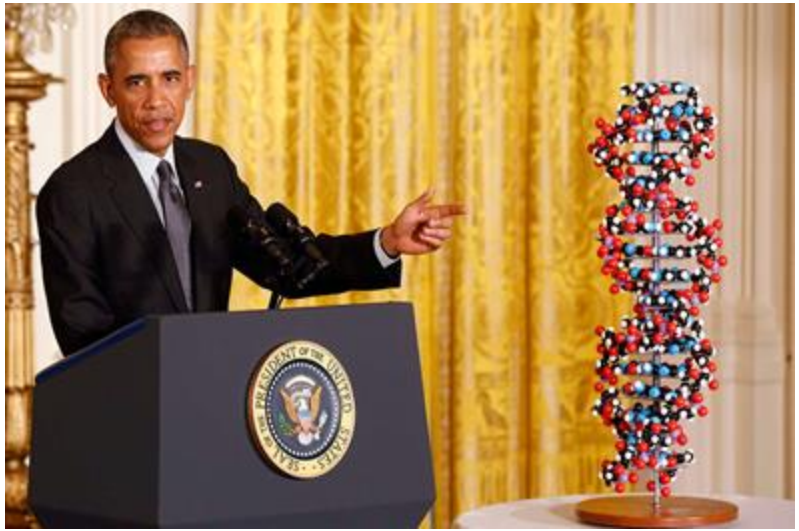
African Americans/Black patients (AA/B) have both higher incidence and mortality rates compared to NHW. Compared to NHW, AA/B typically with more aggressive disease, and stage-matched AA are less likely to receive systemic therapy, surgery, chemotherapy or radiotherapy and more likely to refuse tx

The racial disparity in deaths from breast cancer has remained at 40% or higher for a decade. Black women younger than age 50 had a death rate that was twice as high as White women that age. Plus, Black women are more likely than White women to die of breast cancer at any age.

Cervical cancer incidence is >30% higher in Hispanic women vs. white women. Liver and stomach cancer rates in Hispanic people are 2X those in White people. Prostate cancer though lower in Hispanic men is 44% higher in men living in Puerto Rico

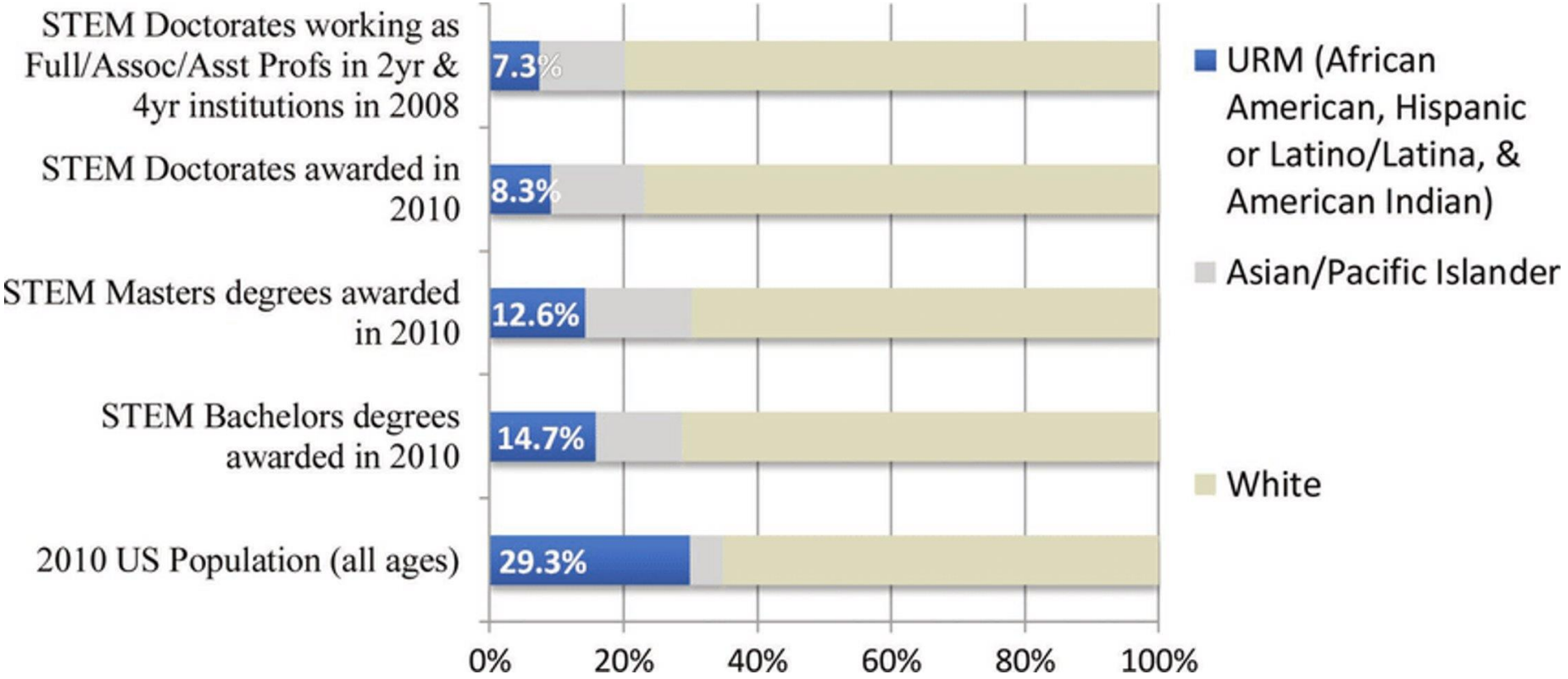


# Precision Medicine “Moonshot” Initiative




“scale up efforts **to identify genomic drivers in cancer** and apply that knowledge in the development of more effective **approaches to cancer treatment**.”

# And yet we're losing you…




Estrada, M et al. (2016) Improving Underrepresented Minority Student Persistence in STEM. Cell Biology Education. 15. es5-es5. 10.1187/cbe.16-01-0038

# Biology Fundamentals

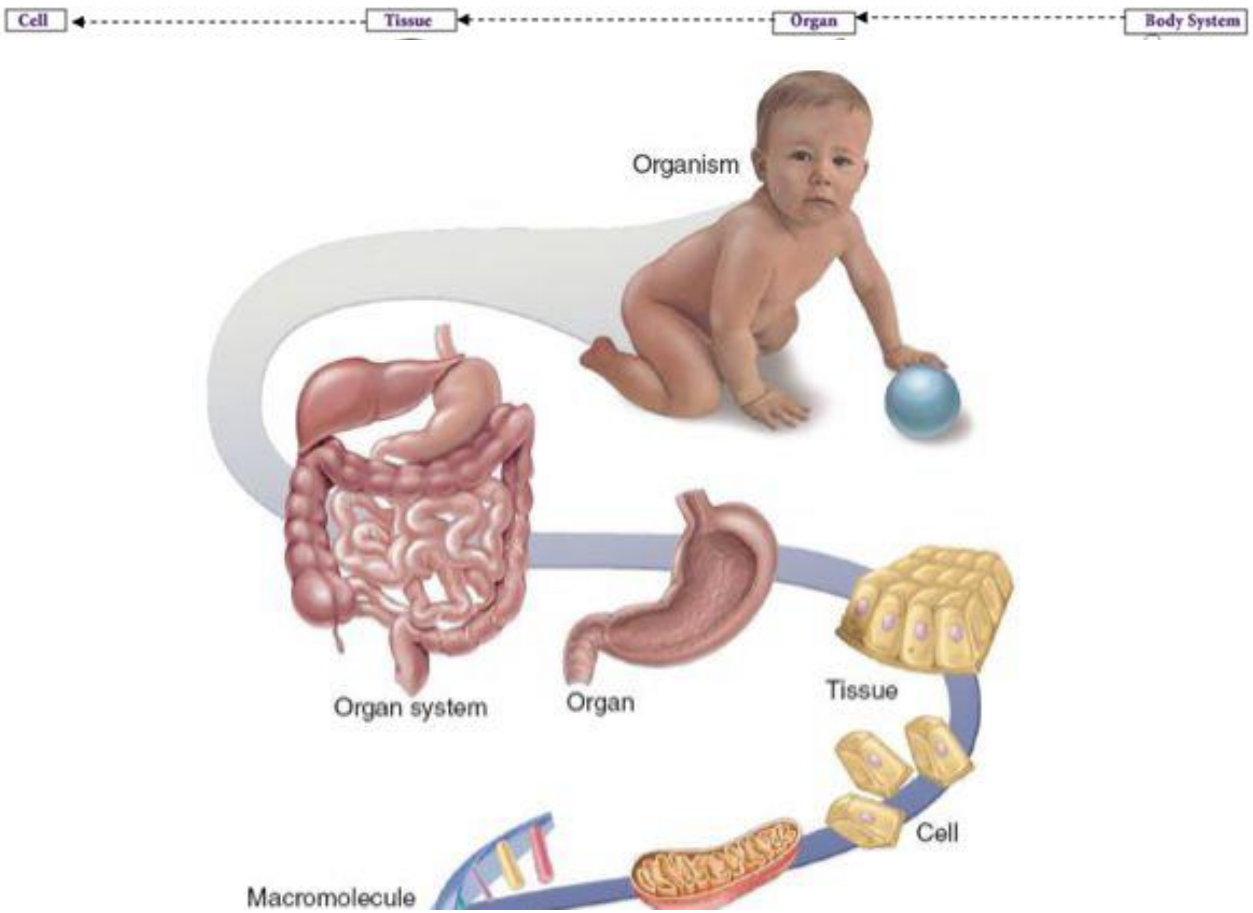
# Today's Lecture Outline

- **The cell**
  - From cells to organisms
- The central dogma
- **The human genome**
  - DNA
  - Gene expression
  - Transcription
  - RNA
  - Translation
- **Mutations: Overview**
  - Oncogenes and tumor suppressor genes
  - Gene mutations
  - Chromosomal mutations

# DNA → RNA → protein → organism

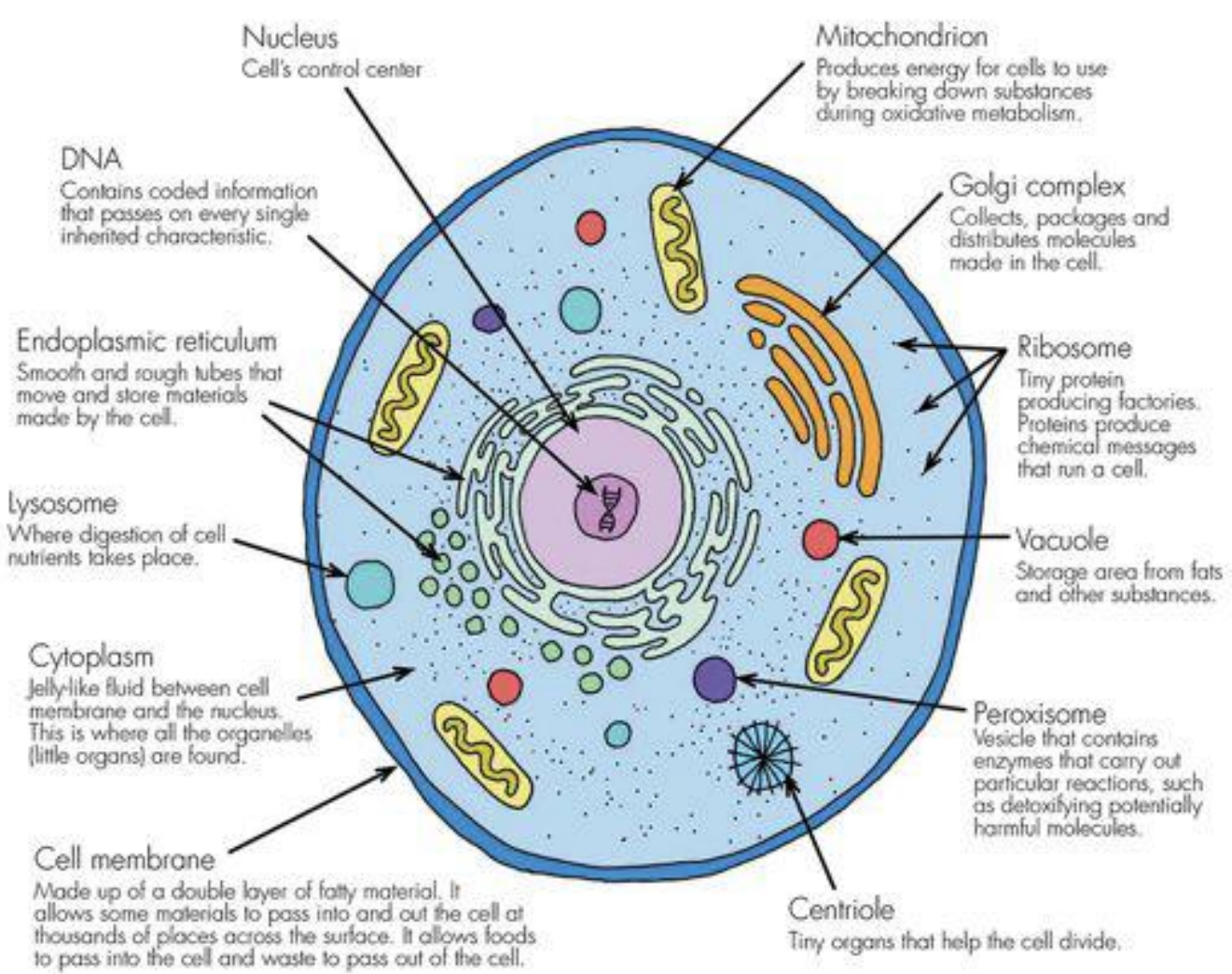
***Blueprint in hieroglyphics →blueprint in English → construction workers scaffolding etc → building with rooms and occupants***

# From Cells to Organisms

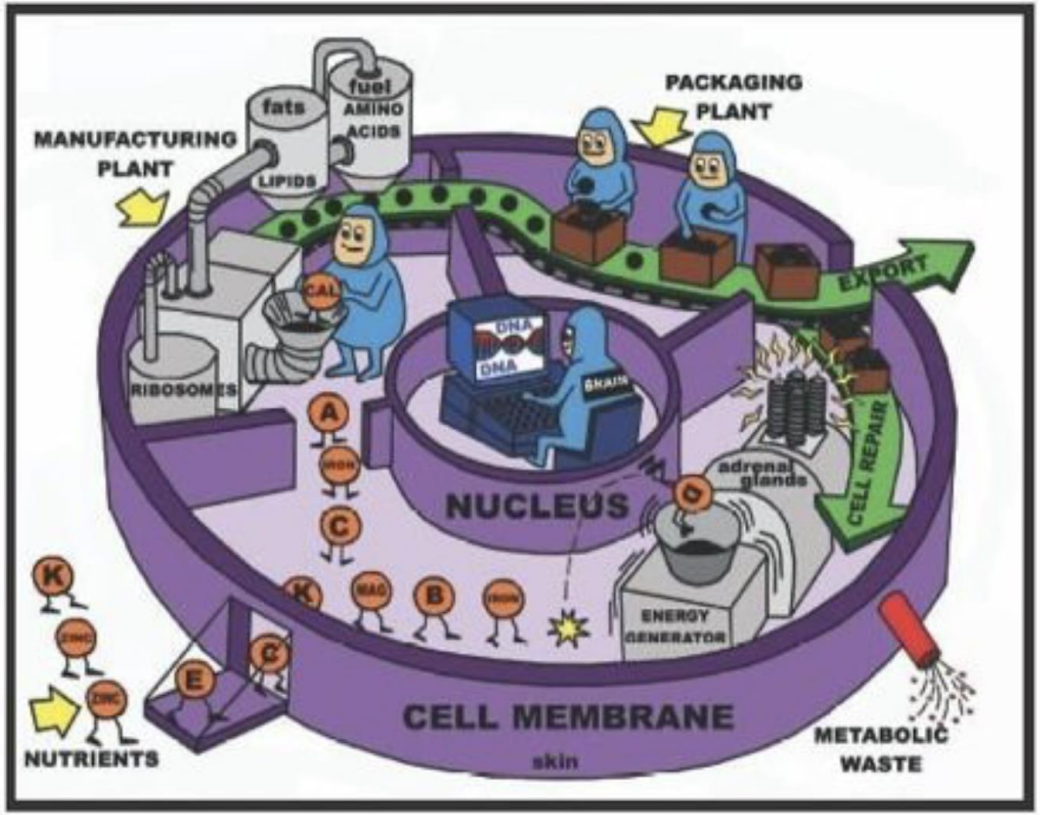


# The Cell

# Cells are the basic building blocks of life



# Cells are like mini-factories




**Nucleus** = control center

**DNA** = blueprint

**Cell Membrane** = shipping and receiving

**Cytoplasm** = factory floor

**Proteins** = workers

# Cells can divide, differentiate or die


Cells divide to produce two identical daughter cells.

Cells stop dividing to specialize in structure and function, a process called **differentiation**.

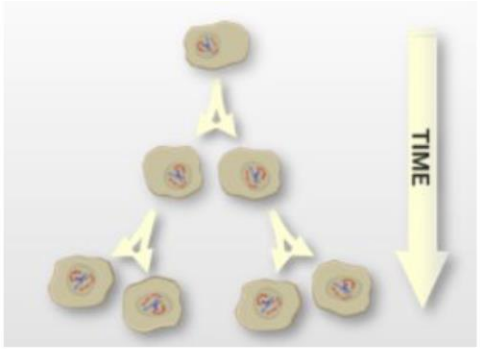
Cells can also undergo programmed cell death, or **apoptosis**, a process that eliminates unnecessary cells during development and removes unhealthy or damaged cells in the mature organism.

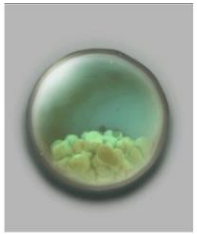
# Cell Division (birth/reproduction)

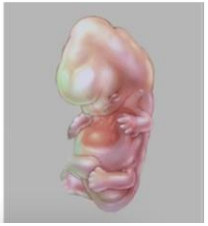
# Cell Division

## Cells division is essential to life

- Multicellular organisms need **cell division** to grow and to replace dead or damaged cells.
- In humans, many types of cells divide.
  - For example, repeated divisions allow a single fertilized egg cell to develop into an adult with more than 37 trillion cells.
- After growth, division remains important in normal cell turnover, such as in our skin and gut, where cells are continuously renewed. Other cells have to divide to heal wounds like skin cuts or broken bones.





https://media.hhmi.org/biointeractive/click/cellcycle/

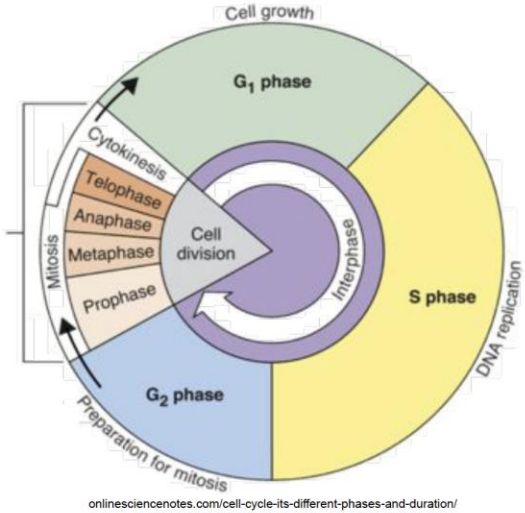
# Cell Division and the Cell Cycle

## The cell cycle

- Each time the cell divides into two, it goes through a sequence of events that includes
  - Growth
  - DNA replication
  - preparation to divide
  - and cell division or **mitosis**
- This is called the **cell cycle**

- *To remain healthy, it's critical for an organism to maintain the right number of cells.*
  - This is achieved primarily by regulating the cell cycle
  - **Cell cycle regulators** are molecular signals that may stimulate or halt cell division, instruct cells to differentiate, or initiate cell death.

https://media.hhmi.org/biointeractive/click/cellcycle/




onlinesciencenotes.com/cell-cycle-its-different-phases-and-duration/

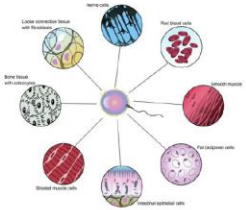
*In cancer, cell cycle regulators do not function properly leading to too many cells.*

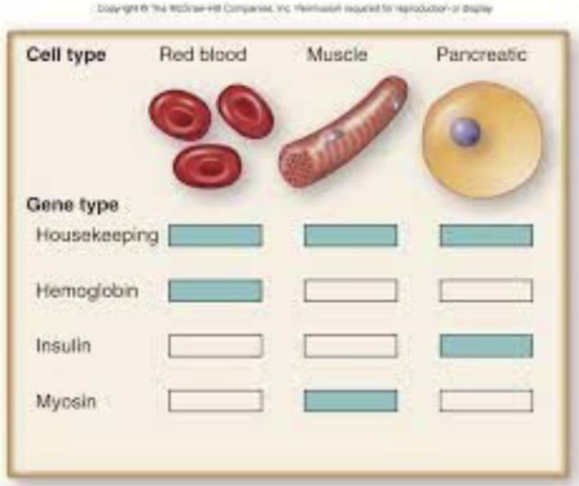
***True or False***

# Cell Differentiation (get a job)

# Cell Differentiation due to different gene expression

All cells have the same DNA, but different cells express different genes






All the cells in a person's body have the **same DNA** and the same genes

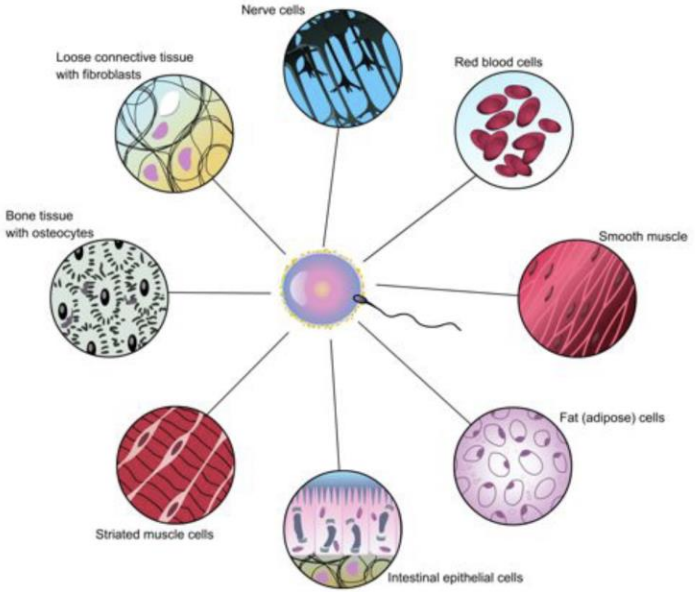
However, the difference between cells in different tissues and organs is that the "expression" of the genes differs between cells

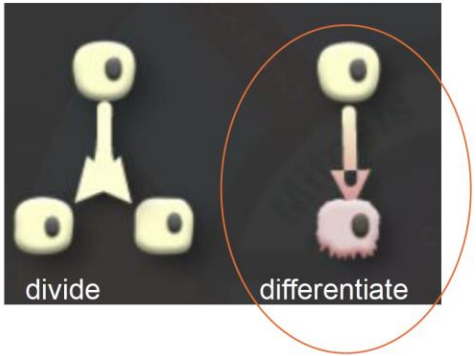
Expression means that the message from the DNA is being copied and made into protein

For example, liver cells express different proteins than skin cells, even though their DNA is the same

https://socratic.org/questions/56116c7e11ef6b17032ddc8b

# Cell Differentiation

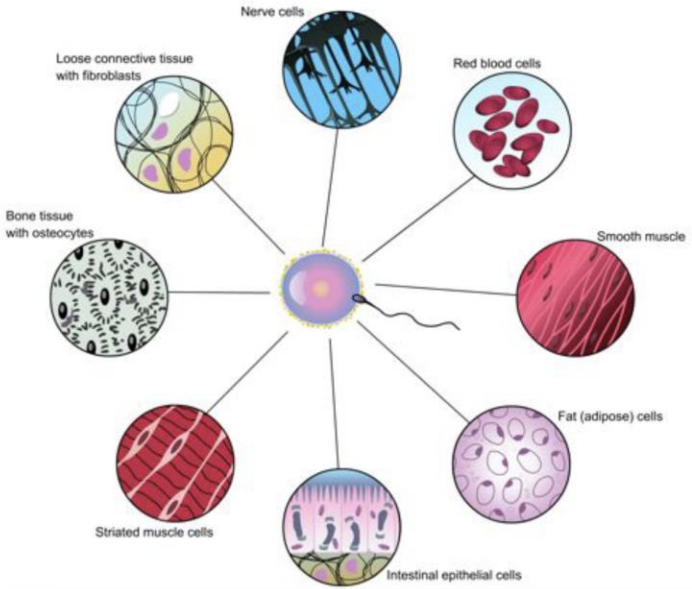



Cells stop dividing to specialize in structure and function

*Isn't it amazing that your body with all of its specialized organs developed from a single cell?*

# Cell Differentiation

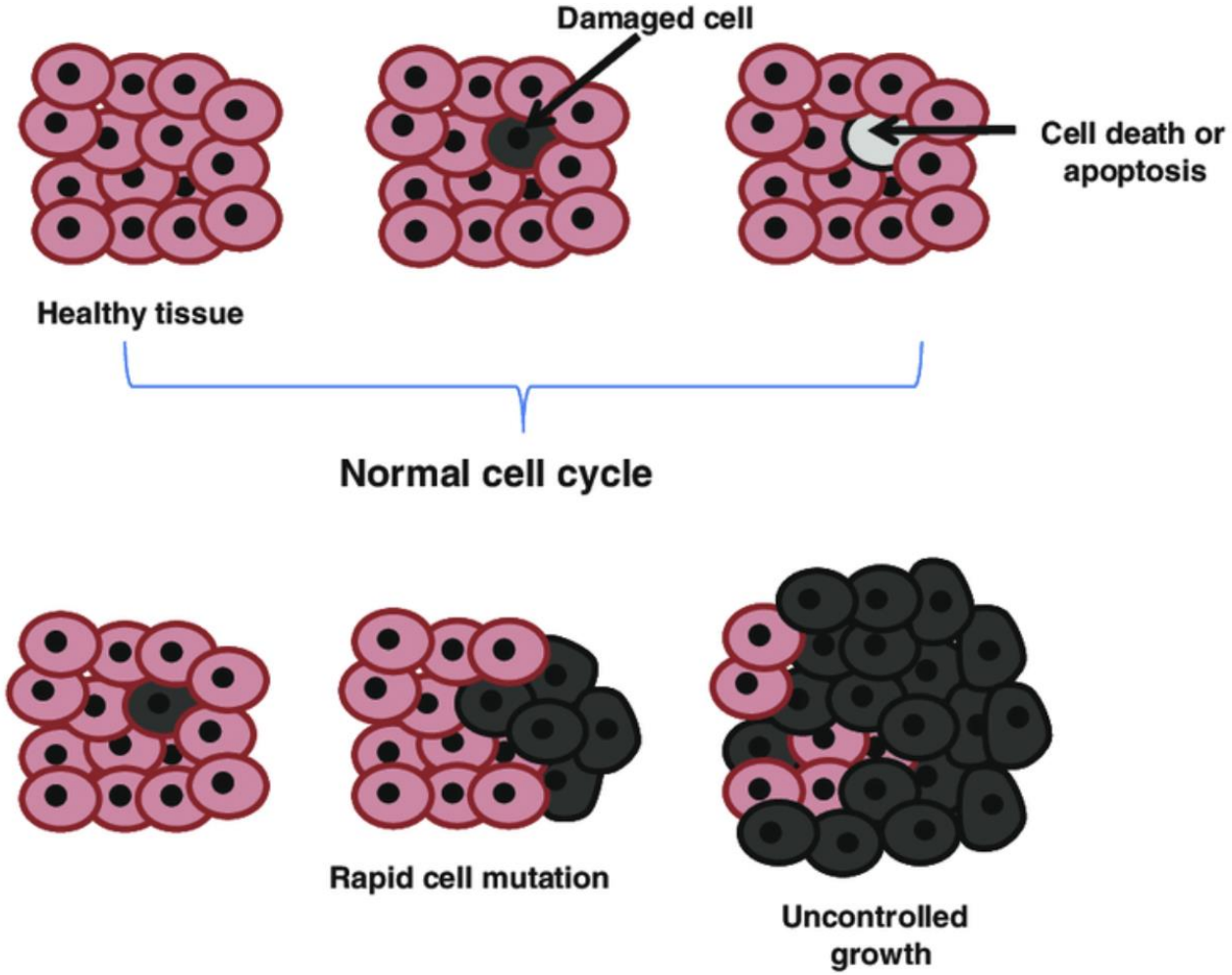



*How do cells become specialized*

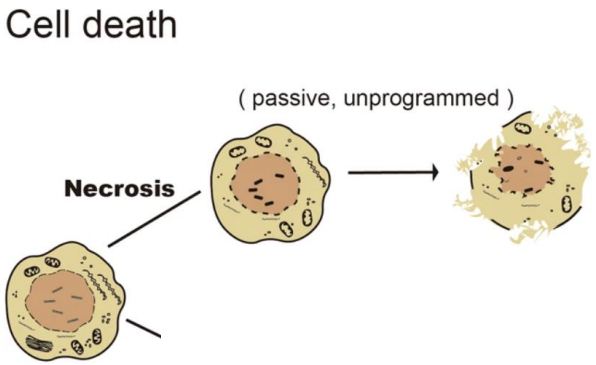
*(ie. how does a lung cell become a lung cell and a blood cell become a blood cell)?*

# Cell Death

***(die and leave a mess or have everything organized)***


Damaged cell
Cell death or apoptosis
Healthy tissue
Normal cell cycle
Rapid cell mutation
Uncontrolled growth

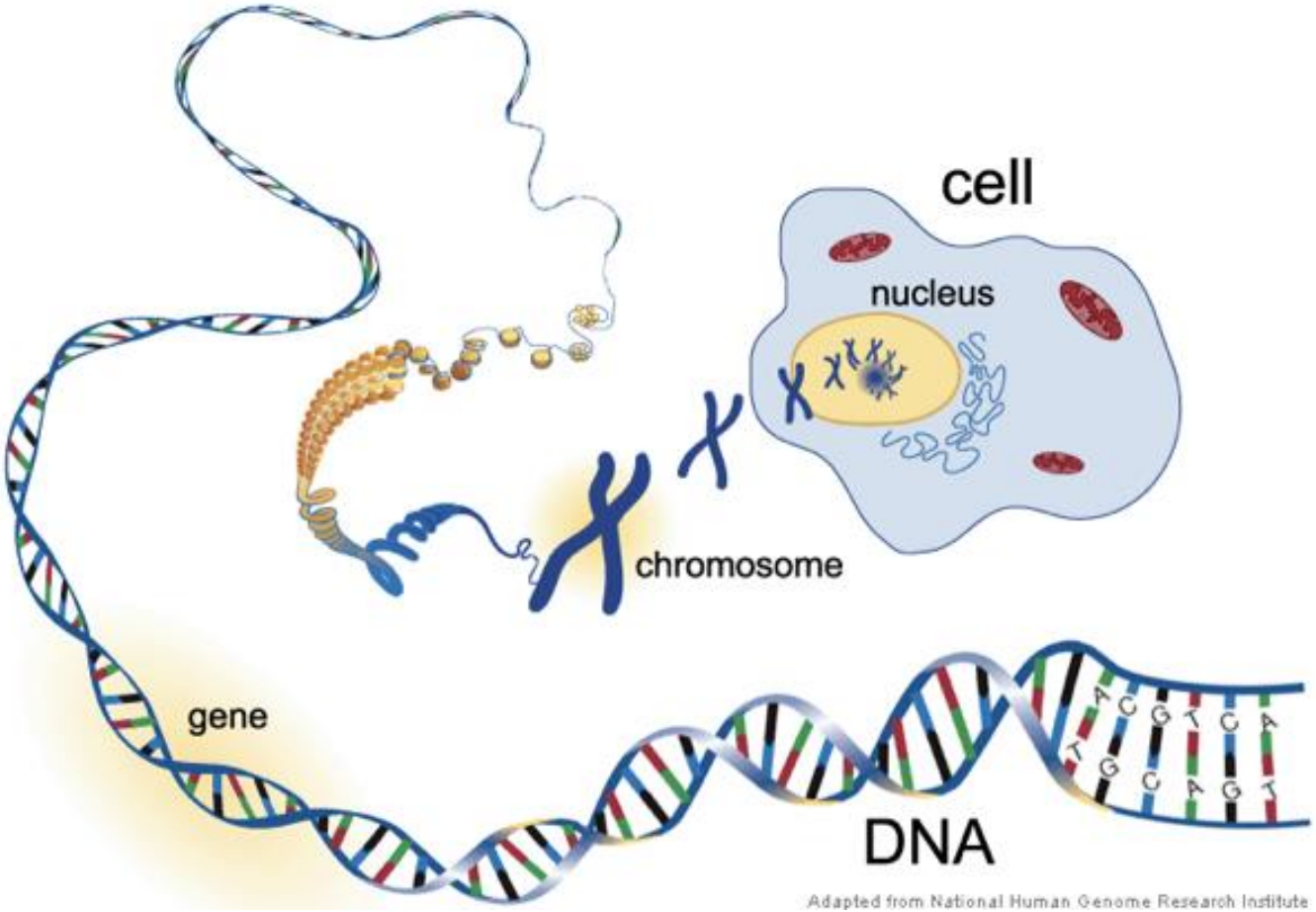
# Cell Death in Normal Cells versus that in Gastric Cancer



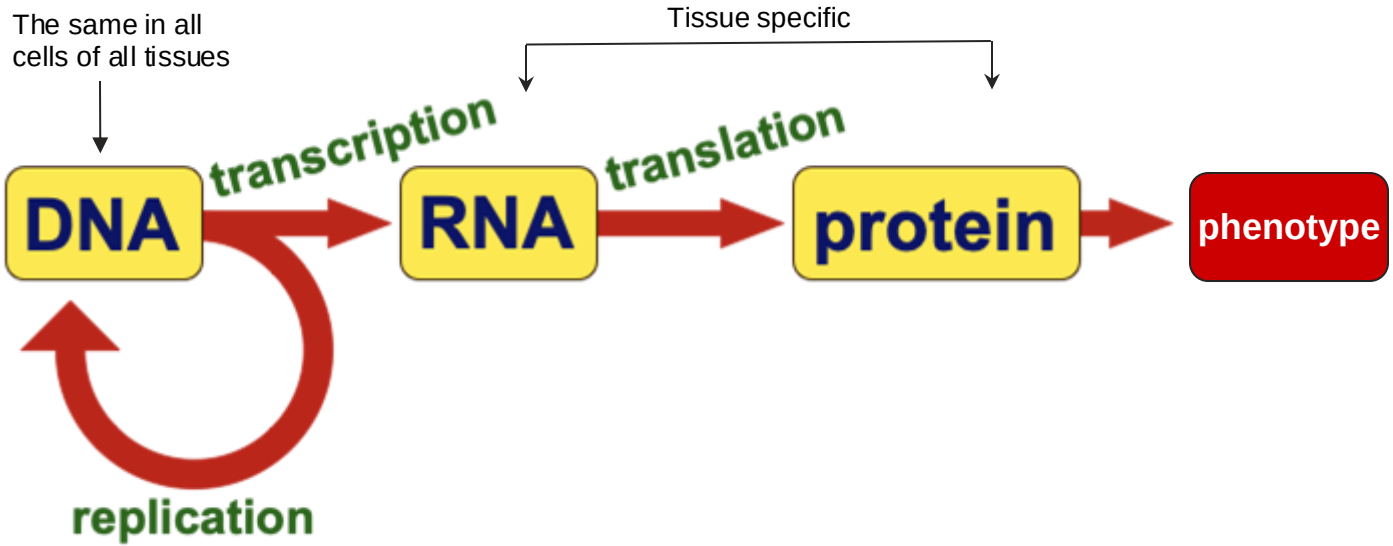

Left: The classification of cell death. Middle: Cells that undergo death in gastric cancer. Right: Effects triggered by different cell death in gastric cancer.

# The Central Dogma
# DNA → RNA → Protein

# Independent of the cell type -- all cells have DNA

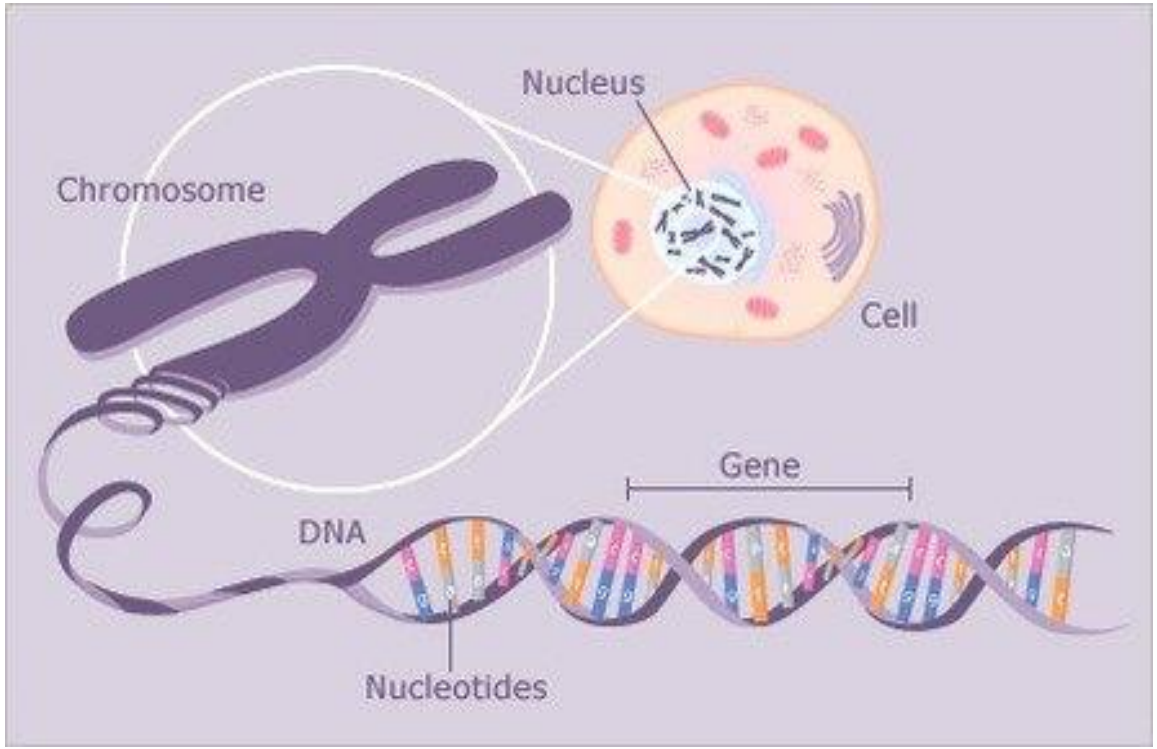


# The Central Dogma



# DNA and genes

- Every cell in your body has the same DNA *(consider DNA as a very thick hand-written book with multiple chapters)*
- Different genes *(words in the book)* are used in different cell types *(in the different chapters)*
- But each nucleotide in the DNA of each gene with varying base-pairs *(each letter in each word)* needs to be transcribed into mRNA *(the selected hand-written chapter needs to typed)*
- Then the mRNA needs to be translated into a functional protein *(the selected typed chapter becomes an episode of a TV show)*




http://jonesgen564s14.weebly.com/uploads/2/6/0/1/26017323/4458113.jpg?446

# mRNA

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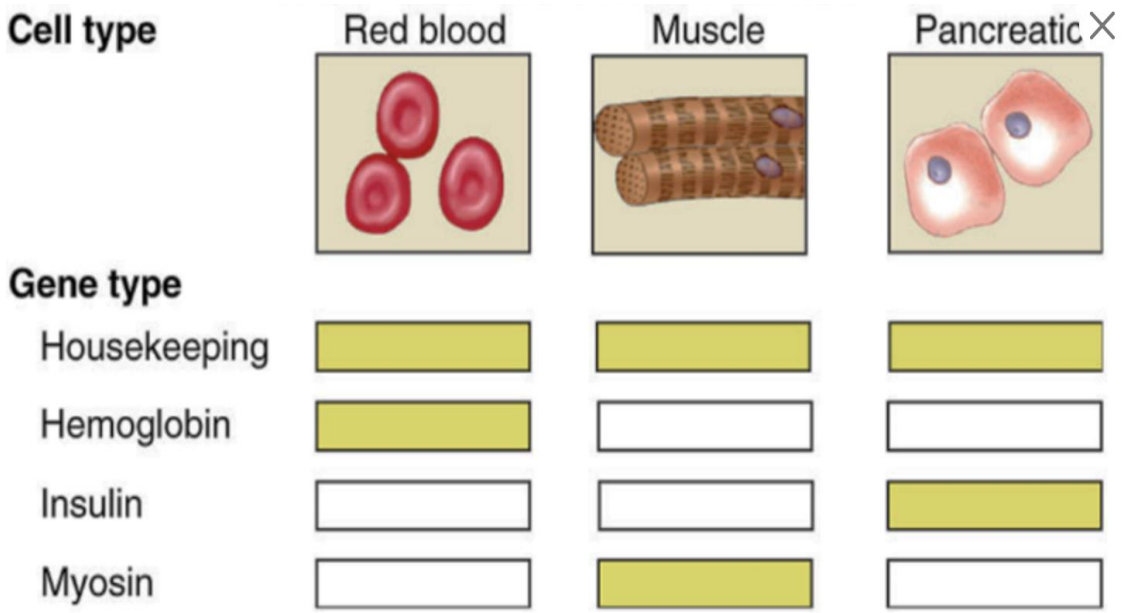

# DNA – *Transcription* → mRNA

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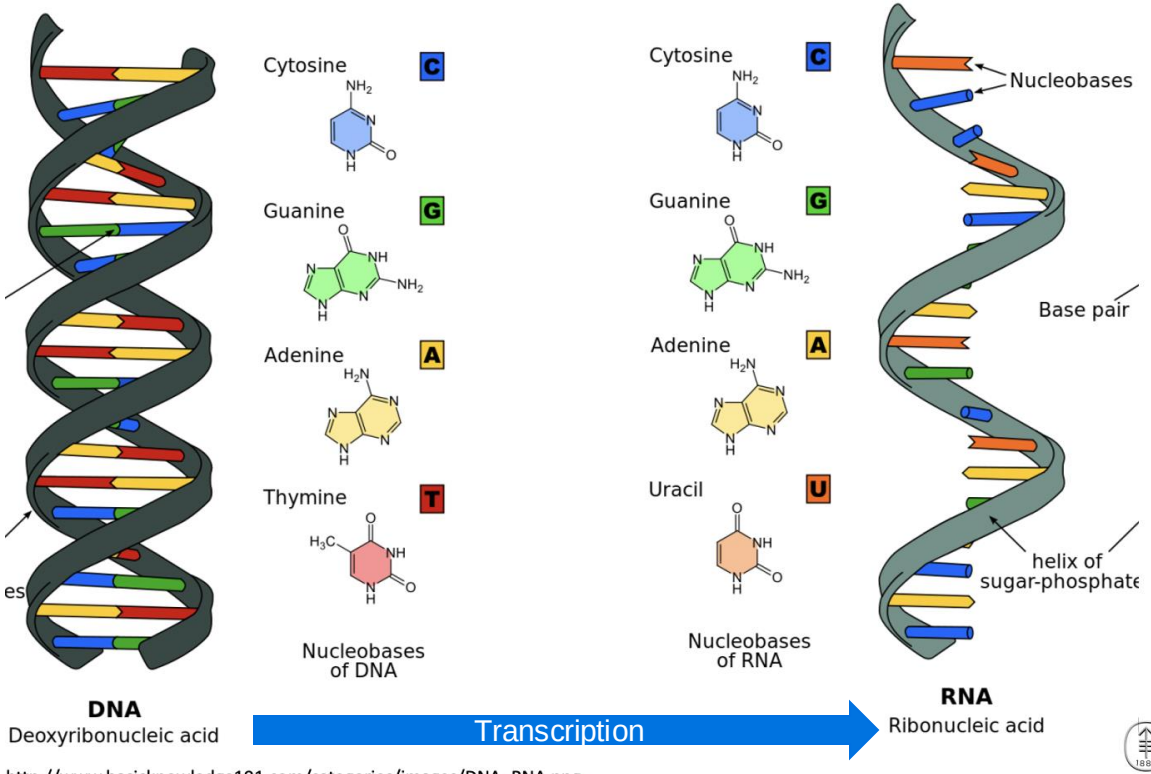


http://www.basicknowledge101.com/categories/images/DNA_RNA.png

# DNA-RNA – *Translation* → Protein

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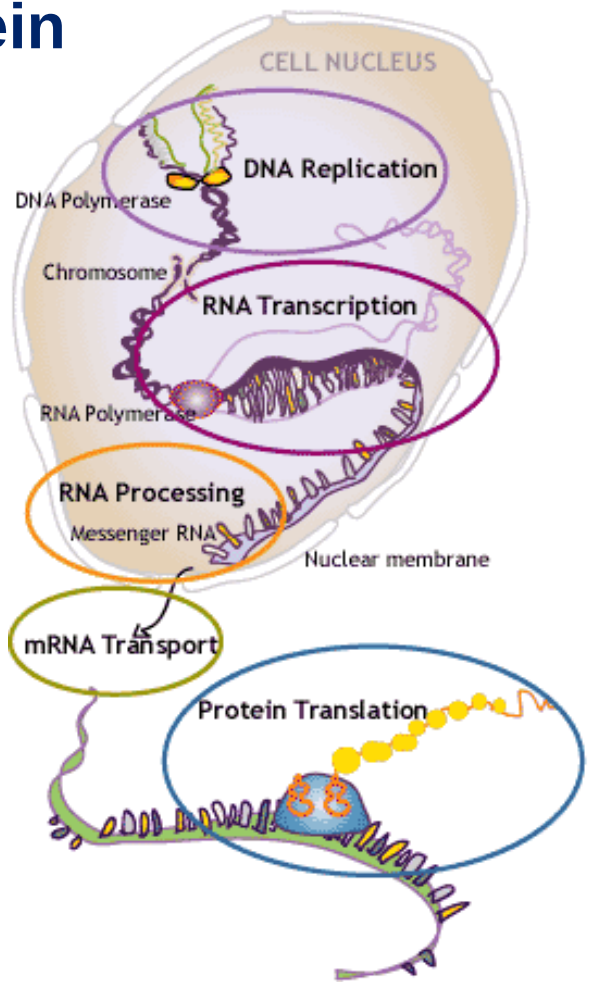
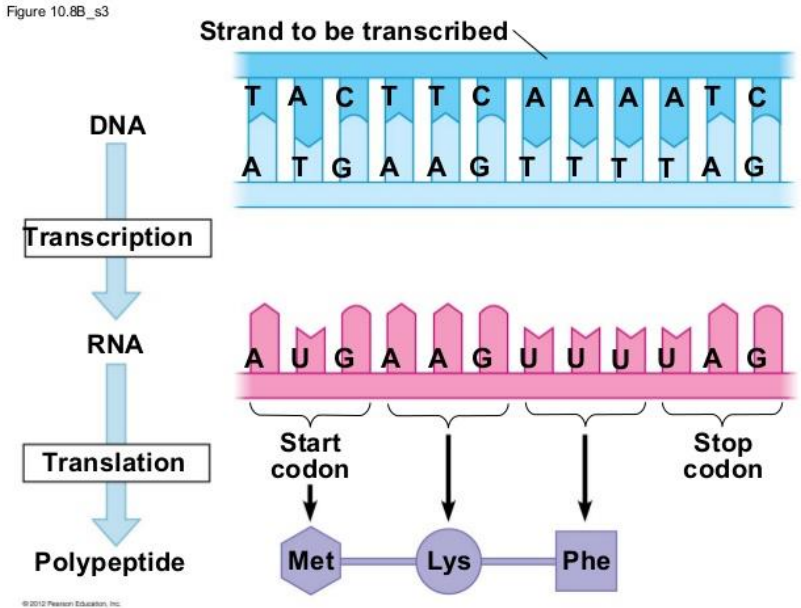



https://www.nobelprize.org/educational/medicine/dna/

# Protein Coding

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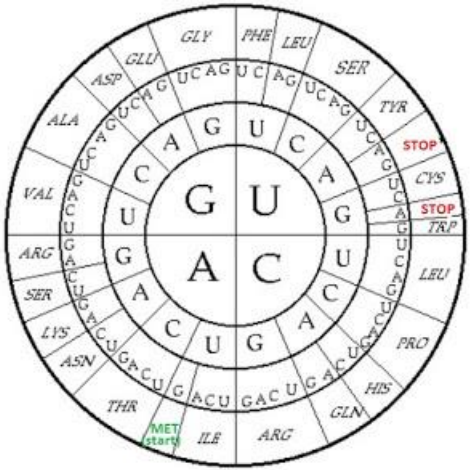
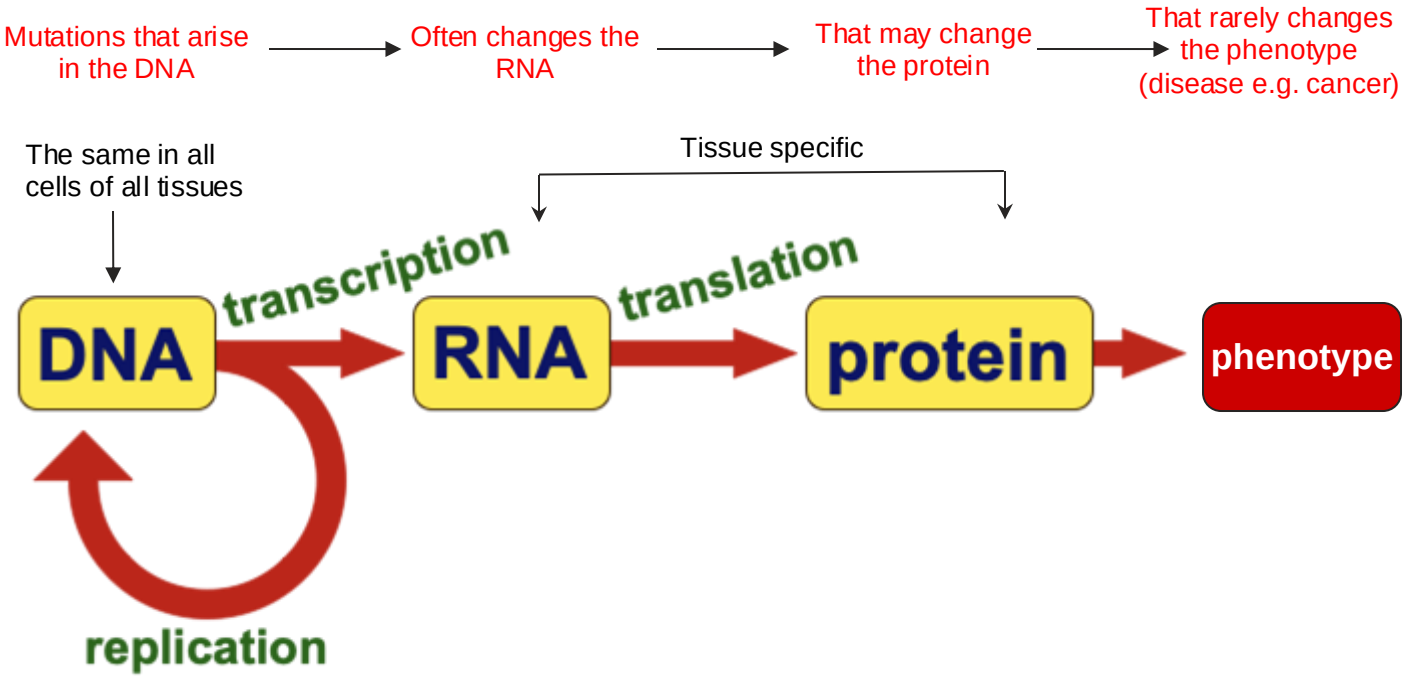



http://lab2webchemistry.blogspot.com/2015/08/protein-manufacturing-coding-in-our-body.html

# What is Cancer?



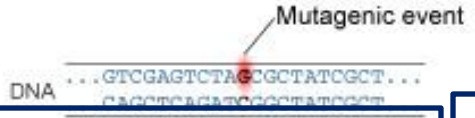

**Cancer is a genetic disease** meaning changes in the DNA *MAY* cause cancer

# Types of Mutation

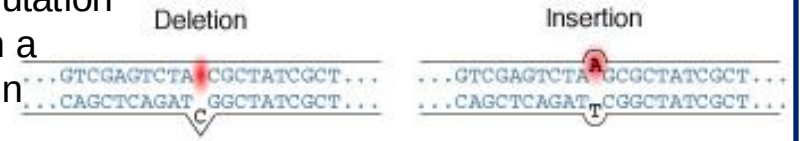
**Silent mutation** is when a base pair change in the DNA doesn't result in a change in the protein

*Micro*

Point mutations




Frameshift mutation that results in a mutant protein

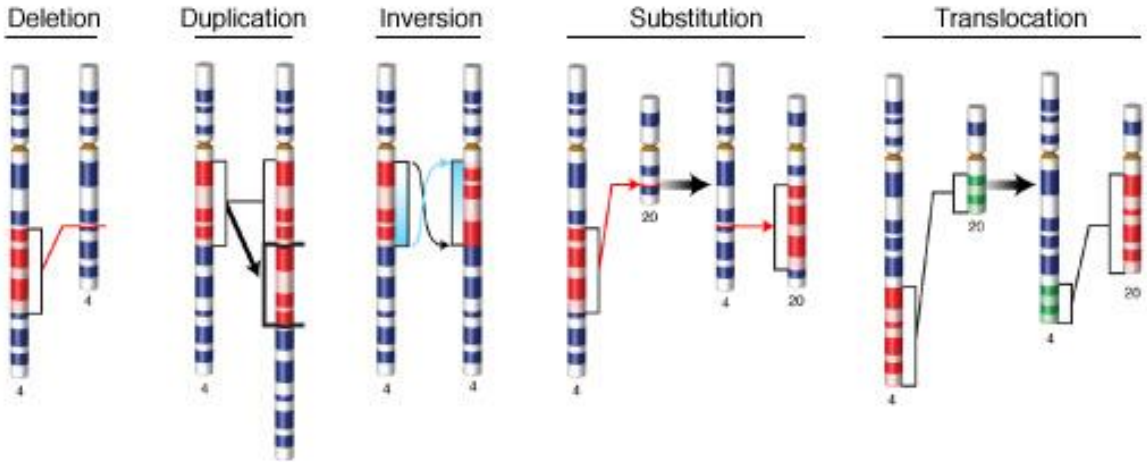




**Missense mutation** that results in a mutant protein

*Macro*

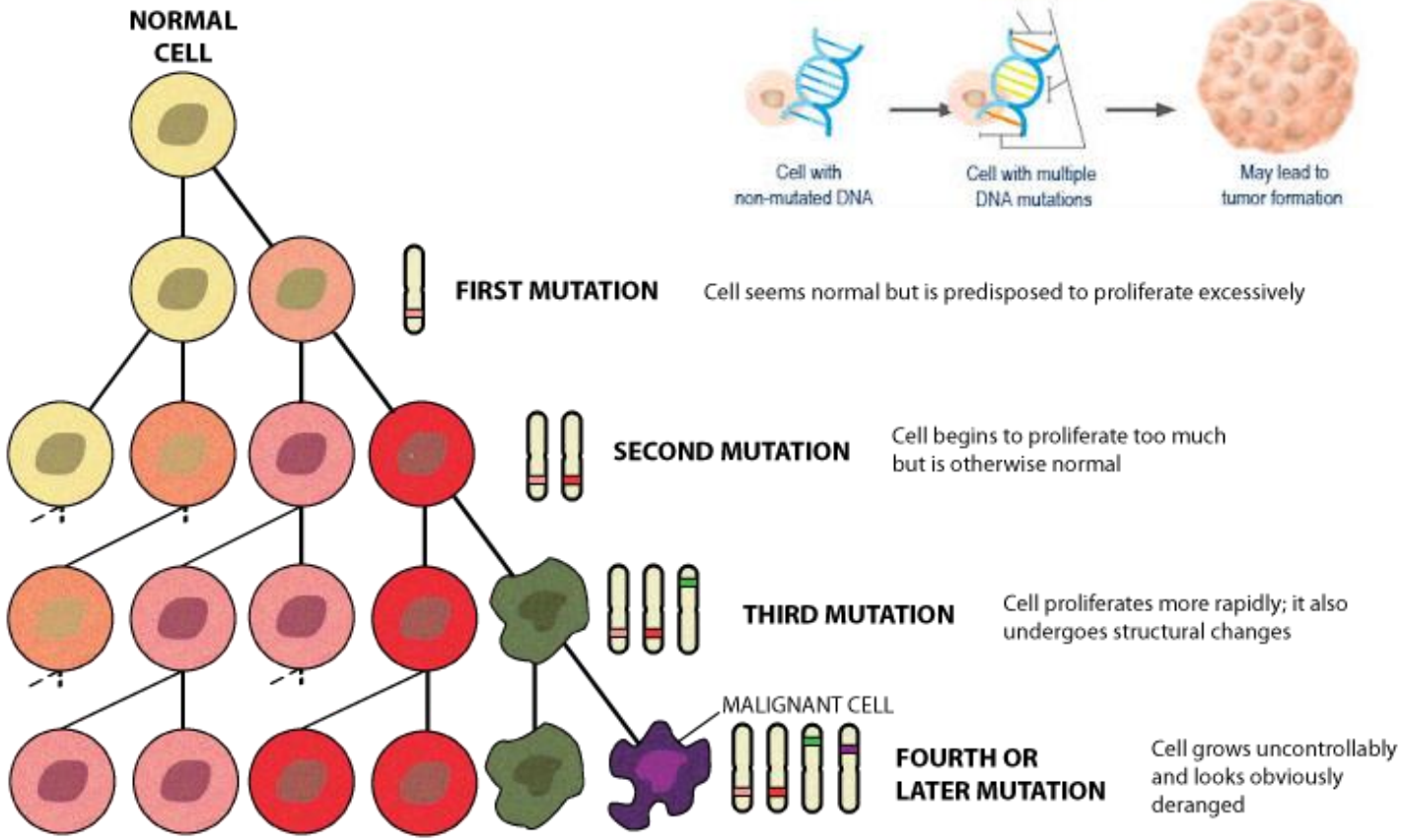
Chromosomal mutations




**Nonsense mutations** A missense mutation which changes the codon that recruits an amino acid to the mRNAinto a stop codon

https://geneed.nlm.nih.gov/images/mutation_sm.jpg

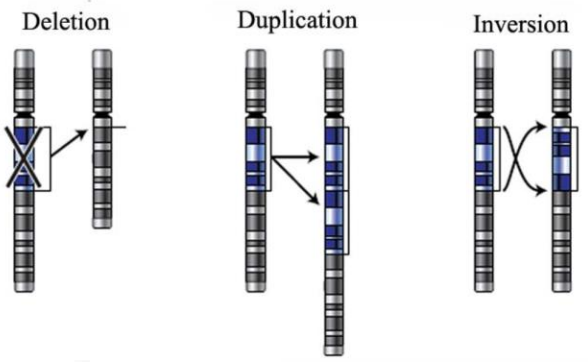
# Mutations may lead to cancer

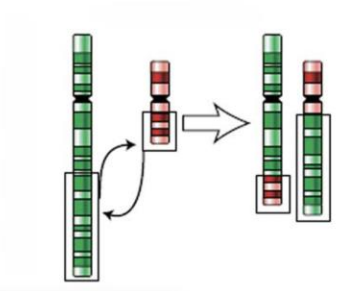



http://www.bu.edu/synapse/files/2011/01/cancerprogression.png

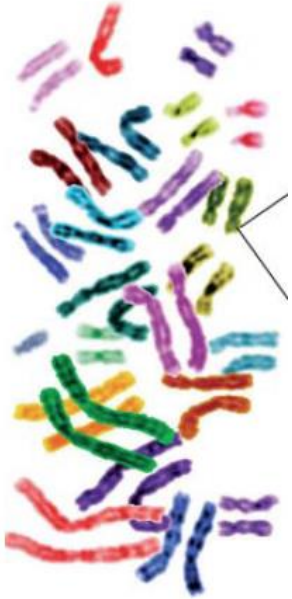
# Types of Mutations

## Chromosomal

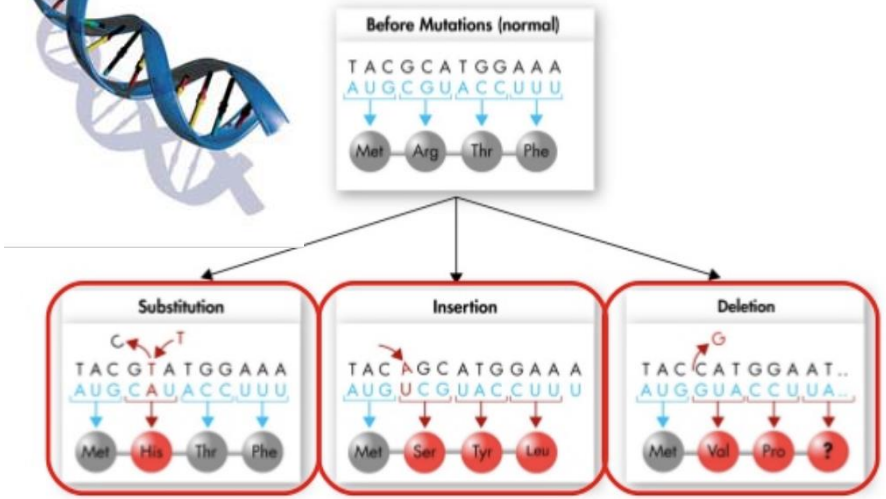


Reciprocal Translocation



## Point Mutations

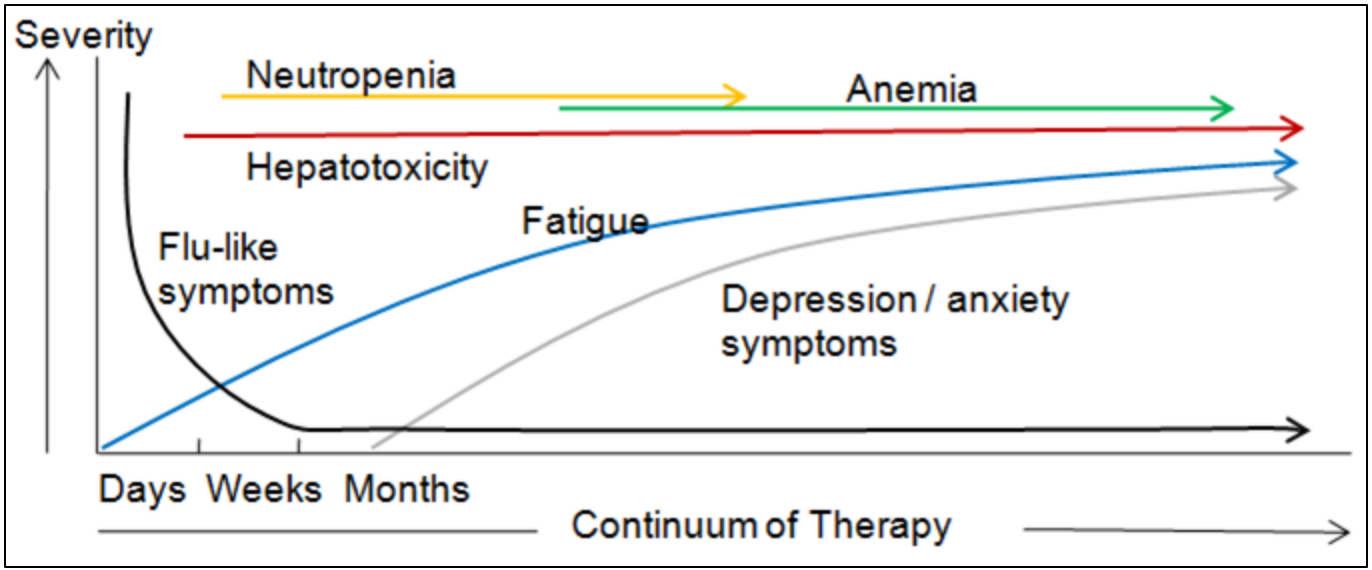


# BCR-ABL1

*a translocation (chromosomal mutation) found in a blood cancer called "Chronic Myelogenous Leukemia" or CML)*

# Before Targeted Therapies…

- Prior to 2001: <1 in 3 CML patients survived 5 years past diagnosis
- The most successful intervention at the time was Interferon a



# Chromosomes 9 and 22 in blood cells of a patient with Chronic Mylogenous Leukemia

## A Minute Chromosome in Human Chronic Granulocytic Leukemia

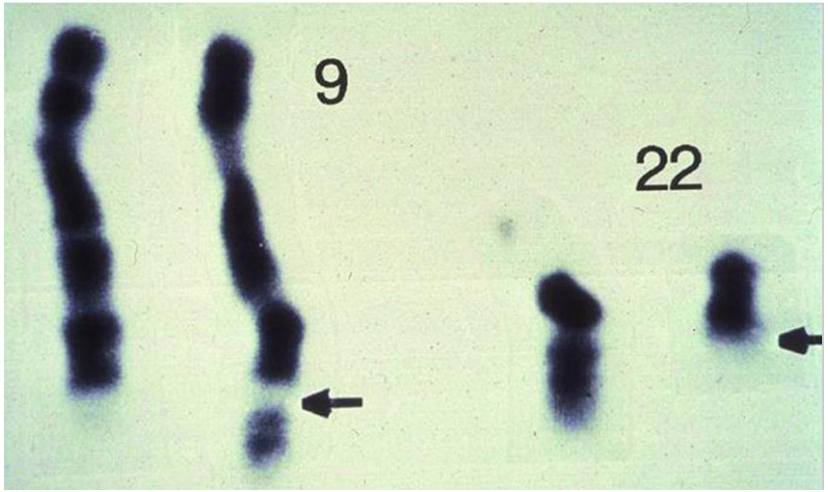
In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of acute granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24–72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al., Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

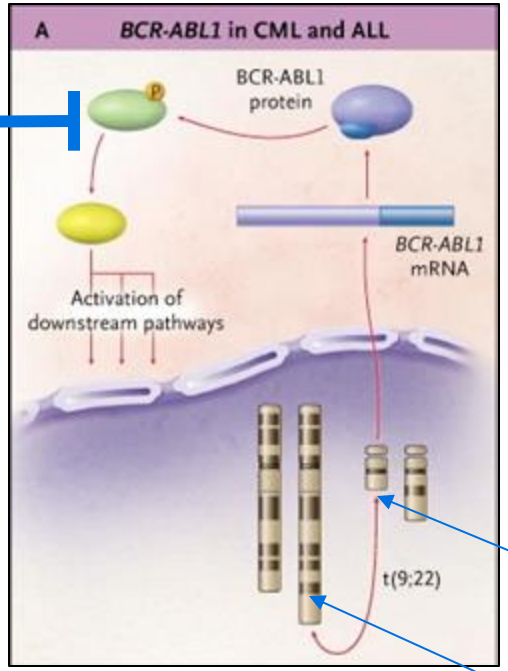
The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL
*School of Medicine, University of Pennsylvania*
DAVID A. HUNGERFORD
*Institute for Cancer Research*

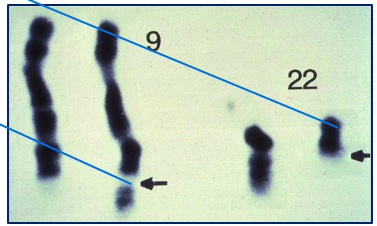
Nowell & Hungerford, 1960 Science 132.1497



# Poster Child for Targeted Therapy: Gleevec

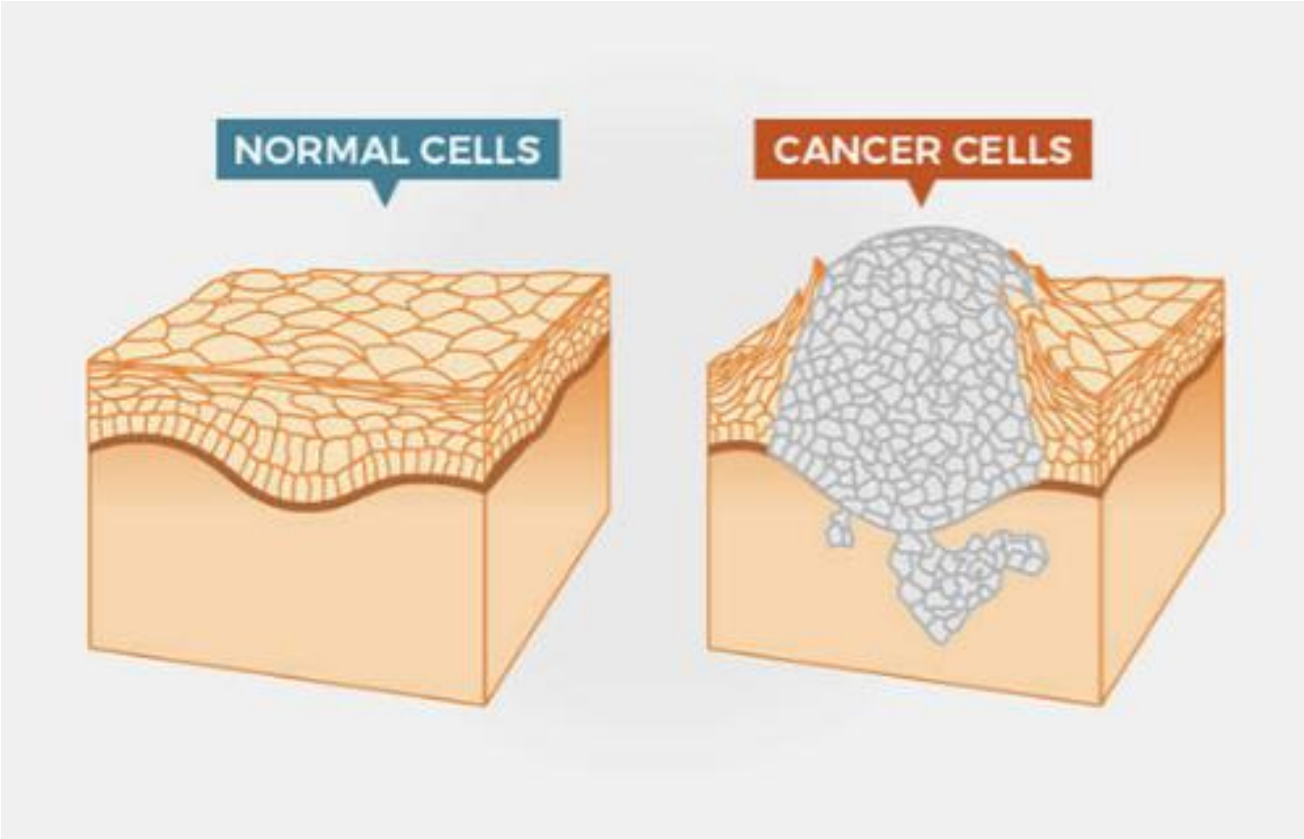







# Cancer Fundamentals

# How does cancer form?

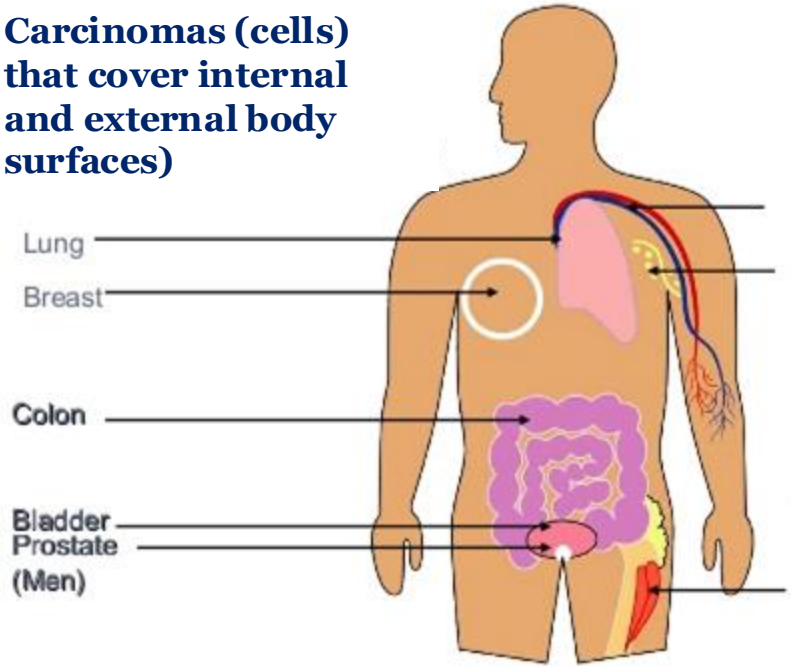



Cancer is a disease caused when cells divide uncontrollably and spread into surrounding tissues.

*"What Is Cancer? was originally published by the National Cancer Institute."*

# Cancer is a collection of different diseases

**Carcinomas (cells) that cover internal and external body surfaces)**

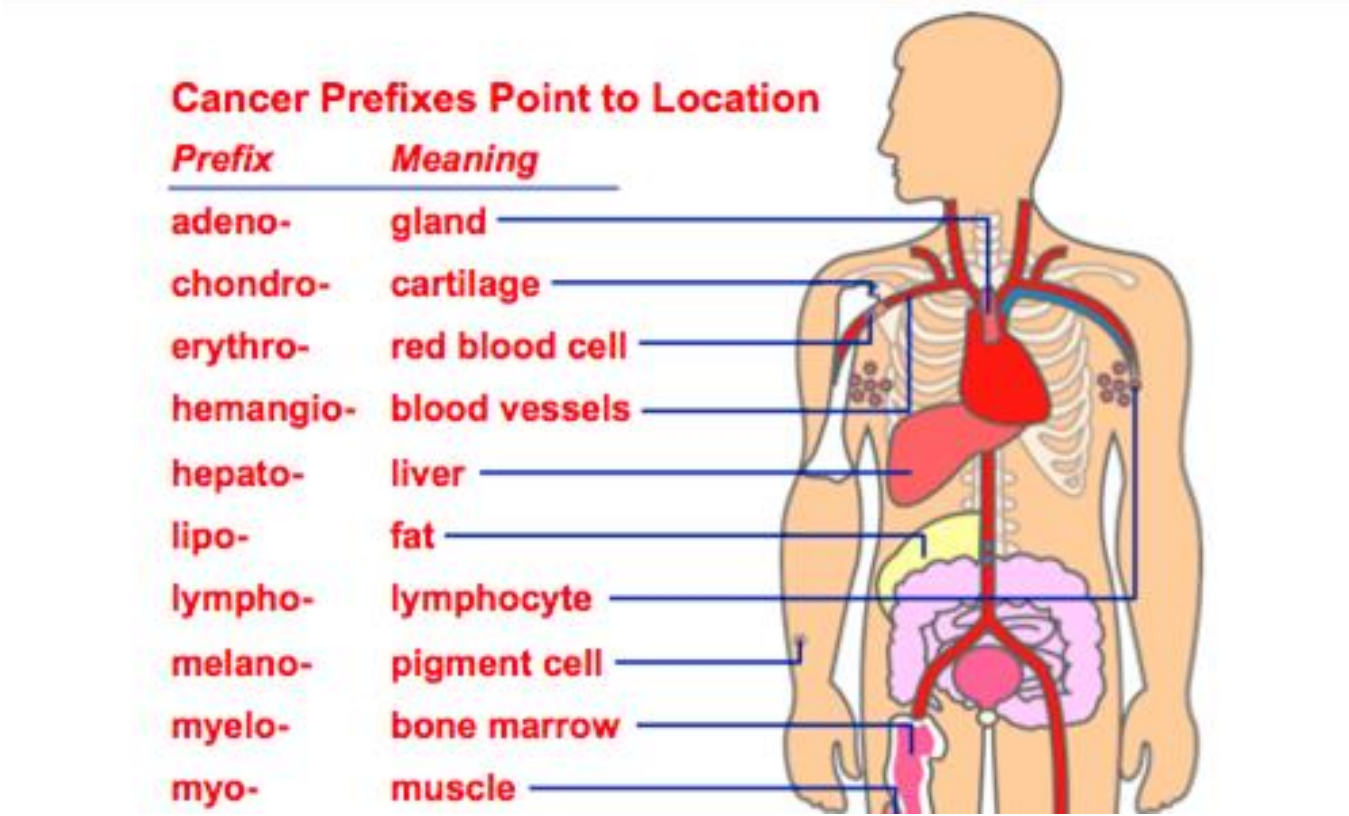



**Leukemia**
(Blood Cells)

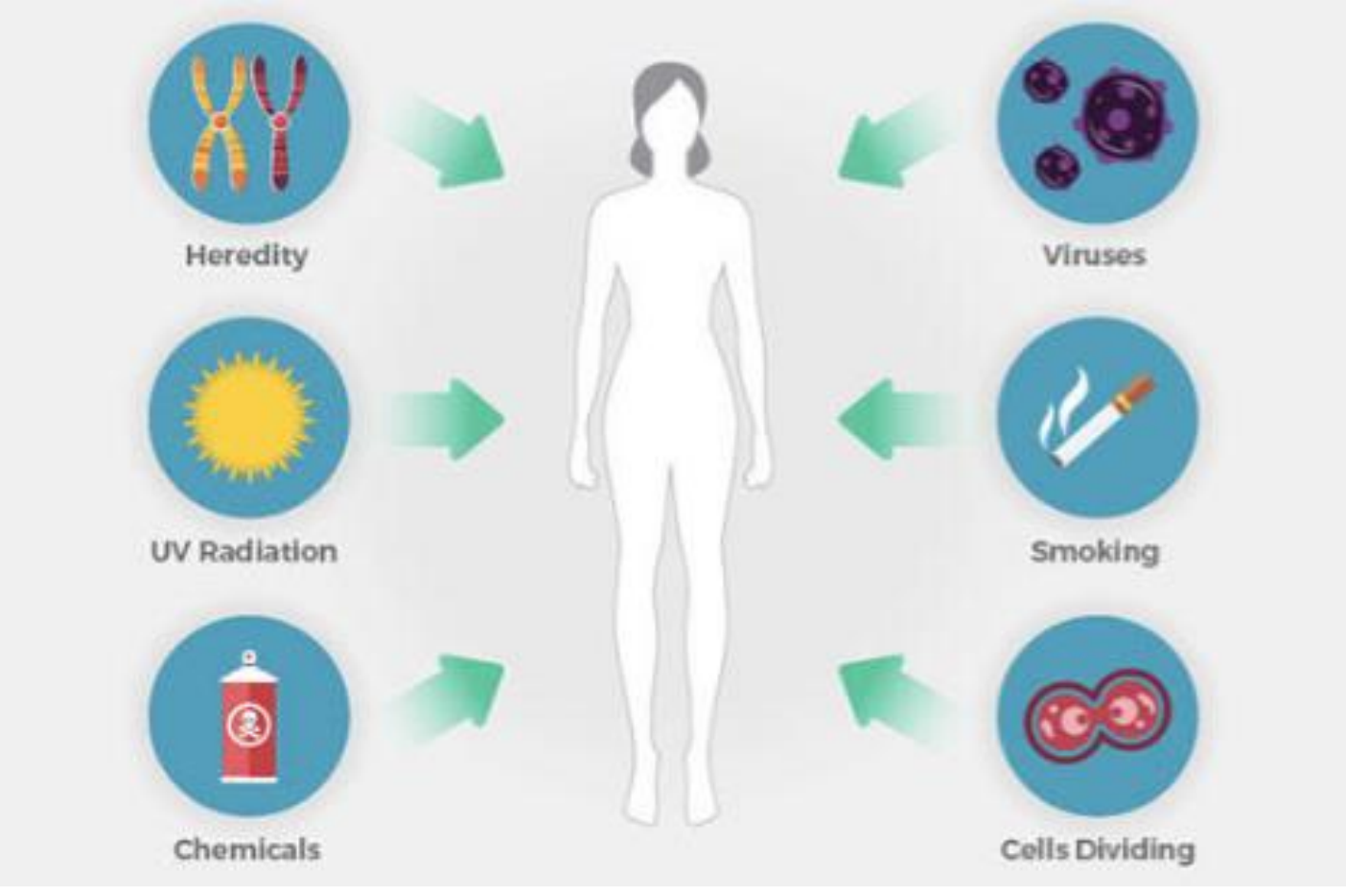
**Lymphomas**
(Lymph nodes & tissues)

**Sarcomas**
(Cells in supportive tissues – Bone, Fat, Muscles )

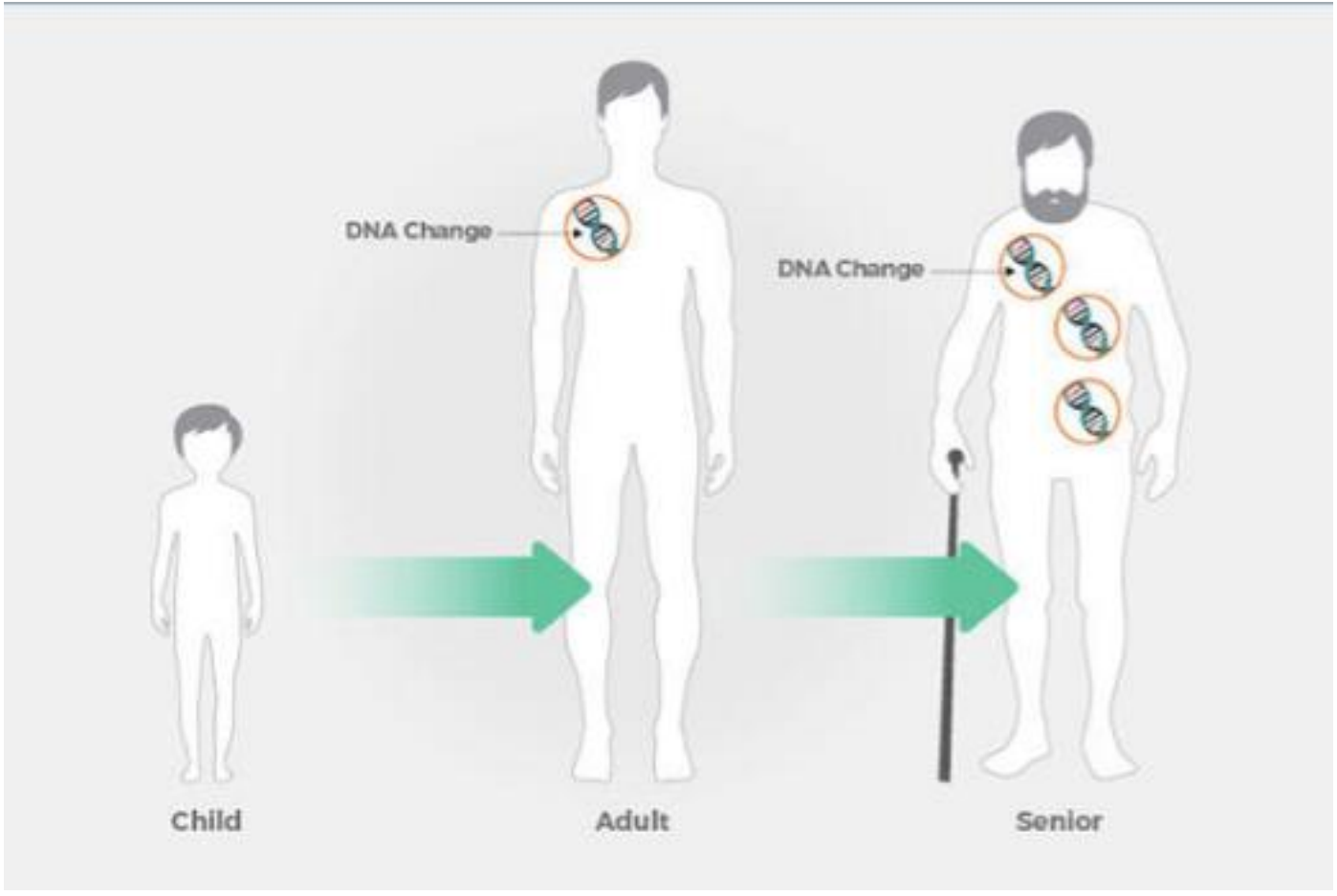
# Naming cancer



# What causes genetic changes in cancer?

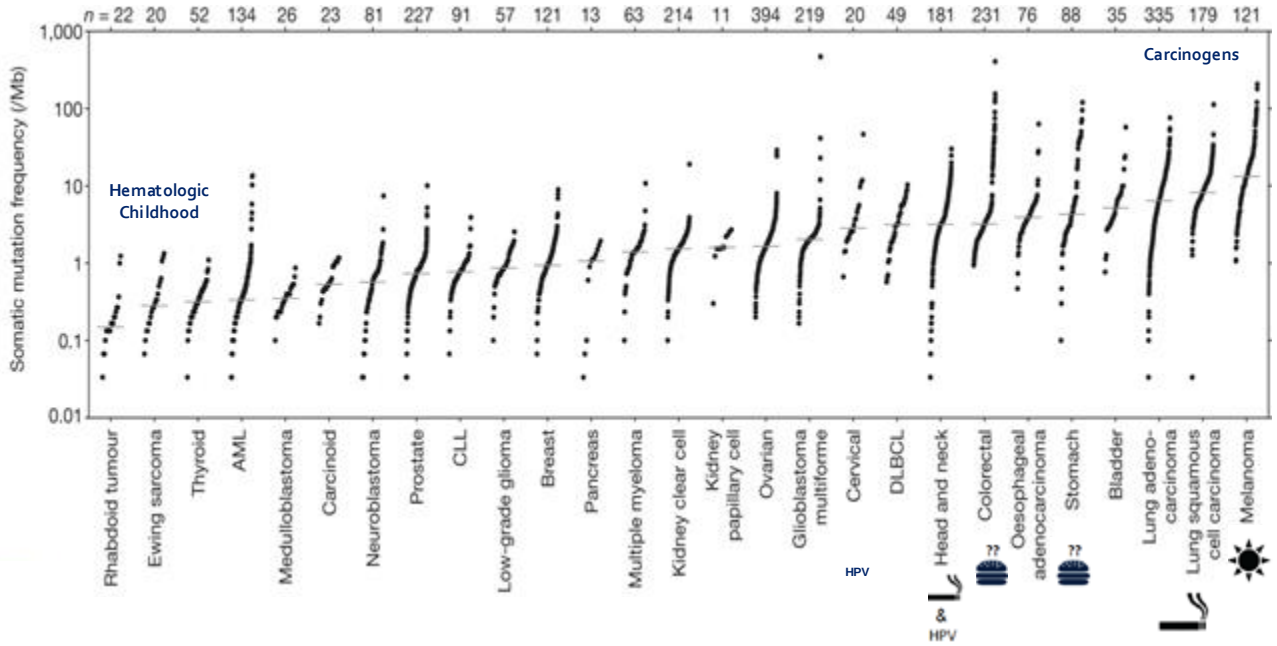


# How does age relate to cancer?



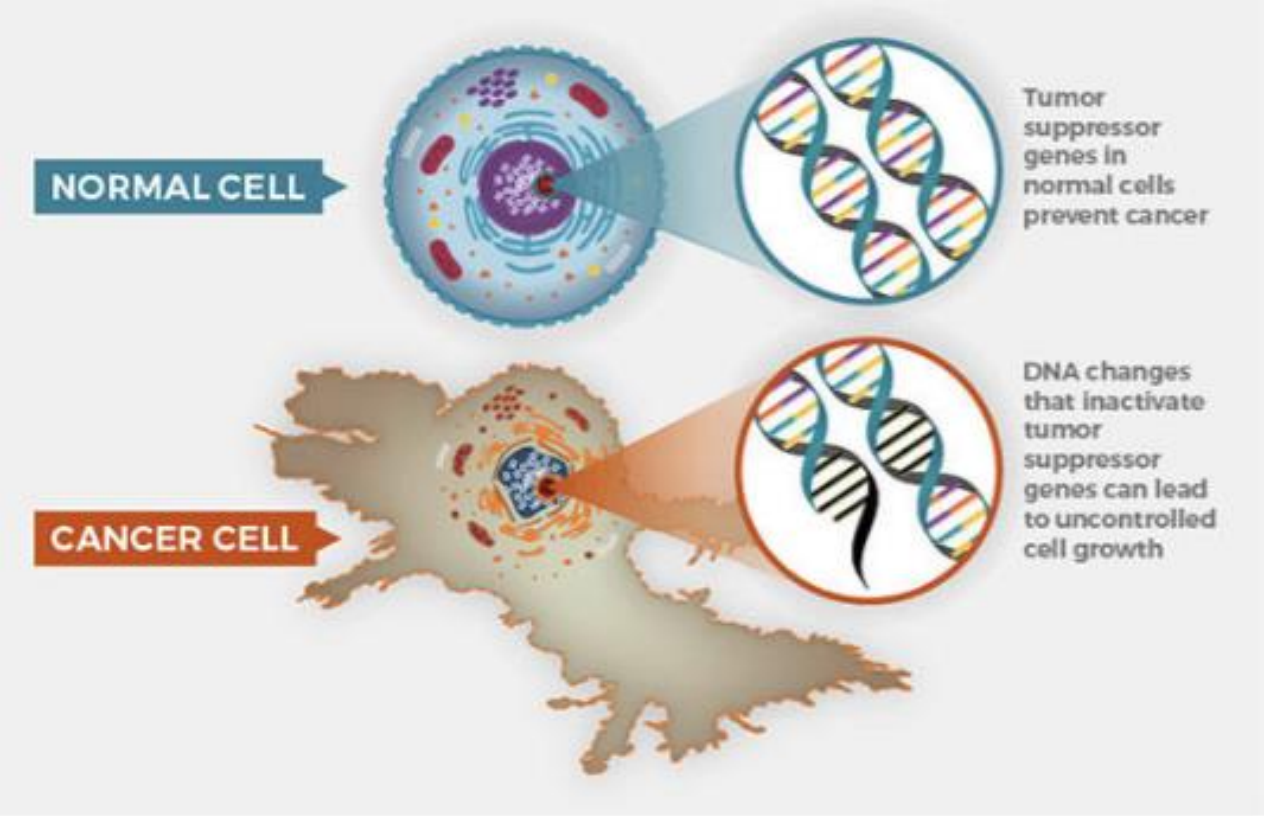
# Cancer is Genetic

## Most mutations in cancer are “passengers”

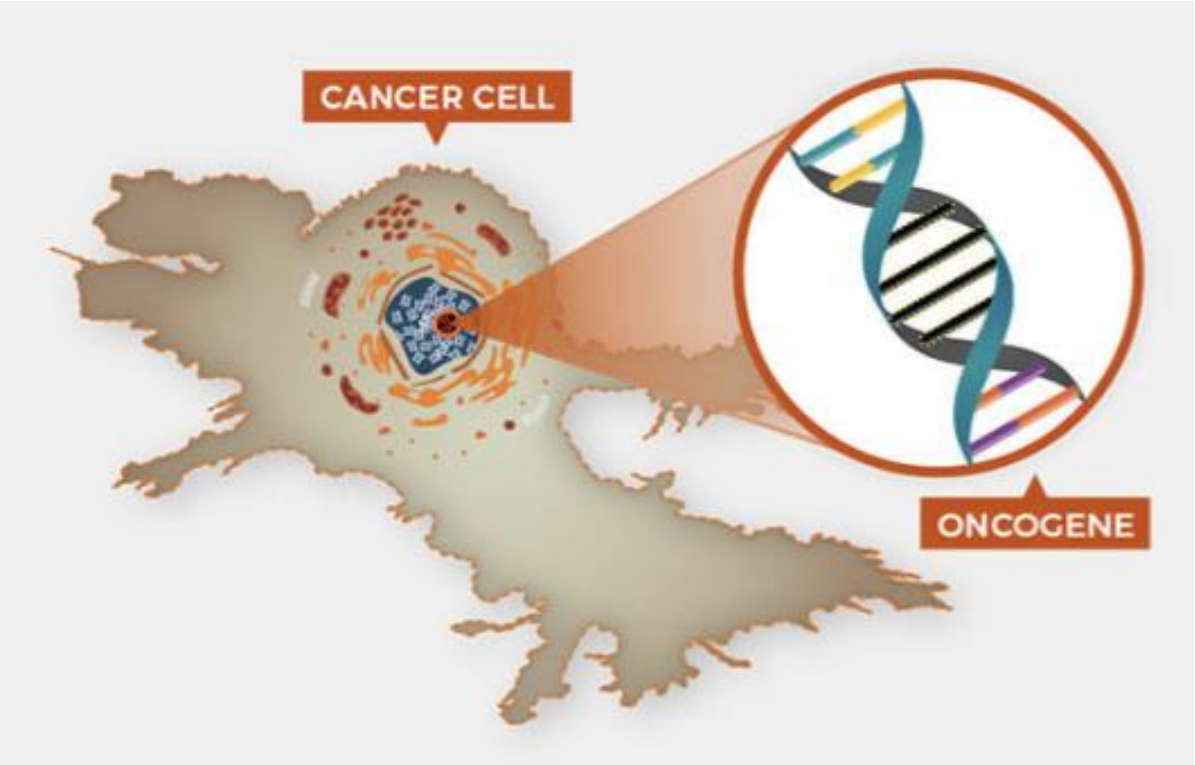



Lawrence, MS et al. Nature. 2013 Jul 11;499(7457):214-8

# Some mutations arise in Tumor Suppressor Genes == DRIVERS



# Some mutations arise in Oncogenes == DRIVERS



## Passengers

Alterations which do not alter cancer cell fitness

KMT2A D2713G

PTEN R297H

STK11 Q1203R

## Drivers

Alterations that confer selective growth advantage to cancer cells

EGFR E804A

*FBXW7* deletion

KRAS G12R

*NF2* gain

*MYC* amplification

GNA11 Q209L

NRAS-SOX5

*TP53* deletion

EGFR T430I

EWSR1-FLI1

### Clinically actionable

Alteration is biomarker predictive of therapeutic sensitivity or resistance

*CSFR1* gain

KRAS-SOX5

*CDKN2A* loss

KRAS G12C

MSI-H

EML4-ALK

BRAF T332*

ETV6-NTRK3

CTNNB1 Y112H

BRAF V600E

AKT1 E17K

TMB-H

*RRAS* gain

*ERBB2* amplification

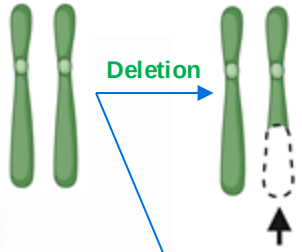
FBXW7 Q390H

C17orf37-ERBB2

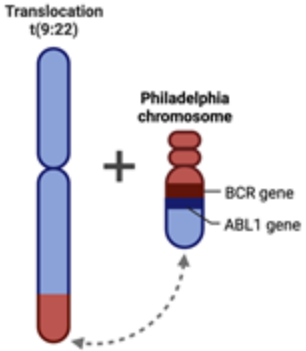
WNT1 Y88N

BRCA2 P2402S

**Copy Number Alterations**




**Translocations**

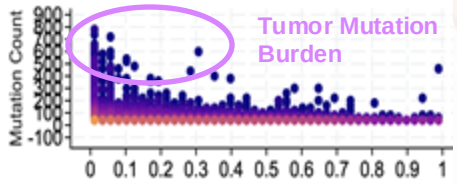



**MSI Status**

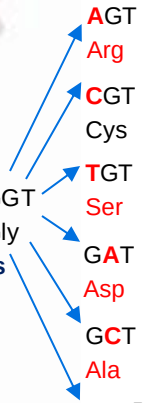
CA

5'—CACACACACACACA– 3'

5'—CACACACACACACA– 3'

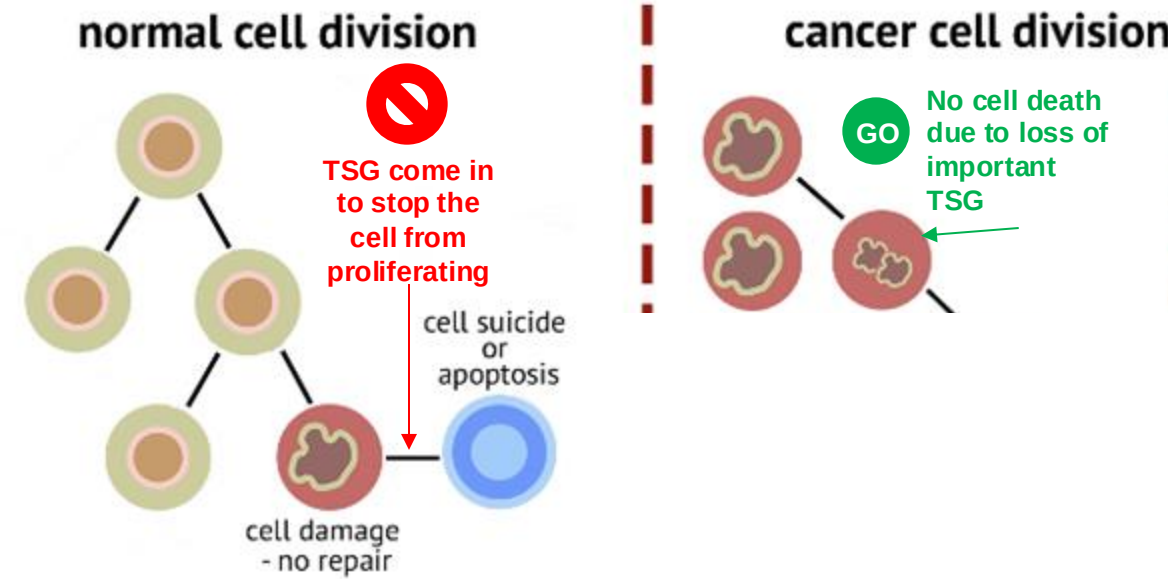



**Point mutations**

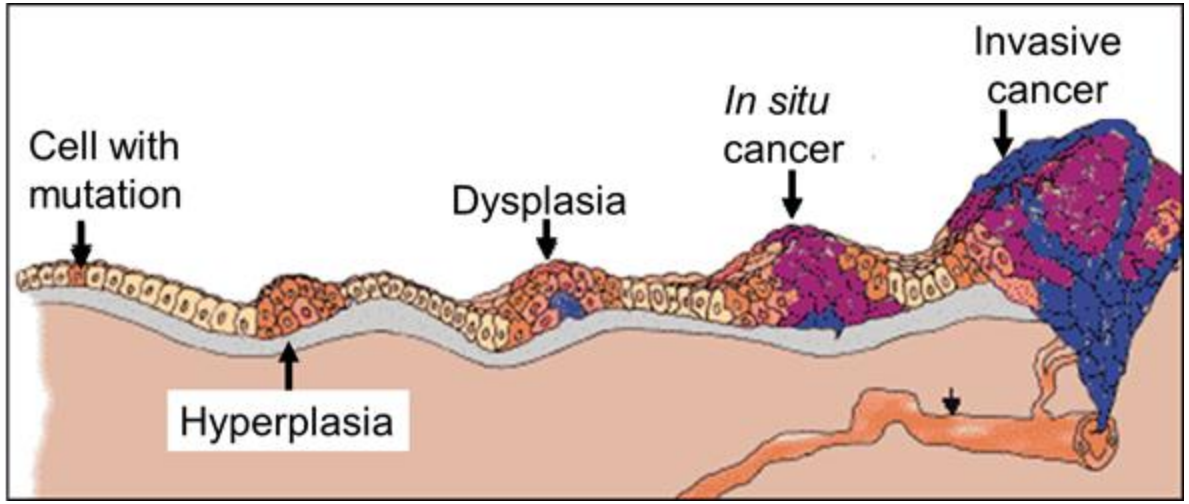


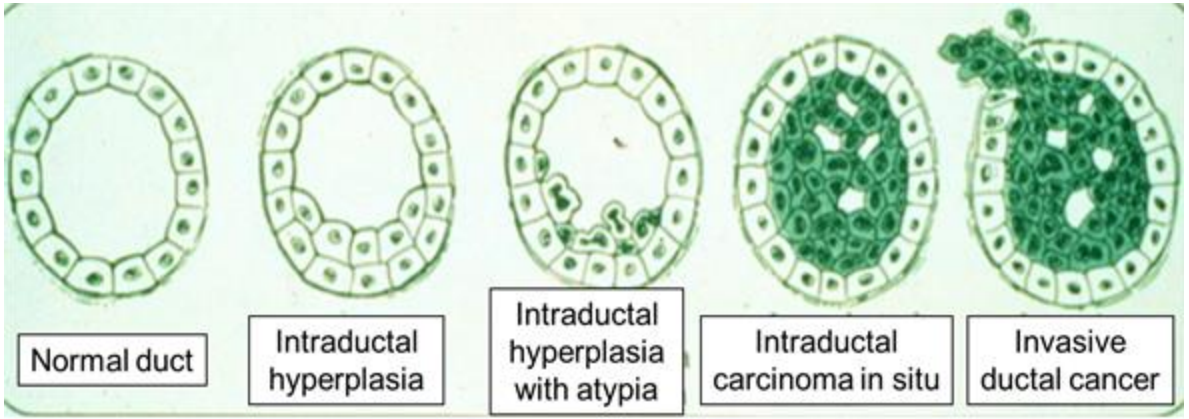
# Processes are in place such that a cell with a driver mutation dies

**However, if the cell accumulates enough mutations → the cell with all its DNA mutations keeps making replicates of itself**

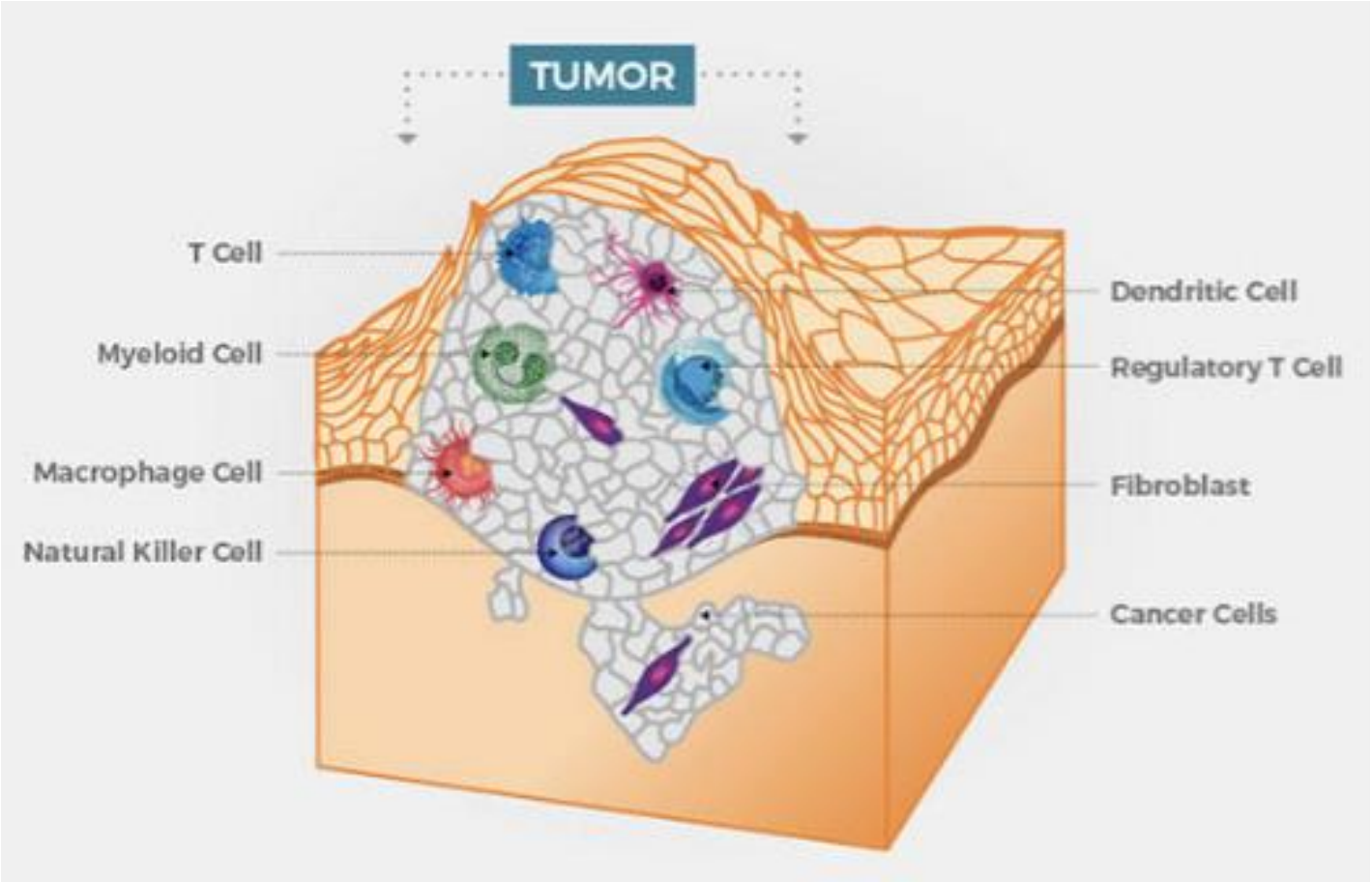


# Normal cells “transform” into cancer cells



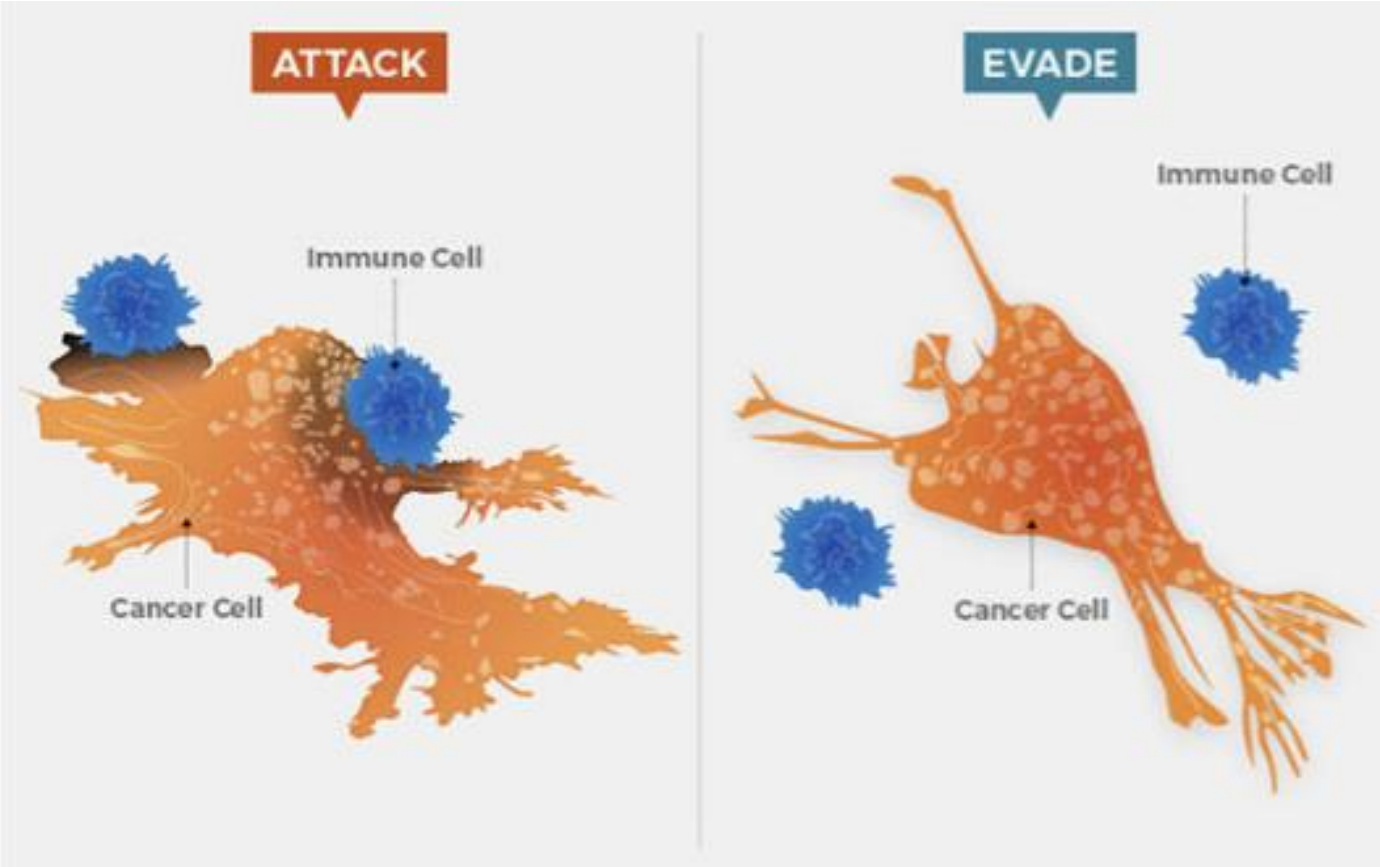



# Cancer cells arise in a tissue surrounded by different types of cells → Tumor Microenvironment

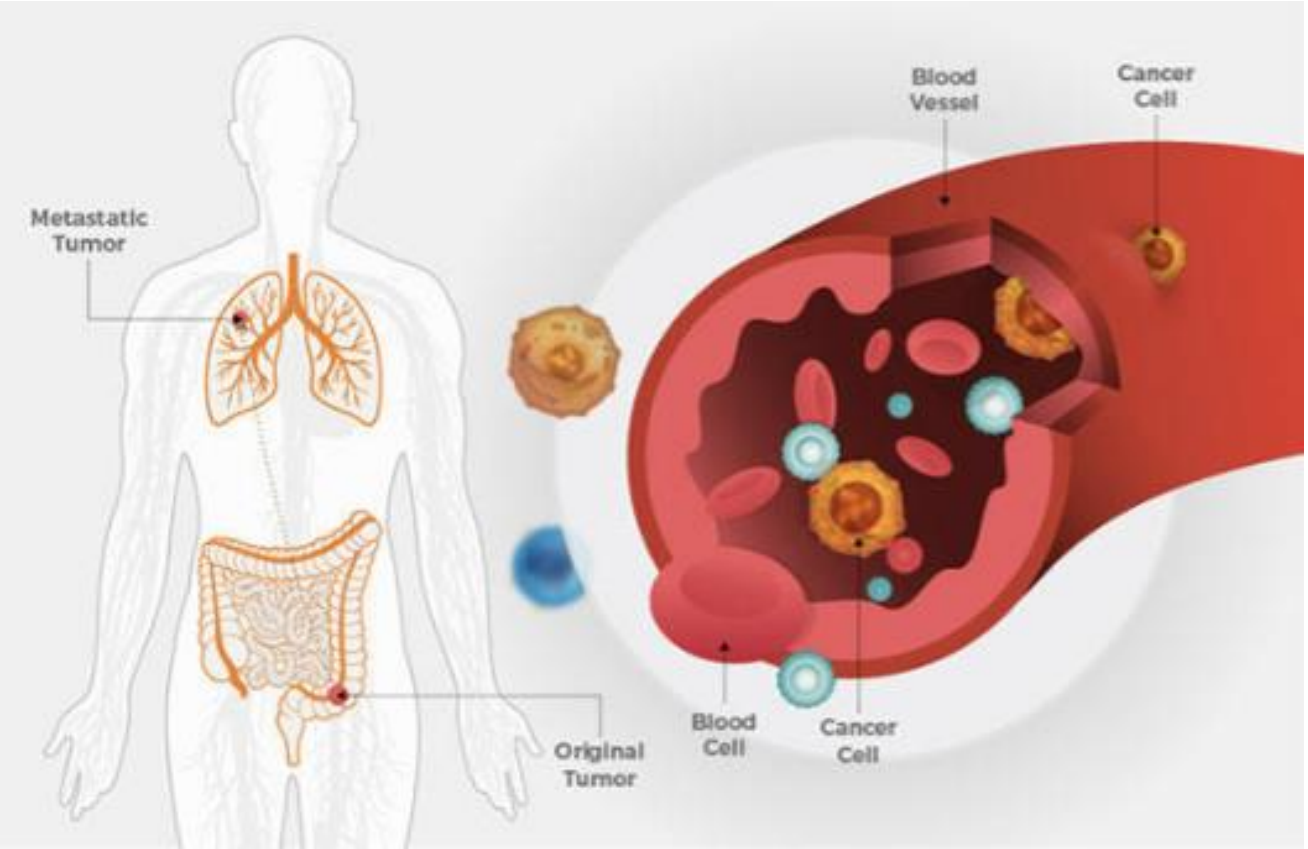


# Interaction between cancer cells and its microenvironment affects their ability to grow and spread

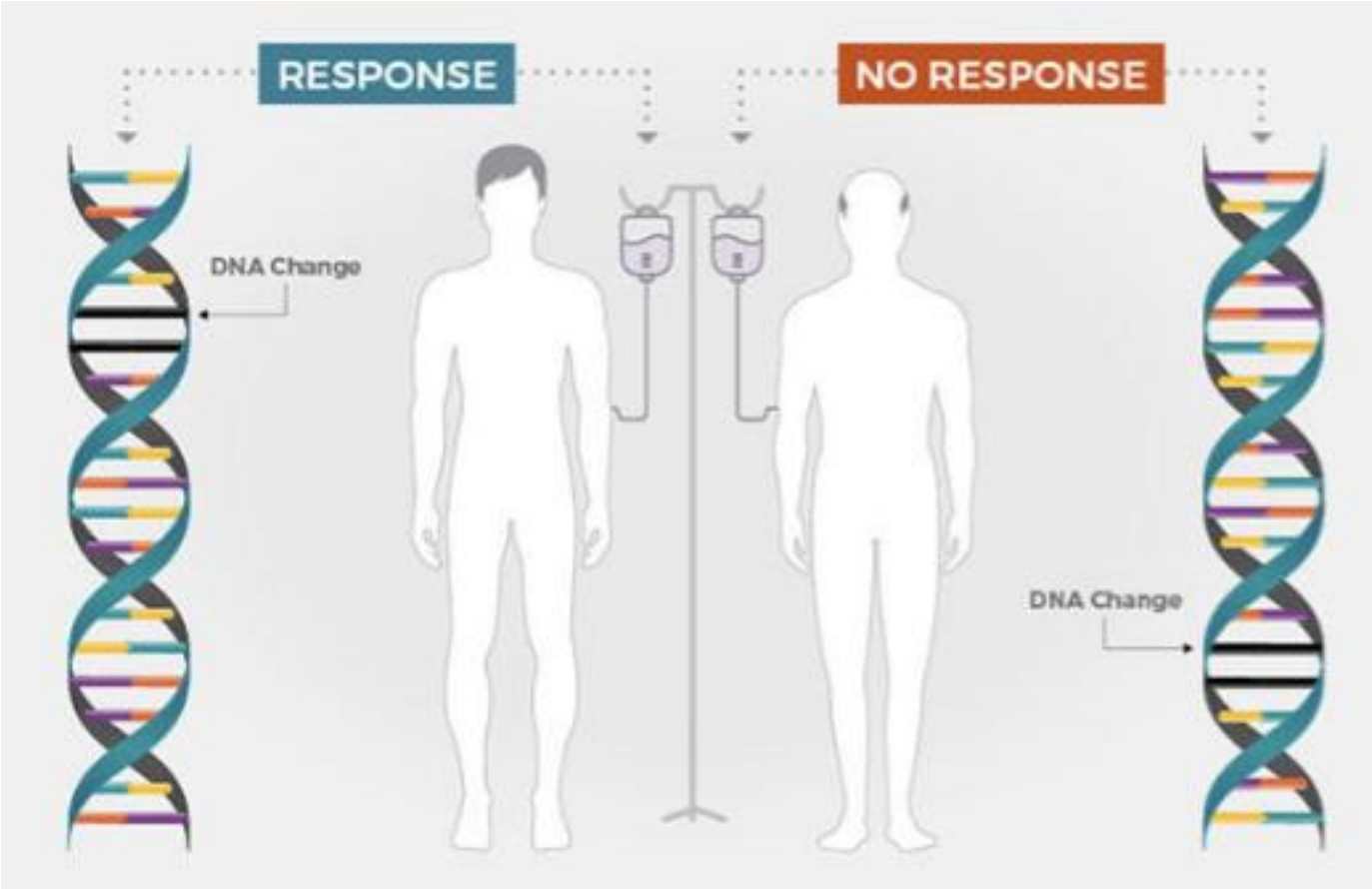
**Particularly a cancer cell's interaction with the immune cells in its microenvironment**



# The cancer cell microenvironment also affects its ability to spread to distant organs (metastasize)

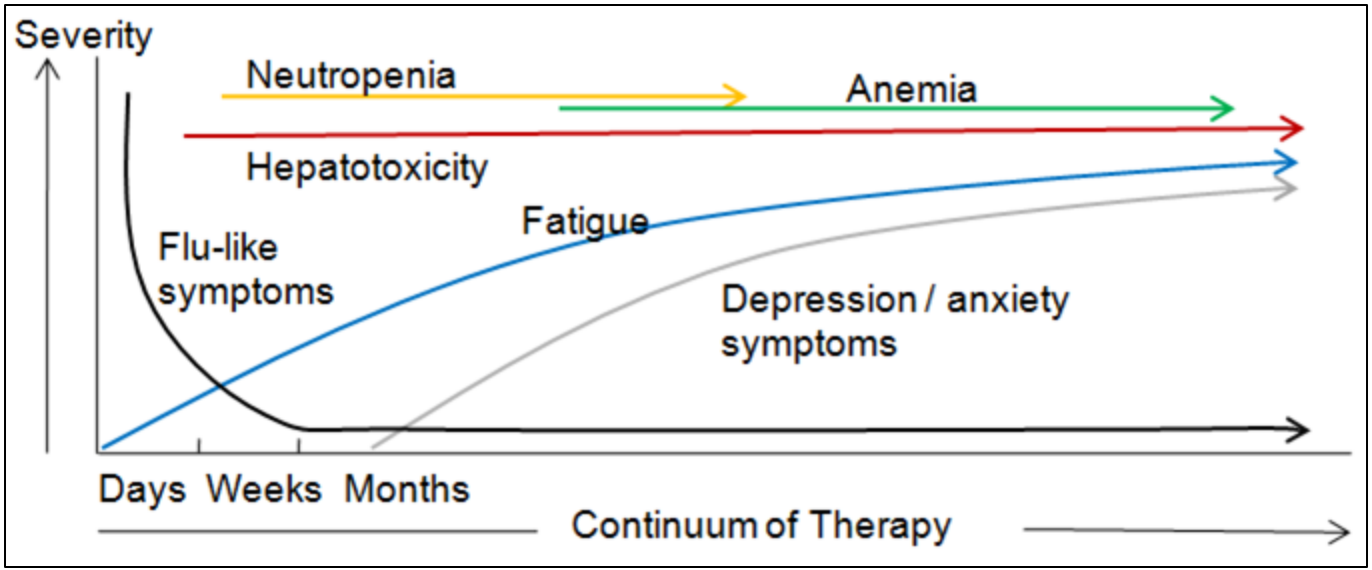


# Genetic mutations can predict a patient's response to certain cancer treatments



# Before Targeted Therapies…

- Prior to 2001: <1 in 3 CML patients survived 5 years past diagnosis
- The most successful intervention at the time was Interferon a



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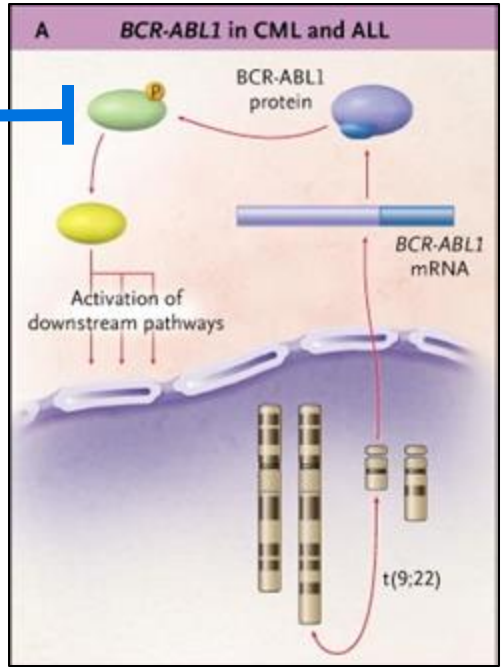
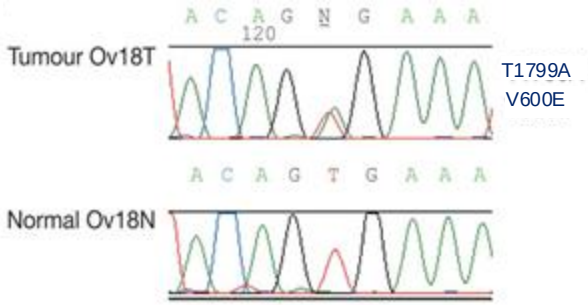
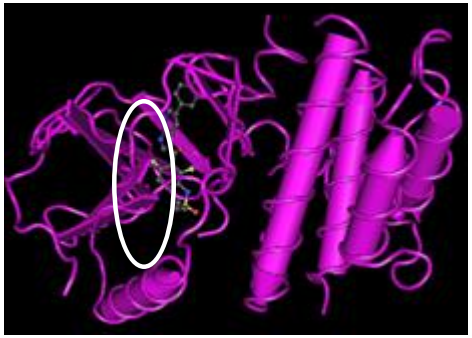



# From sequencing to drug to treatment?

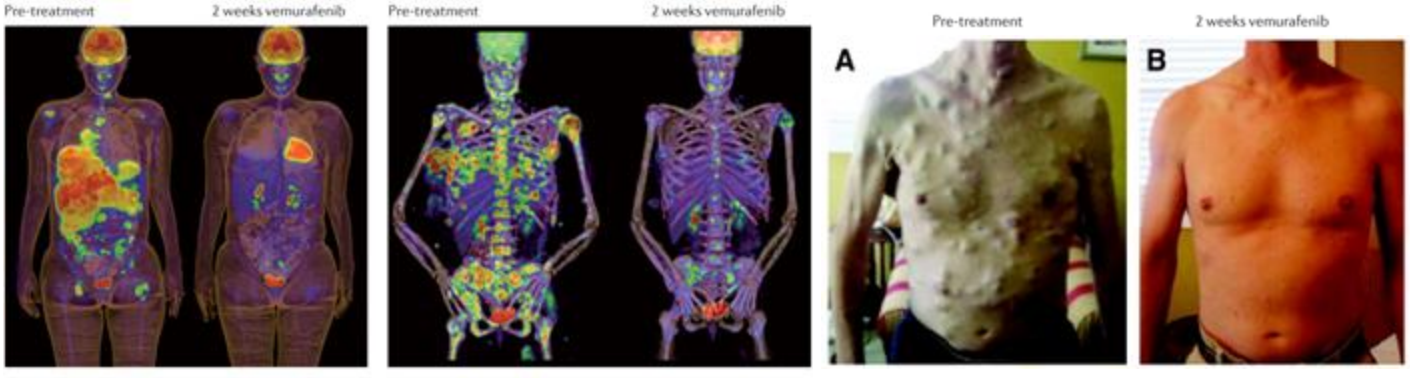
**DNA Sequencing** → Discovery of a driver mutation
**BRAF V600E**



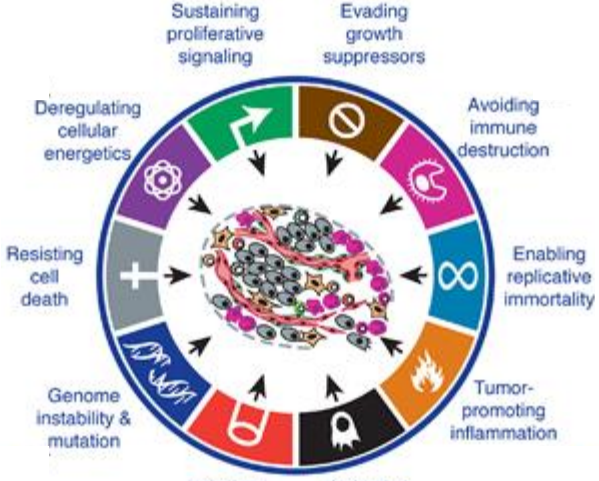

**Drug** → Inhibits the encoded protein
**Vemurafenib**



**Changes in Clinical Practice**



# Hallmarks of Cancer Cells




Hanahan, Douglas et al. Cell , Volume 144 , Issue 5 , 646 - 674

# Questions??