

The background of the slide is a light blue color with a repeating pattern of cartoon sharks. The sharks are grey on top and white on the bottom, with a red, jagged line representing their mouths. They are scattered across the slide, with some larger and more prominent than others.

Mechanisms of Disease

Session 1: Genetic Diseases

Clair Travis

Introductions

- Name (correct me if I butcher it)
- Grade you will be in the fall
- What disease interests you the most

TB IS THE TOP INFECTIOUS DISEASE KILLER IN THE WORLD

IN 2016

1.7 MILLION PEOPLE DIED FROM TB
INCLUDING NEARLY 400 000 PEOPLE WITH HIV-ASSOCIATED TB

10.4 MILLION PEOPLE FELL ILL FROM TB

TB IS THE MAIN CAUSE OF DEATHS RELATED TO ANTIMICROBIAL RESISTANCE AND THE LEADING KILLER OF PEOPLE WITH HIV

EACH DAY - 4700 PEOPLE LOSE THEIR LIVES AND 28,500 PEOPLE FALL ILL DUE TO TB

MEASLES & RUBELLA MOVE FAST

Failure to vaccinate children against measles & rubella puts them at risk of severe health complications, such as

- Measles: Pneumonia, Diarrhea
- Rubella/CRS: Brain Damage, Deafness, Blindness, Heart Disorders

100,000 babies are born with CRS each year globally

A pregnant woman unvaccinated against rubella who is infected during her first trimester has up to a 90% chance of giving birth to a baby with congenital rubella syndrome (CRS)—that is if the baby survives.

Vaccination prevents mothers from giving birth to babies with CRS

A SNAPSHOT: BLOOD PRESSURE IN THE U.S.

Make Control Your Goal

High blood pressure is a major risk factor for heart disease and stroke, the first and fourth leading causes of death for all Americans.

HIGH BLOOD PRESSURE BASICS

1 IN 3 American adults have high blood pressure

High blood pressure contributes to **~1,000 DEATHS/DAY**

When your blood pressure is high:

- You are **4x** more likely to die from a stroke
- You are **3x** more likely to die from heart disease
- 69%** of people who have a first heart attack...
- 77%** of people who have a first stroke...
- 74%** of people with chronic heart failure...

HAVE HIGH BLOOD PRESSURE

Annual estimated costs associated with high blood pressure:

\$51 BILLION in direct medical expenses

\$47.5 BILLION in indirect medical expenses

BLOOD PRESSURE CONTROL

Reducing average population systolic blood pressure by only 12-13 mmHg could reduce:

- 37%** Stroke
- 21%** Coronary heart disease
- 25%** Deaths from cardiovascular disease
- 13%** Deaths from all causes

ONLY ABOUT HALF (47%) of people with high blood pressure have their condition under control

MAKE CONTROL YOUR GOAL, EVERY DAY

- Check your blood pressure regularly—at home, at a doctor's office, or at a pharmacy
- Quit smoking—or don't start. **1-800-QUIT-NOW** or **Smokefree.gov**
- Eat a healthy diet with:
 - More fruits, vegetables, potassium, and whole grains
 - Less sodium, saturated fat, trans fat, and cholesterol
- Adults should limit alcohol to no more than:
 - 1 drink per day for women
 - 2 drinks per day for men
- Read nutrition labels and lower your sodium intake
 - Most of the sodium we eat comes from processed and restaurant foods
 - About 90% of Americans eat too much sodium
- Get active and maintain a healthy weight
 - Aim for 2 hours and 30 minutes of moderate physical activity every week

Source: Centers for Disease Control and Prevention, 2014
This infographic was developed by the Centers for Disease Control and Prevention's Division for Heart Disease and Stroke Prevention in support of achieving the Million Hearts® initiative goal to prevent 1 million heart attacks and strokes by 2021.

millionhearts.hhs.gov/aboutus/blood_pressure.html

Causes of Death in the World

VECTOR-BORNE DISEASES

VECTORS MAY BE A THREAT TO YOU, AT HOME AND WHEN TRAVELLING

VECTORS ARE SMALL ORGANISMS THAT CARRY SERIOUS DISEASES

WITH JUST 1 BITE they can transmit diseases such as:

- Malaria
- Dengue
- Leishmaniasis
- Lyme disease
- Yellow fever
- Japanese encephalitis

Diseases spread by vectors kill a million people every year and

WORLDWIDE 14.1 MILLION

NEW CANCER CASES ARE DIAGNOSED EACH YEAR

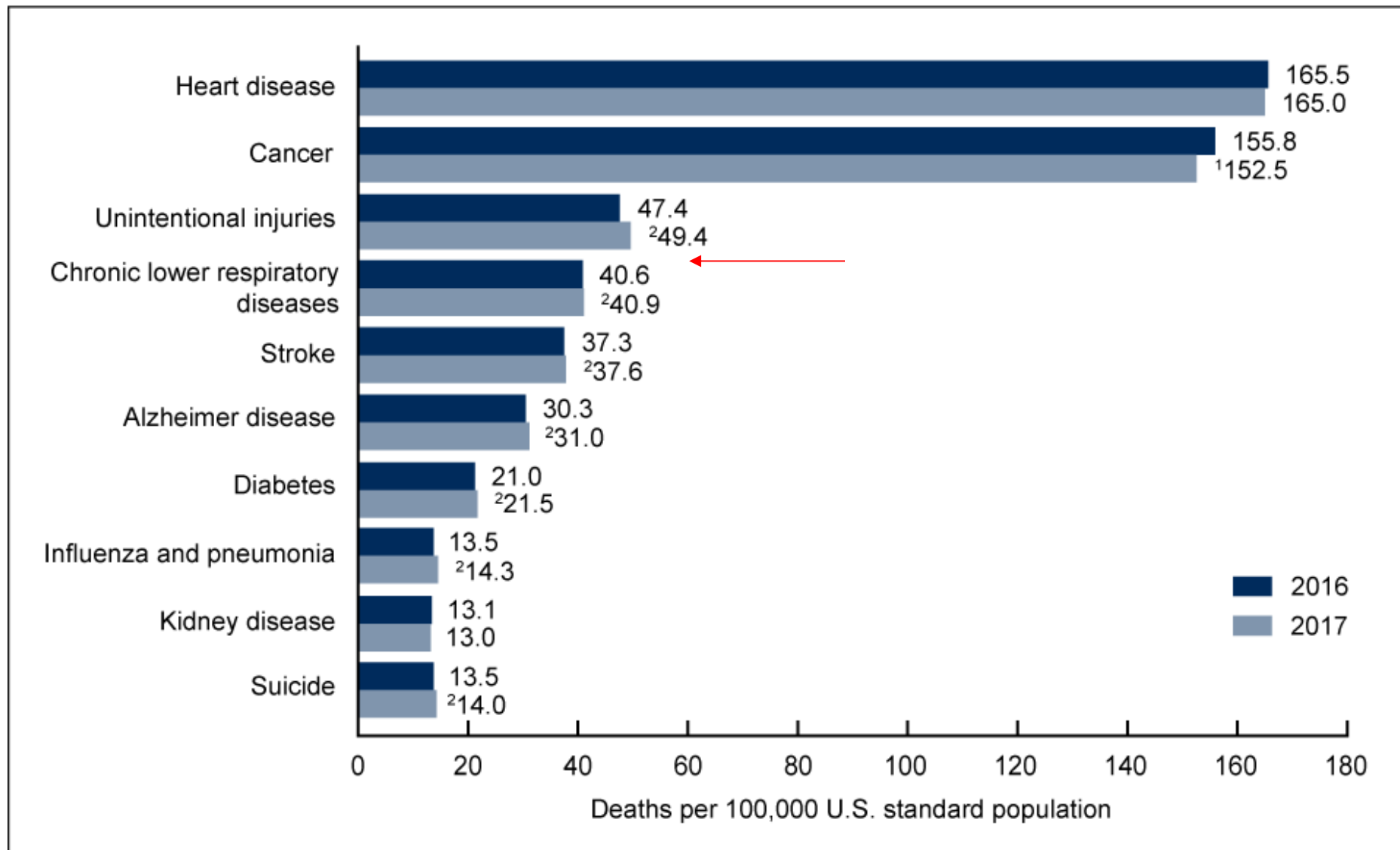
57% or 8 MILLION ARE IN LESS DEVELOPED REGIONS

IN THESE REGIONS, THE MOST COMMON TYPES ARE

- LUNG** 1.1 MILLION CASES
- BREAST** 883,000 CASES
- STOMACH** 677,000 CASES
- LIVER** 648,000 CASES
- COLORECTAL** 624,000 CASES

Images courtesy of the CDC and WHO

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017



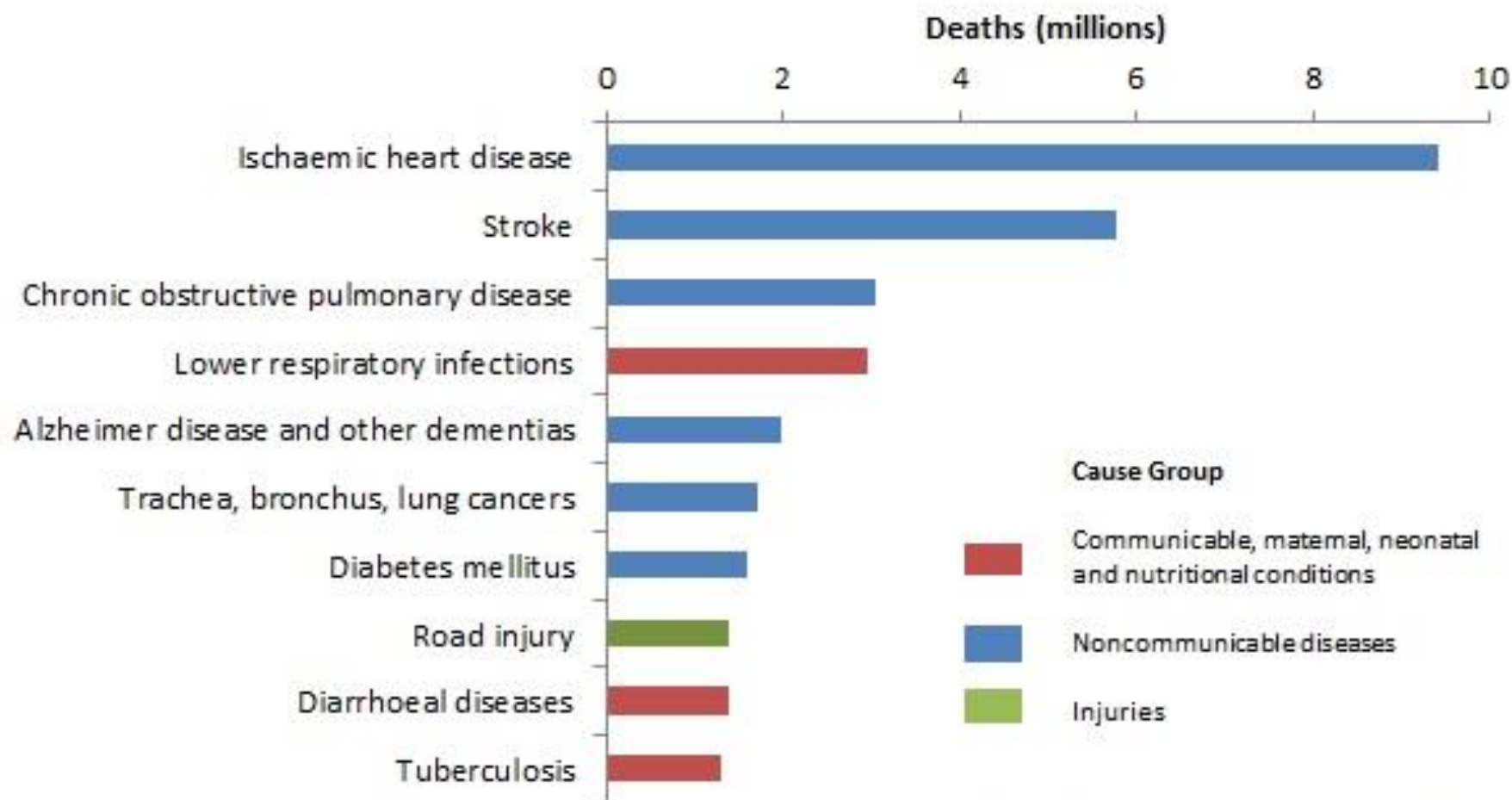
¹Statistically significant decrease in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).

²Statistically significant increase in age-adjusted death rate from 2016 to 2017 ($p < 0.05$).

NOTES: A total of 2,813,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. Rankings for 2016 data are not shown. Data table for Figure 4 includes the number of deaths for leading causes. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db328_tables-508.pdf#4.

SOURCE: NCHS, National Vital Statistics System, Mortality.

Top 10 global causes of deaths, 2016

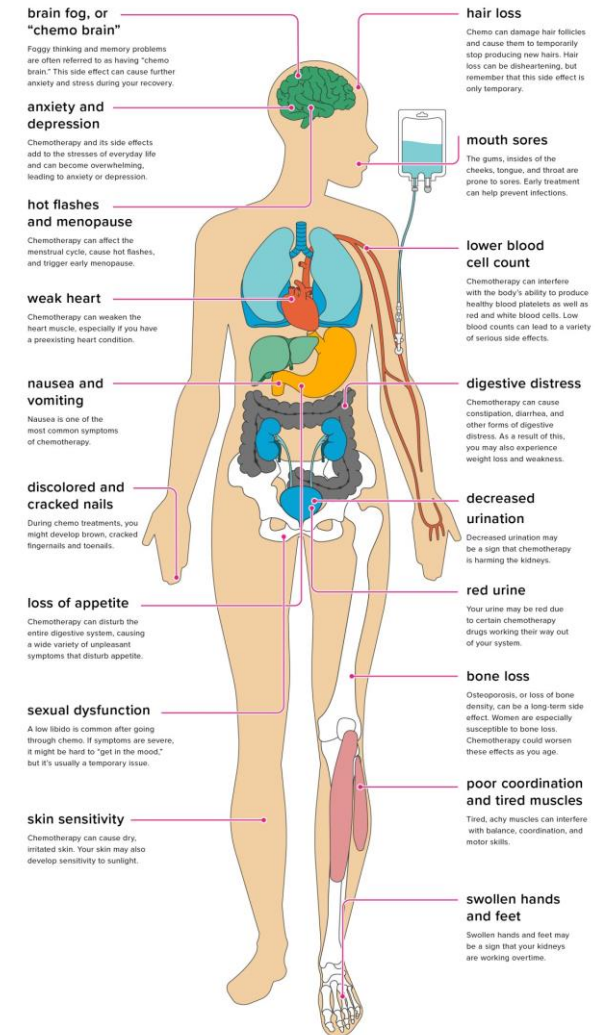


Source: Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.

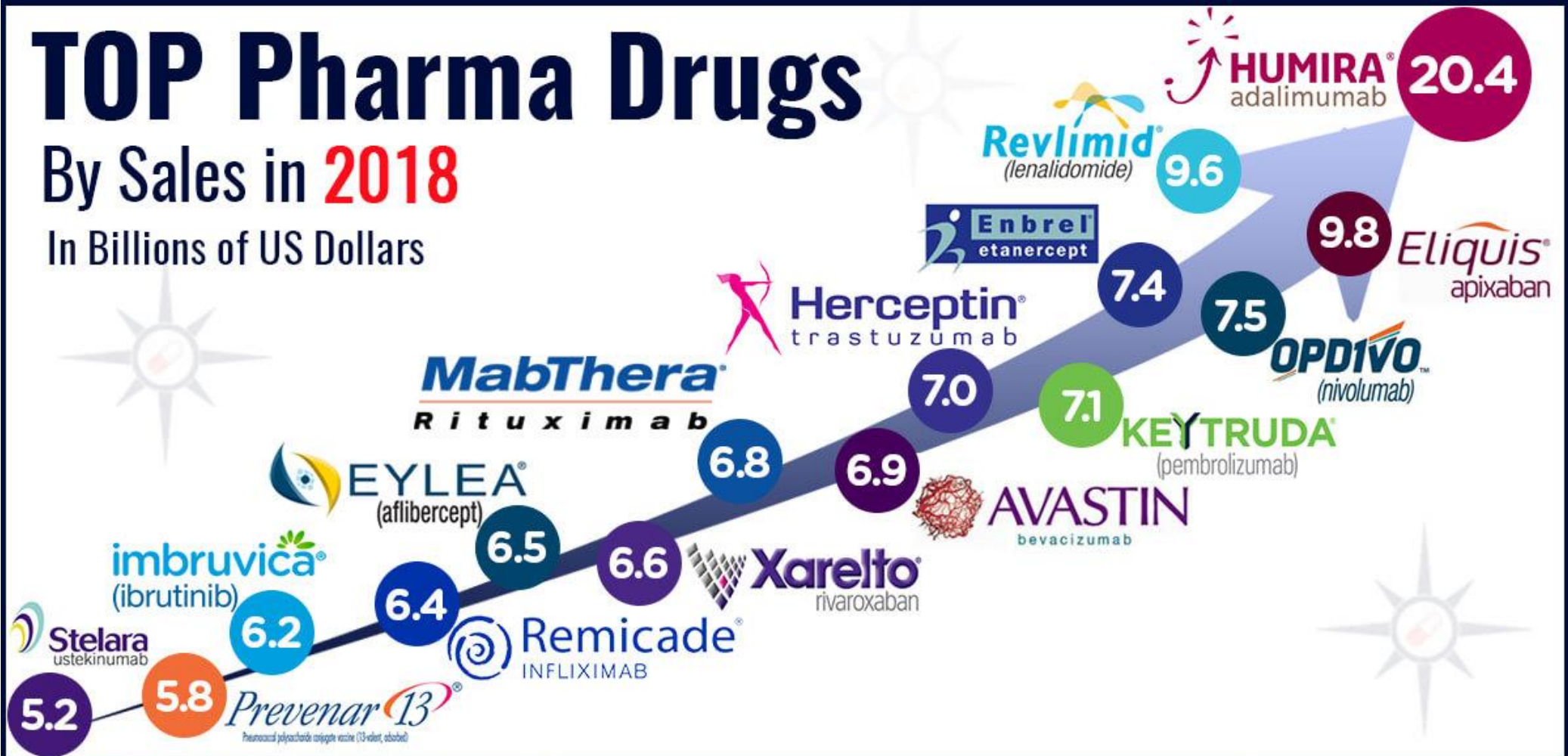
Why care about mechanisms?

Chemotherapy-Non targeted treatment

- Chemotherapy is basically poison
 - It kills rapidly dividing cells like Cancer
- Understanding the mechanism of a particular cancer can allow the use of more targeted and less toxic therapies.
- Without mechanisms we can only guess



Pharma cares about mechanisms



Review of Biology and Genetics

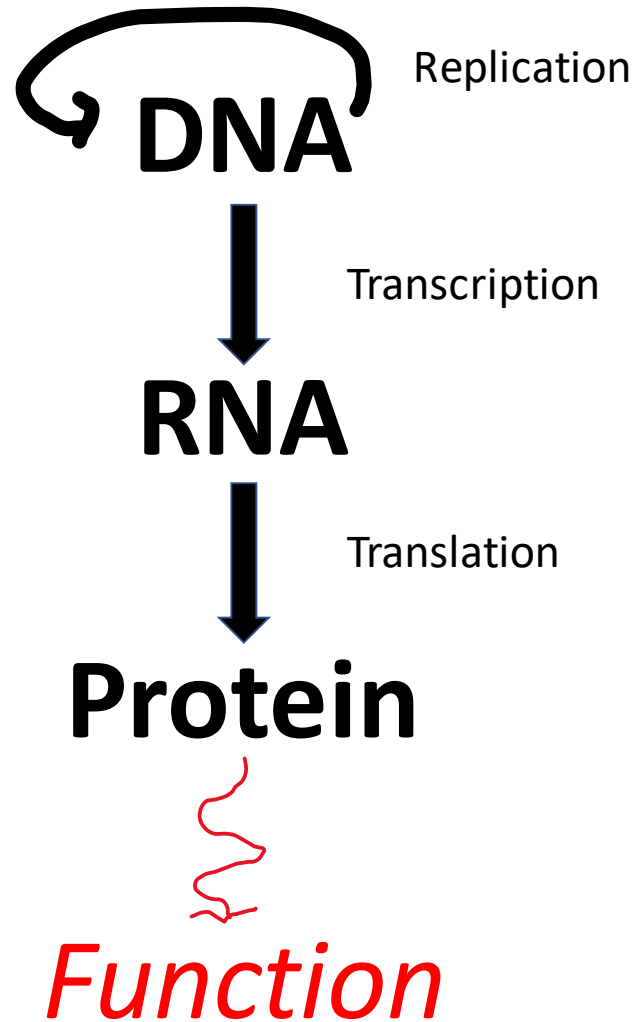
Pop Quiz

- What is the “Central Dogma” (ie core principle) of Biology?
 - A. All living things must maintain homeostasis
 - B. DNA->RNA->Protein
 - C. The transmission of genetic information via DNA
 - D. Natural Selection
- What macromolecule stores genetic information?
 - A. DNA
 - B. RNA
 - C. Proteins
 - D. Lipids

Pop Quiz: Part 2

- What macromolecule transfers genetic information?
 - A. DNA
 - B. RNA
 - C. Proteins
 - D. Carbohydrates
- What macromolecule carries out most cellular functions?
 - A. DNA
 - B. RNA
 - C. Proteins
 - D. Cofactors

Central Dogma of Biology (Review)

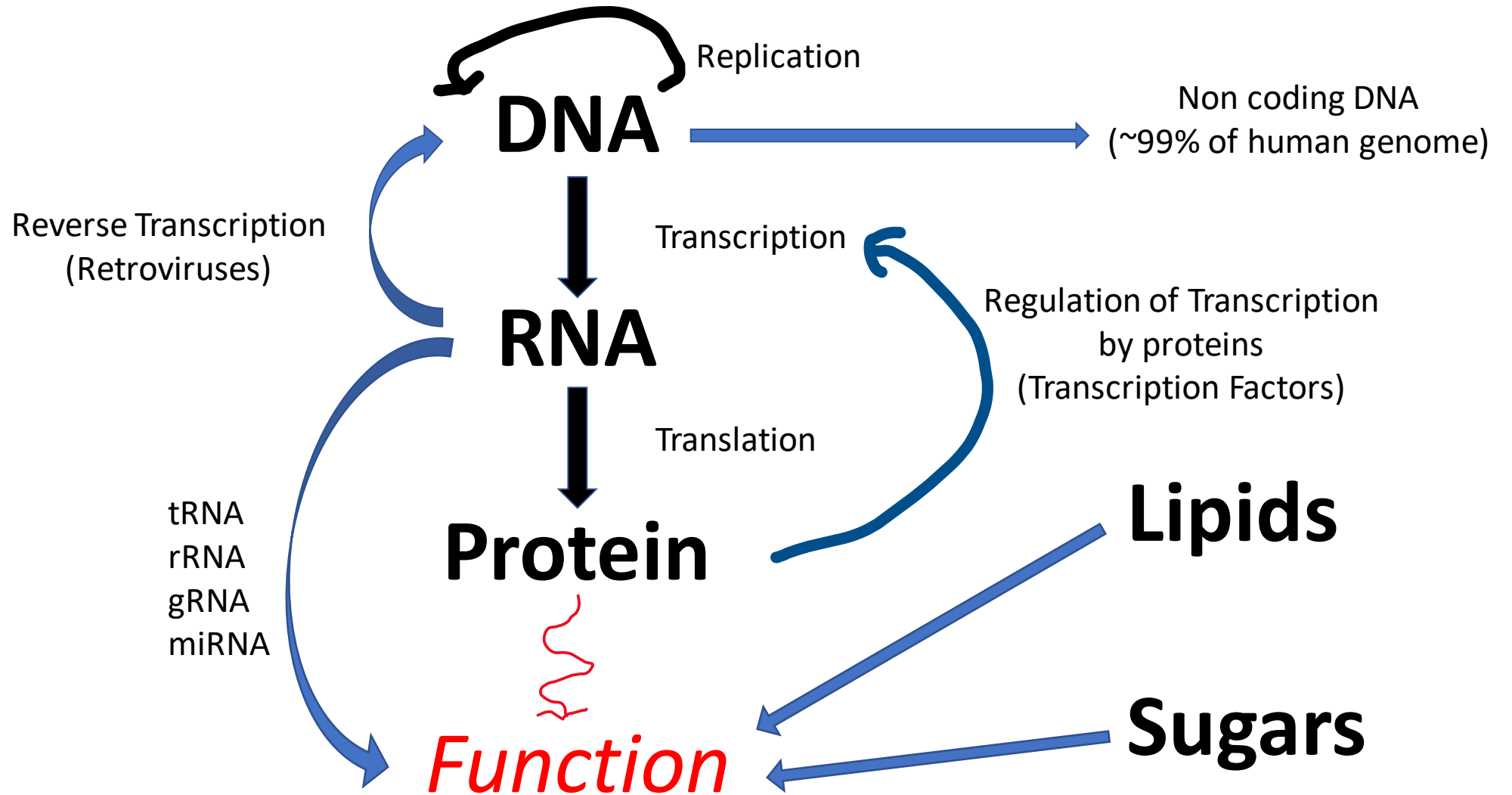


Interactive Questions

- What are some things that “break” the Central Dogma?

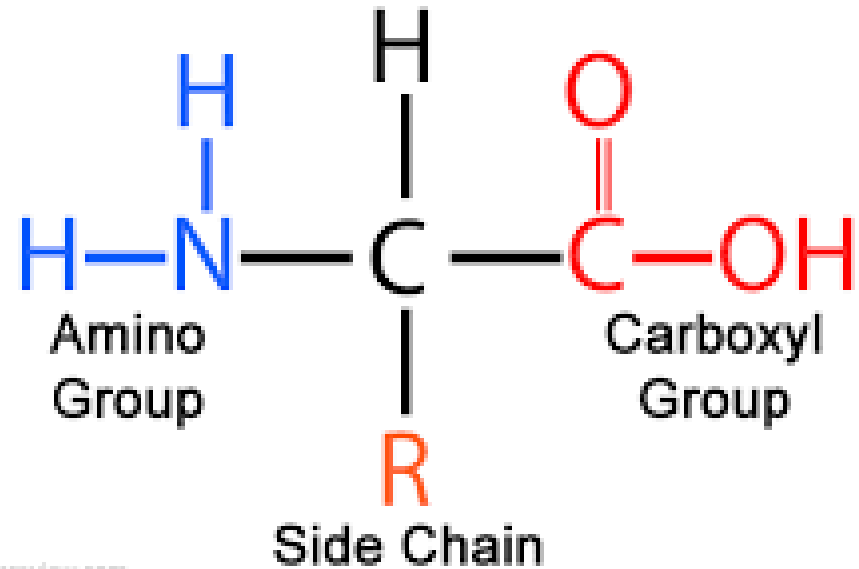
- What other molecules have chemical functionality in biology?

Central Dogma of Biology (Review)



Codons: Taking Nucleic Acids to Amino Acids

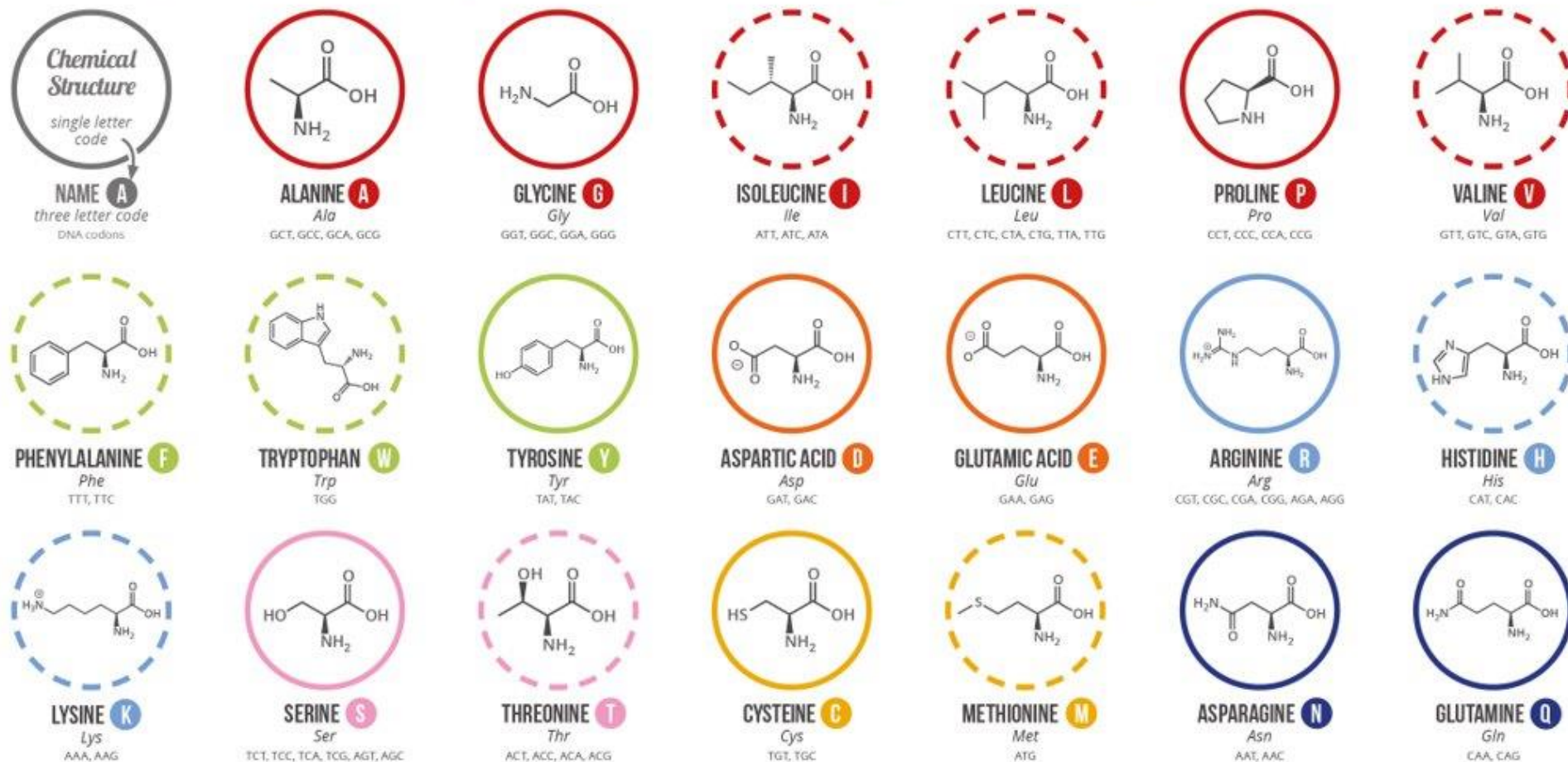
		Second letter				
		U	C	A	G	
First letter U	UUU } Phe	UCU } Ser	UAU } Tyr	UGU } Cys	U	
	UUC } Phe	UCC } Ser	UAC } Tyr	UGC } Cys	C	
	UUA } Leu	UCA } Ser	UAA Stop	UGA Stop	A	
	UUG } Leu	UCG } Ser	UAG Stop	UGG Trp	G	
First letter C	CUU } Leu	CCU } Pro	CAU } His	CGU } Arg	U	
	CUC } Leu	CCC } Pro	CAC } His	CGC } Arg	C	
	CUA } Leu	CCA } Pro	CAA } Gln	CGA } Arg	A	
	CUG } Leu	CCG } Pro	CAG } Gln	CGG } Arg	G	
First letter A	AUU } Ile	ACU } Thr	AAU } Asn	AGU } Ser	U	
	AUC } Ile	ACC } Thr	AAC } Asn	AGC } Ser	C	
	AUA } Ile	ACA } Thr	AAA } Lys	AGA } Arg	A	
	AUG Met	ACG } Thr	AAG } Lys	AGG } Arg	G	
First letter G	GUU } Val	GCU } Ala	GAU } Asp	GGU } Gly	U	
	GUC } Val	GCC } Ala	GAC } Asp	GGC } Gly	C	
	GUA } Val	GCA } Ala	GAA } Glu	GGA } Gly	A	
	GUG } Val	GCG } Ala	GAG } Glu	GGG } Gly	G	



A GUIDE TO THE TWENTY COMMON AMINO ACIDS

AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

Chart Key: ● ALIPHATIC ● AROMATIC ● ACIDIC ● BASIC ● HYDROXYLIC ● SULFUR-CONTAINING ● AMIDIC ○ NON-ESSENTIAL ○ ESSENTIAL



Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

Hydrophobic Effect

Types of Disease we'll cover

Physiological Diseases

Infectious Diseases

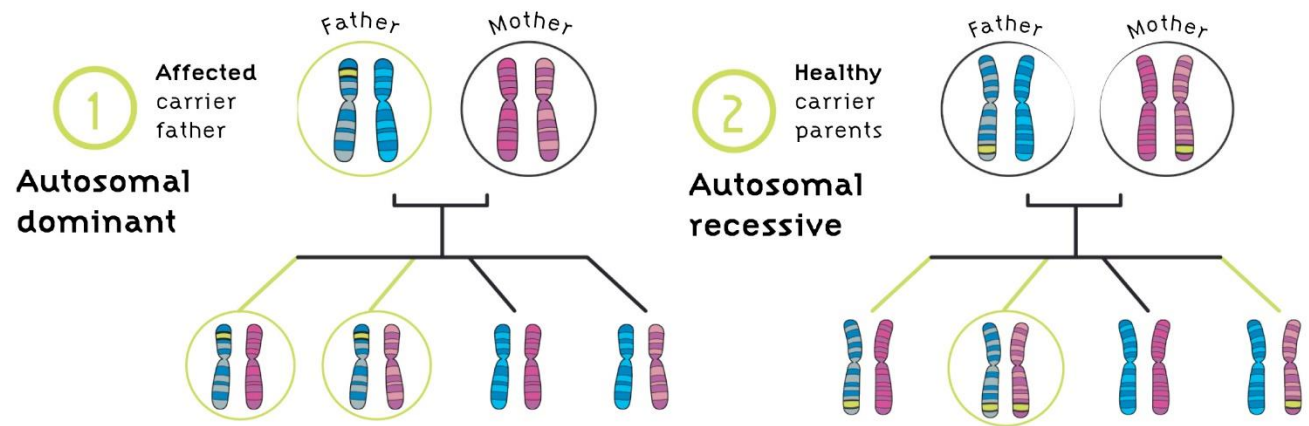
Genetic Diseases

Nutritional Diseases

Genetic Diseases

- Occur when one or both alleles of an essential gene(s) is/are mutated
- Types of mutations
 - Silent
 - Indels
 - Missense
 - Nonsense
- Germ line vs. Somatic mutations
- Heritable

GENETIC DISEASES Transmission of a genetic disease



Questions!

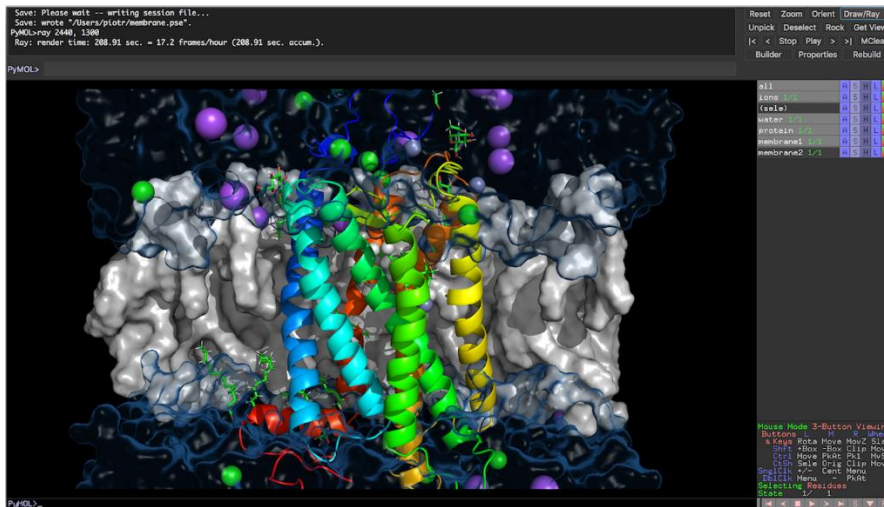
- What is generally worse a missense or a nonsense mutation?
 - Missense
 - Nonsense
 - It depends
- If I go out in the sun too long, there's a good chance the UV light may cause a mutation in my skin. Can I pass this on to my (hypothetical) kids?
 - Yes
 - No

Recessive/Dominant on a molecular Level

- “Loss of Function” mutations
 - Function of a protein is destroyed in 1 allele
 - If there is still a functional copy, the organism will appear normal
 - Often give rise to **recessive** phenotypes
- “Gain of Function” mutations
 - Function of a protein is changed in 1 allele (ie always on)
 - If there is a normal copy, the organism will still have that gained function
 - Often give rise to **dominant** phenotypes

Quick Side Note on Proteins

- Structure is important in determining function
- Protein databank
- PyMol
- Fold it



RCSB PDB 166301 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

Enter search term(s)

Advanced Search | Browse Annotations

PDB-101 PDB EMDataResource Worldwide Protein Data Bank Foundation

Welcome

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

COVID-19 CORONAVIRUS Resources

July Molecule of the Month

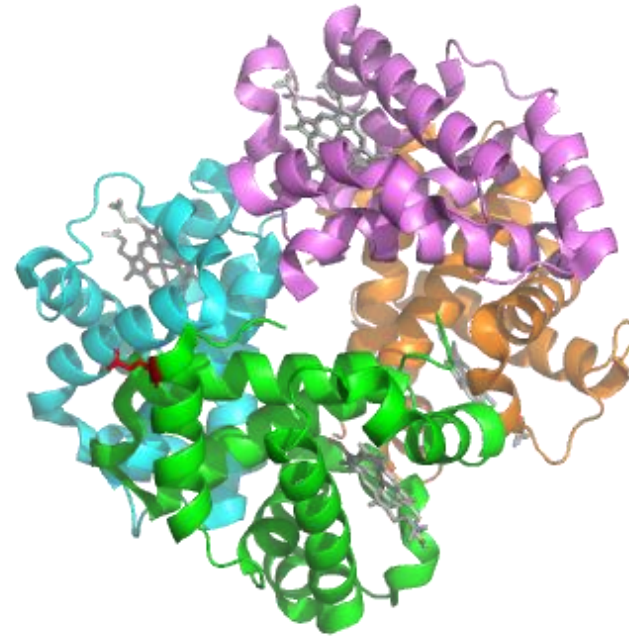
myelin

axon

Myelin-associated Glycoprotein

Sickle Cell Anemia

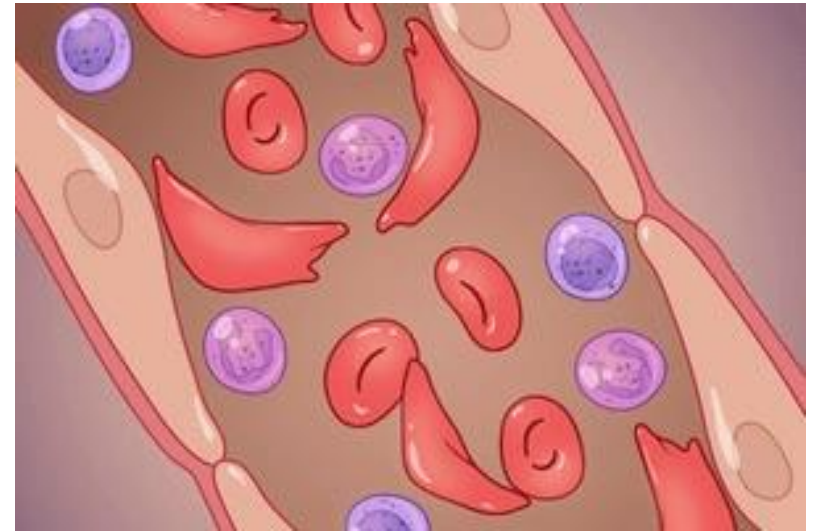
- Autosomal Recessive
- Caused by a single base pair missense mutation in beta globin subunit of hemoglobin
 - GAG -> GTG causes a glutamate to valine single amino acid change
- This mutation causes hemoglobin molecules to stick together and form rigid rods which deform red blood cells



Possible treatments?

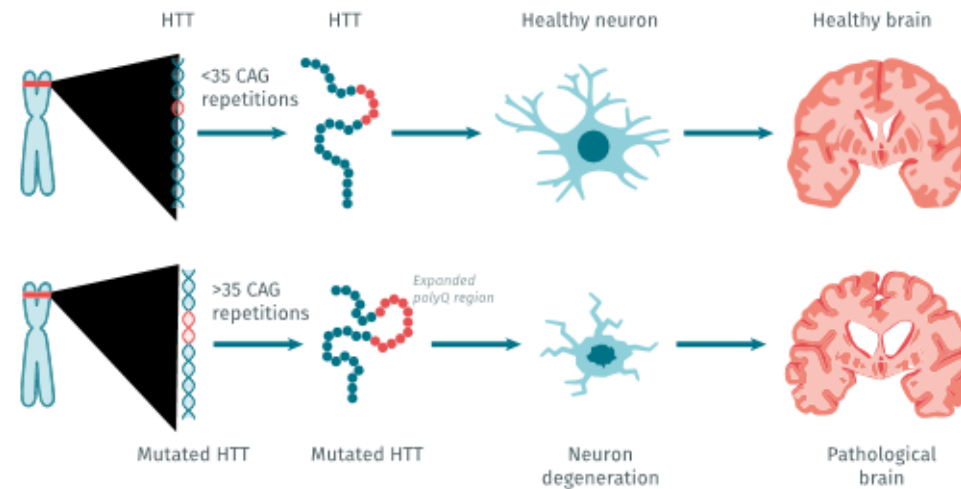
Treatments

- Blood Transfusions
 - Bone marrow transplant
- Medication
 - Hydroxyurea: Increases production of fetal hemoglobin
 - Pain relievers
 - L-glutamine: Modulates chemical redox balances, decreases sickle cells sticking to vessels
 - <https://www.youtube.com/watch?v=G1boPRrUu0I>
 - Voxelotor: Inhibits polymerization of sickle cell hemoglobin
 - <https://libproxy.mit.edu/login?url=https://www.nejm.org/doi/10.1056/NEJMdo005560/full/>
 - Crizanlizumab: Blocks P-selectin a protein expressed on the surface of the endothelium (blood vessel cells) which sickle cells adhere to.
 - <https://www.youtube.com/watch?v=CWTW5pDPPDQ>



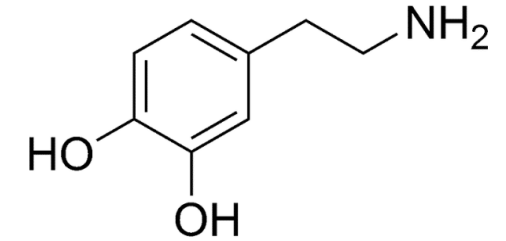
Huntington's Disease

- Autosomal Dominant
- Rare neurodegenerative disease
- Caused by mutations in the Huntingtin protein
 - Extra CAG repeats (encoding glutamine) at the end of the first exon
- Exact mechanism is unknown but
 - Healthy individuals have 10-35 CAG repeats and more CAG repeats cause earlier development of the disease
 - These repeats are cut by proteases and form toxic clumps that bind other proteins like CBP which affects gene regulation. Eventually cause neuronal cell death.



Possible Treatments?

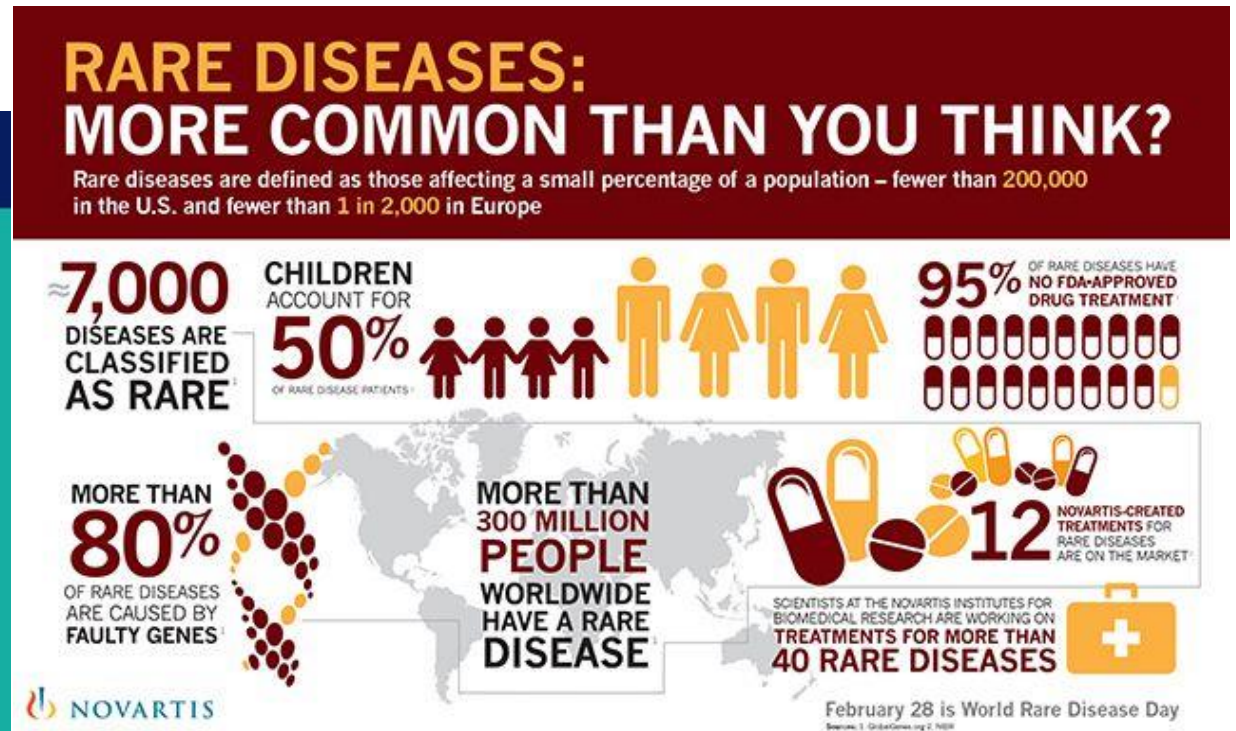
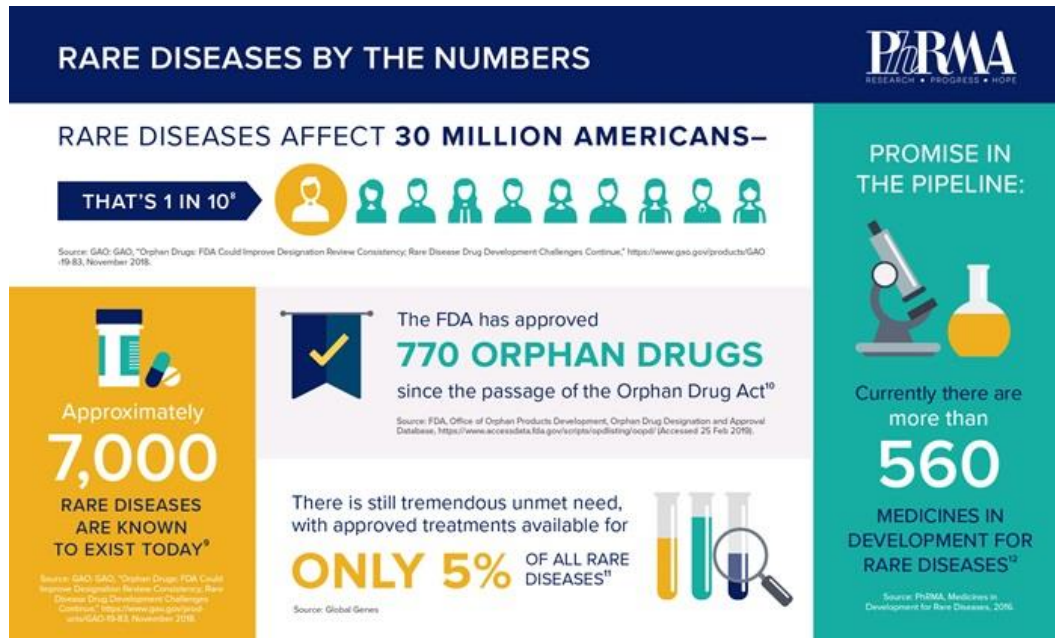
Treatments



- Treatment of symptoms (no cure)
 - This is the case for most neurodegenerative disorders
- Tetrabenazine (TBZ): Depletes dopamine to treat excessive movements
 - Dopamine signaling disrupted in Huntington's with possible loss of inhibitory neurons.
- Haloperidol: Blocks effects of dopamine (anti-psychotic)
- Anti-depressants
- Mood stabilizing agents

Other Genetic Disorders

- Several metabolic genetic disorders can be treated with “enzyme replacement therapy”
- Many have no treatment



Questions??

- Gene editing resources:

- CRISPR:

- <https://en.wikipedia.org/wiki/CRISPR>
 - <https://www.broadinstitute.org/research-highlights-crispr>
 - <https://www.sciencemag.org/news/2017/02/how-battle-lines-over-crispr-were-drawn>
 - https://en.wikipedia.org/wiki/He_Jiankui_affair

- CAR-T

- <https://www.cancer.gov/about-cancer/treatment/research/car-t-cells>

- Enzyme replacement therapy resources:

- <https://www.stanfordchildrens.org/en/topic/default?id=medical-genetics-treatment-with-gene-and-enzyme-replacement-therapy-90-P02162>
 - <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6128977/>