"Genetic Education for Native Americans" (GENA®) Objective 16: Pharmacogenetics

Objective 16: The participants will be able to describe selected physical and cultural benefits and drawbacks related to pharmacogenetics.

QUESTION 1: How many people die each year in the U.S. from medication side effects?

QUESTION 2: How many people suffer from serious side effects from medications in the U.S. each year?

QUESTION 3: How "close" is pharmacogenetics research to making personalized medicine for most of us?

ANSWERS ARE BOTTOM of inside cover

What is pharmacogenetics?

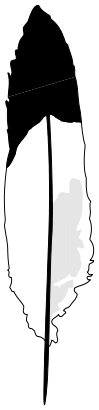
- The study of how an individual's genetic inheritance affects the body's response to drugs.
- ... decoding drug responsiveness
- ... the development of genetic tests that will tell doctors which people should get which drugs, to maximize drug effectiveness and minimize side effects.

The goal is to (eventually) result in:

- Safer drugs (reduction of side effects)
- Increased drug effectiveness
- Alternative drugs for "standard treatments"
- Dosages based on an individual's genetics
- More effective and safer vaccines

Factors that can influence how a person responds to medication

- Weight
- Diet
- Food in stomach
- Fatigue
- Age
- Sun exposure
- Physical condition / lack of exercise
- Drug interactions (i.e., Cross reactivity, synergism)
- Genetic make-up



Human Beings are 99.9% Similar to One Another

- 3 billion base pairs of DNA in our genome
- 3 million base pairs differ throughout the genome (3,000,000,000 X 0.001 = 3,000,000 base pairs / or 3 million)
- 2% of that or 60 thousand base pairs would be found in the coding regions.
- Differences in noncoding RNAs could be as much as 2.94 million.
- There is a possibility for new therapeutics because scientists have focused on the 2% rather than the 2.94 million base pairs.

Why is this important?

- Getting away from "one size fits all" drugs.
- We all have different polymorphisms.

What does "polymorphism" mean?

- Naturally occurring variations in (base pairs) DNA sequence.
- The encoded protein's function may or may not be altered

Possible Benefits to Native People from Pharmacogenetics?

- Reduce or eliminate side effects from medications
- Access “designer” drugs
- Increase effectiveness of treatments
- More effective and efficient treatments tailored to the individual
- Of those individuals who metabolize a drug too quickly to benefit from any effect
  - Like codeine
  - Some people currently are erroneously labeled “drug addicts” because they request additional pain killers
  - Medical staff erroneously thinks the patient has high tolerance
  - With pharmacogenetics, such mislabeling is less common

What are examples of Native American concerns related to participating in pharmacogenetics research?

- Genetic information may be used to create “designer drugs” that can annihilate the community.
- Specimens may be stored or used for uses other than testing for medication effectiveness
- Researchers may discover something that could benefit the tribe but the information is withheld due to personal greed / patenting desires, etc.
- Disbelief that they personally or their community will be able to benefit from such research currently can’t obtain “quality” medications

Possible Drawbacks to Native People from Pharmacogenetics?

- Labeling or stereotyping (increased risk for anomaly).
- Finding a mutation other than the one anticipated.
- Patient needs “designer drug” that is inaccessible through IHS or Tribal Formulary.
- Drug companies may limit their testing to specific groups excluding poorer populations.
- People are worried that their genetic profiles will fall into the wrong hands.
- Doctors may not want to give out the new drugs because they don’t want to be liable for lawsuits
  - Because they didn’t “do enough tests” prior to prescribing a medication.
  - Rx “summary cards” misinterpreted for Natives

How can Native concerns ethically be addressed?

- More understandable informed consent protocols.
- More time spent with the patient explaining pharmacogenetics.
- Better protections included within research protocols (e.g., allow specimens to be disposed of in culturally acceptable manner and verify excess specimen will not be stored).
- Strong “participatory / partnership” agreements that all the community is to benefit from discoveries.
- Pharmaceutical “guarantees” that poor communities have ways to obtain quality medications.

ANSWERS To Questions

Question 1: 100,000

Question 2: 2 million

Question 3: Only a few medications will impact the public before 2020

Question 4: No. the drug doesn't work on people with this KRAS mutation in their tumor

Cytochrome p-450 enzymes

What are cytochrome p-450 enzymes?

- Located 7q22
- Super-family of cytochrome p-450 enzymes
- Enzyme = Cytochrome P-450 3A4
- Gene = CYP3A4 (an ***essential*** enzyme)
- Expressed in the liver and intestines (i.e., involved in detoxification)
- Contribute to the metabolism of ~ half of all medications
- Examples of medicines ...
  - Codeine (opiate to treat pain or relieve cough)
  - Acetaminophen
  - Diazepam (dye az' e pam)
  - Cyclosporin A
  - Erythromycin
- Located on chromosome 22q13
- 2D6 is one enzyme that is required for the metabolism of codeine to morphine
- Most people are “extensive metabolizers” that allows them to effectively metabolism codeine to morphine

What are factors that affect the metabolism or the balance of 2D6 and 3A4?

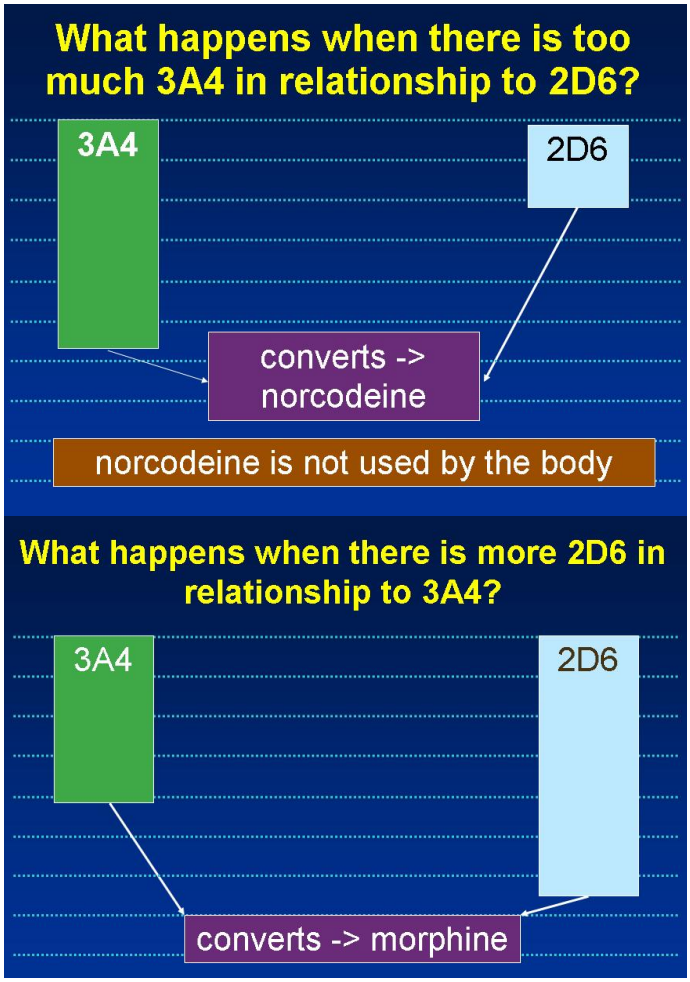
- Some medications inhibit codeine metabolism
- Examples: Quinidine (Quinidine Gluconate, Quinidine Sulfate
  - Medication that is used to correct disturbances in the rhythm of the heart (antiarrhythmic).
  - Also used to treat malaria
  - Quinidine inhibits 2D6

What are other things that can affect the balance of CYP3A4 and 2D6?

- Grapefruit juice before you take some drugs can reduce your 3A4.

How does the balance of 3A4 and 2D6 affect Codeine metabolism?

- You always have 3A4 (essential enzyme) .... but if the balance of 3A4 is too high compared to 2D6, then the bioavailability of codeine is reduced
  - If too much 3A4, codeine doesn’t metabolize to morphine
  - 3A4 converts “codeine” to “norcodeine” which cannot be used by the body



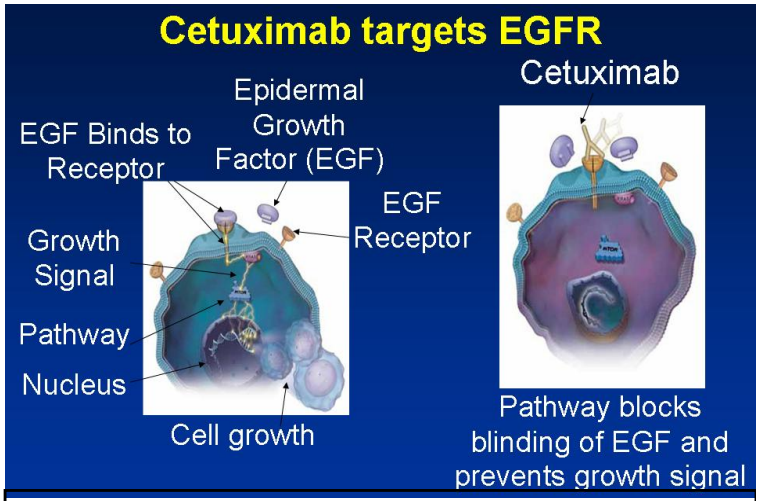
What are the “different” types of metabolizers?

- A “Poor Metabolizer” (PM) cannot metabolize codeine (not enough 2D6)
- “Extensive Metabolizers” (EM) metabolize codeine (“most people” / “normal”)
- “Ultrarapid Metabolizer” metabolizes too quickly to be able to effectively benefit from the codeine (too much 2D6)

What is an example of a drug that is showing progress?

Cetuximab Is an antibody (protein acceptable to human body) that attacks the receptors on cancer cells so that the cancer cell cannot multiply

- Attacks oncoproteins such as EGFR
  - EGFR is a receptor on the cell's surface
  - Found on many cancer cells (lung, CRC)
- The EGFR protein gives improper signals to the cell to grow grow grow grow grow
- If you give the patient cetuximab, the cetuximab goes to the EGFR protein and blocks its ability to send "grow grow grow" signals

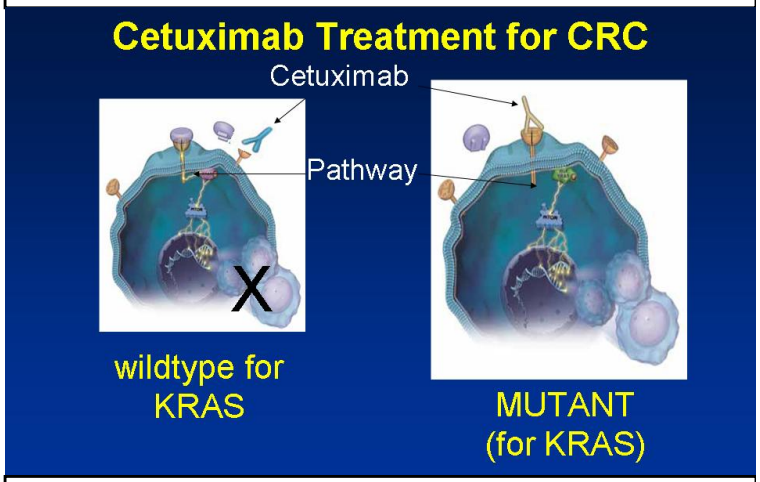


Graphics modified from Cure.com

What is the impact of this type of research?

- Patient is tested for KRAS mutation prior to CRC treatment
  - Currently the clinical lab needs a biopsy of the tumor
  - The NEW test for KRAS is a blood test

QUESTION 4: If the patient has the KRAS mutation, should the patient receive cetuximab?



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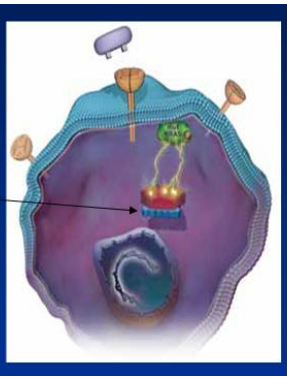
95% of pancreas cancers have KRAS Mutation

This is why cetuximab cannot be used to treat pancreas cancer

Likely to need a different drug (e.g., mTOR inhibitors) to target this signal



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