Pharmacogenomics

Genetics in Medicine - 0504321

2022-2023 Second Semester

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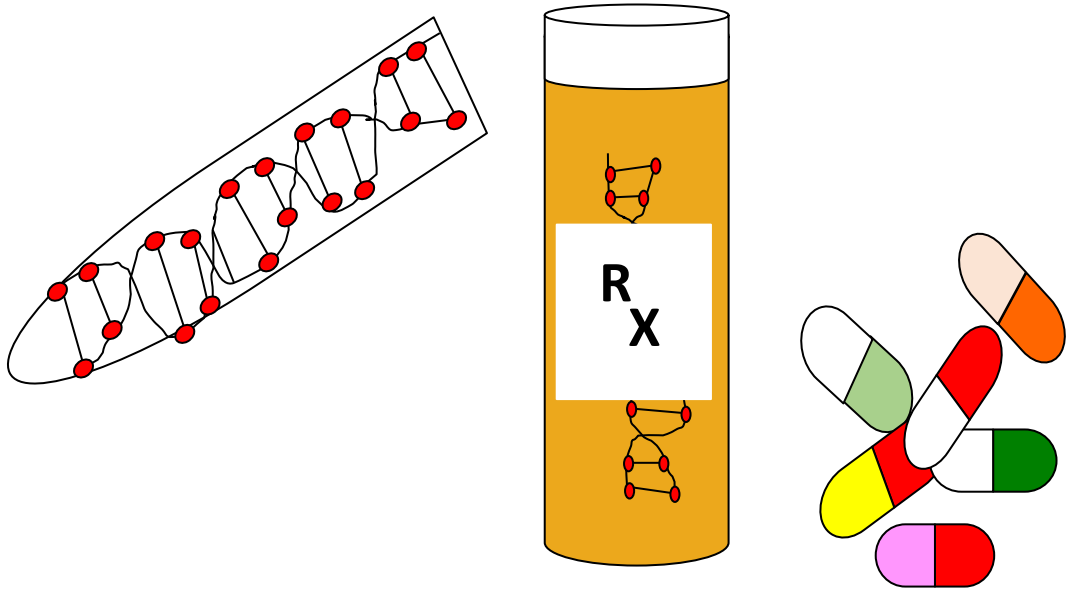
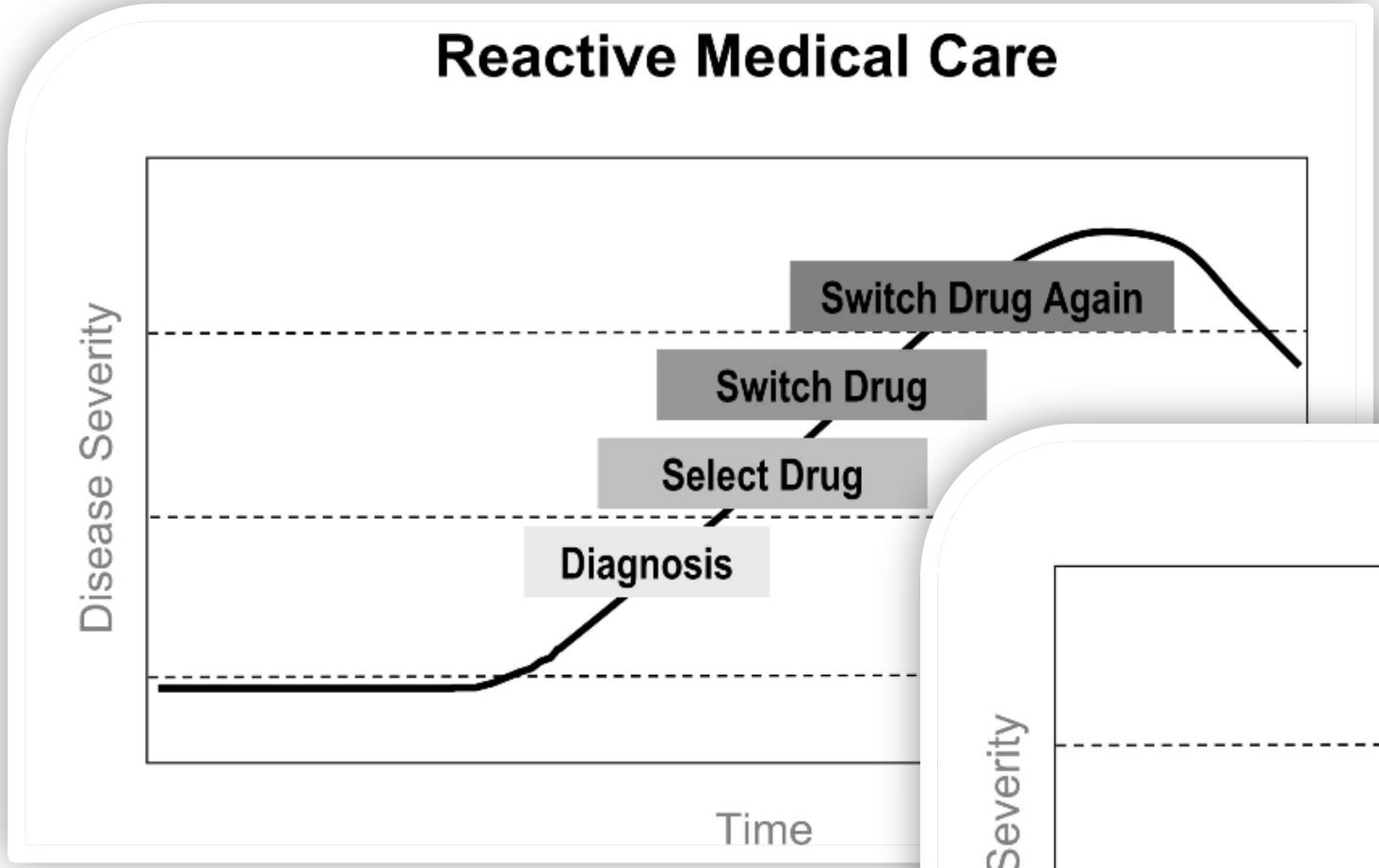
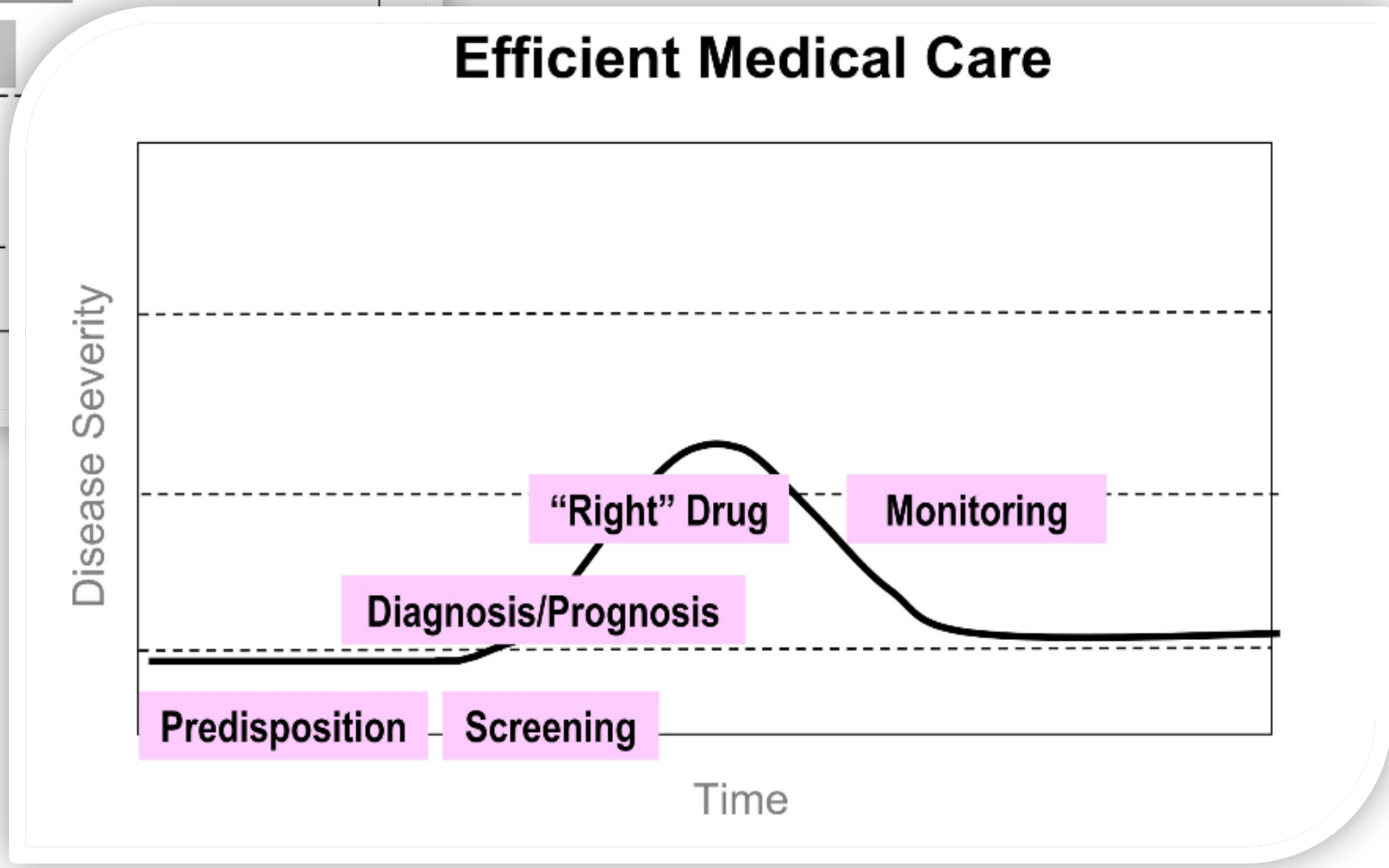
What is Pharmacogenomics?

Pharma = drug or medicine
Genomics = the study of genes

Personalized medicine tailored to <u>your</u> genes




Reactive Medical Care
Disease Severity
Switch Drug Again
Switch Drug
Select Drug
Diagnosis
Time


Efficient Medical Care
Disease Severity
"Right" Drug
Monitoring
Diagnosis/Prognosis
Predisposition
Screening
Time

Emergence of Personalized Medicine

- Right Dose of
- Right Drug for
- Right Indication for
- Right Patient at
- Right Time

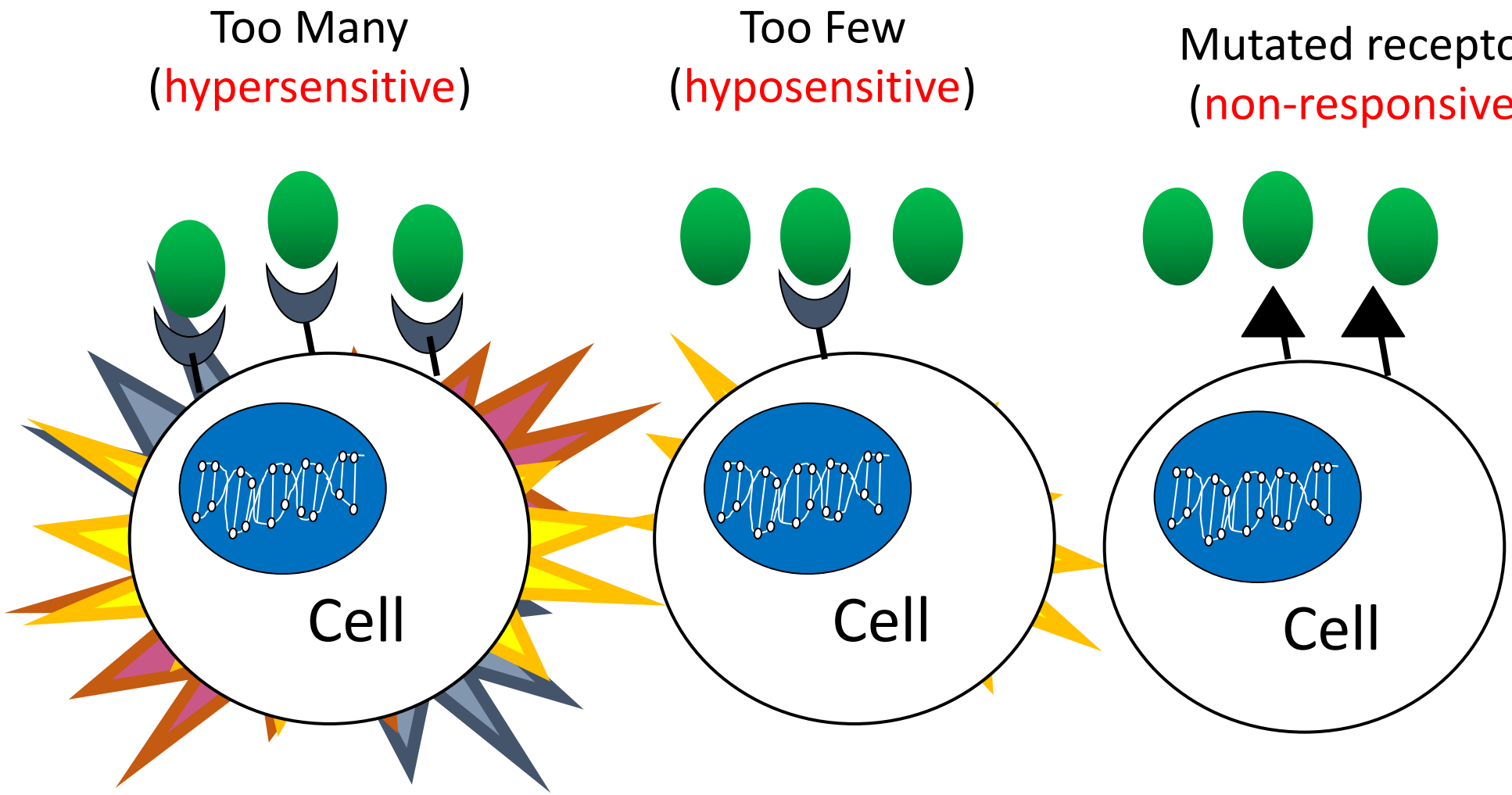
"Here's my sequence..."

The New Yorker

- Unrelated people share 99.9% identity, the less than 0.1% translates into difference in 3 million nucleotides.
- The completion of the Human Genome and SNPs haplotyping, enabled pharmacogenomics across individuals and populations
- In 2014, **eight of 41** of the new drugs approved were genetic biomarkers relative to efficacy, safety, or pharmacokinetics & pharmacodynamics

DNA and Drugs

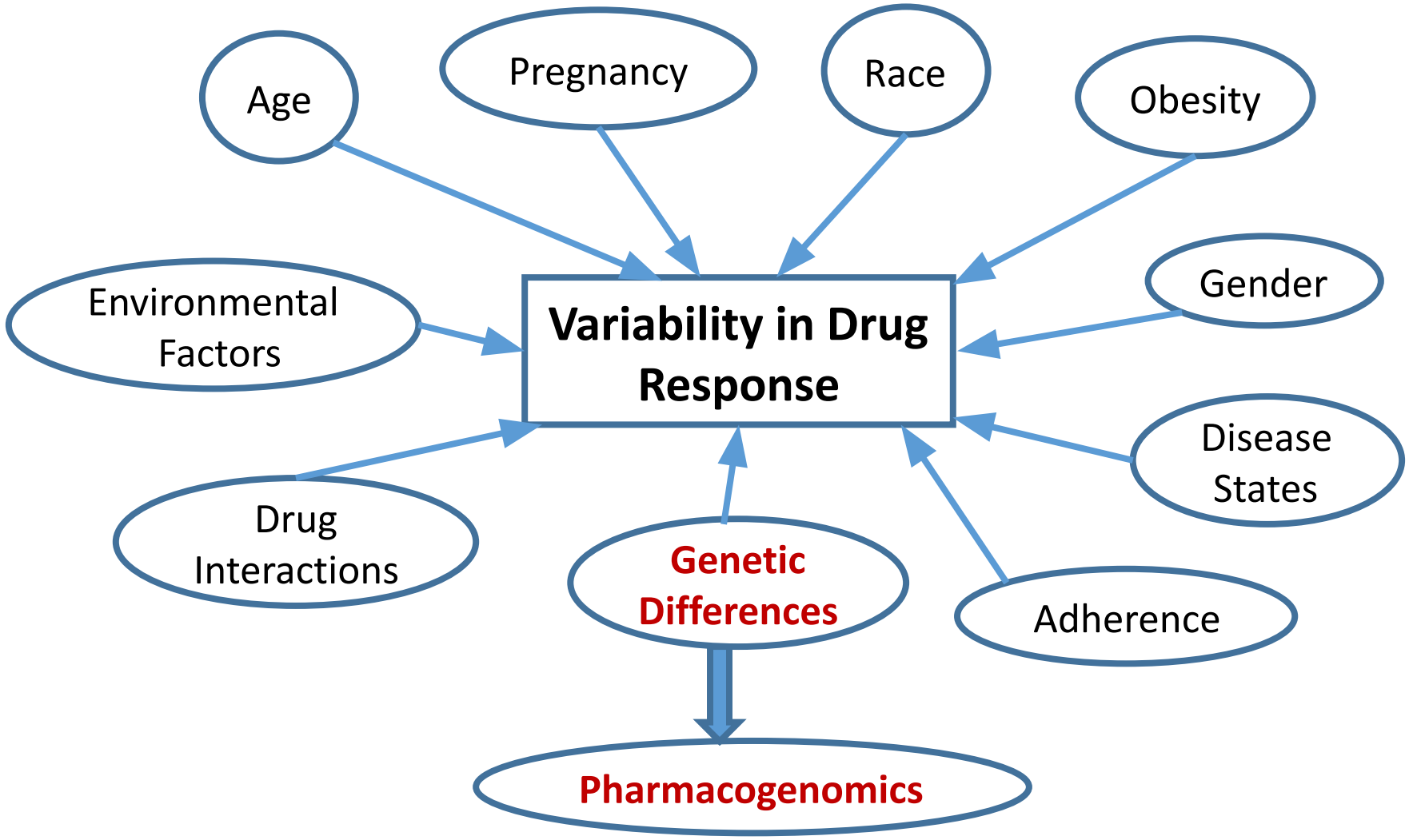
Variation in genes can cause variation in receptors



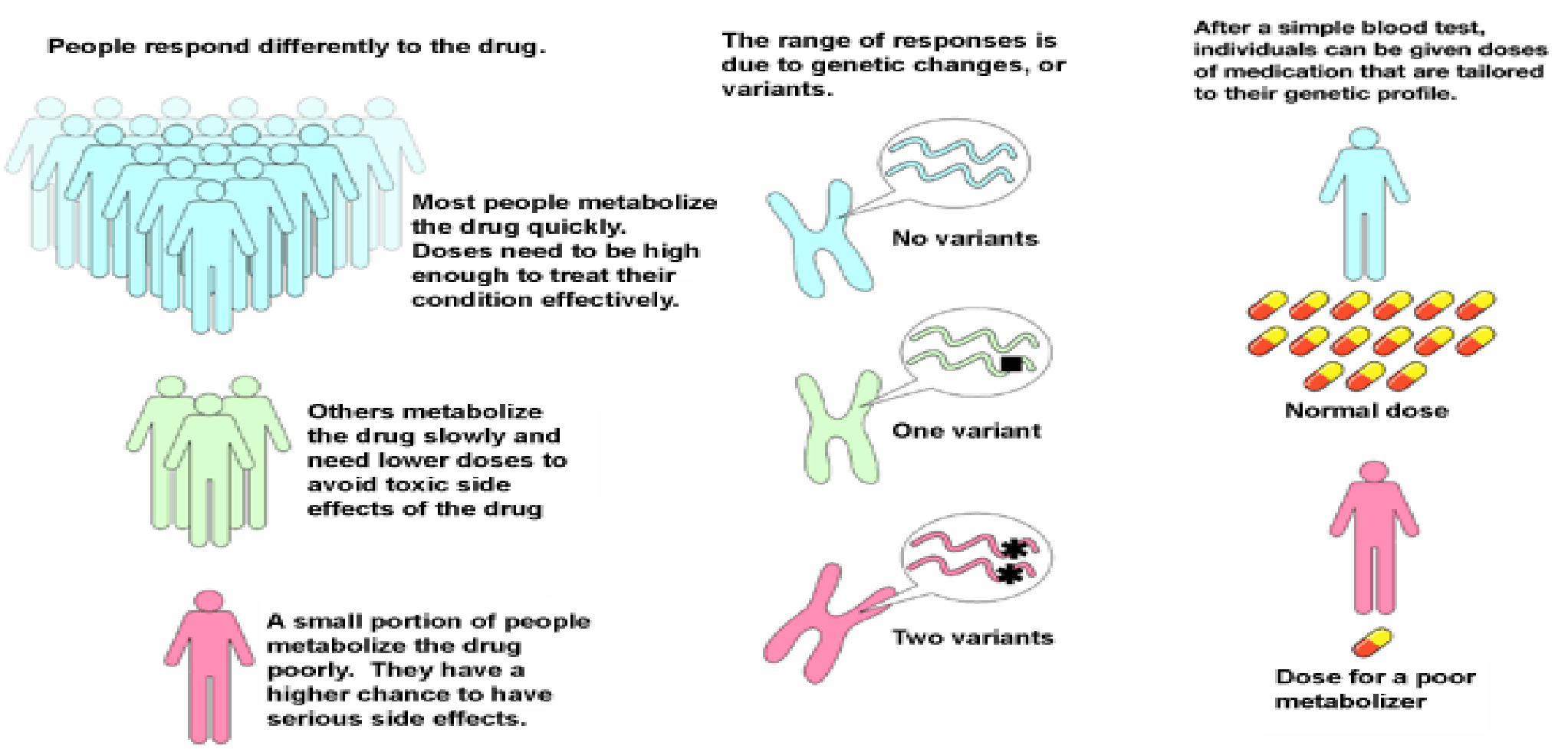
Peripheral neuropathy in some TB patients treated with **isoniazid** in some patients due to genetic diversity in the enzyme ***N*acetyltransferase**

The rate of acetylation of a drugs determines the rate of elimination of the drug from the body and affects toxicity

Sources of Variation in Response to Drugs



Using Genetics to Tailor Drug Therapy



https://atlantichealth.dnadirect.com/grc/patient-site/warfarin-response/what-affects-warfarin-response.html

Associated Definitions

- Genomics – The study of the entire set of genes, their interactions and functions

- Pharmacogenetics (PGt) –denotes the science about how heritability differences affect the response to drugs, mainly metabolizing enzymes

- Pharmacogenomics (PGx) – is a branch of pharmacology concerned with how DNA is used to understand respond to drugs and guide drug development and testing

Courtesy National Human Genome Research Institute http://www.genome.gov/Glossary/index.cfm?textonly=&search. Accessed January 24, 2014.

DRUG METABOLISM PATHWAYS

- **Phase I Pathway:** the most common is **CYP450** superfamily that chemically modify drugs into their water-soluble products to facilitate the excretion by kidney and/or liver
- **Phase II pathway:** drugs or metabolites from phase I pathways are enzymatically conjugated with a hydrophilic endogenous compounds with the help of **transferase enzymes**.
- **Phase III pathway:** transmembrane proteins that facilitate the transport of large and/or ionized molecules in and out of the cells. Classified into 2 main superfamilies: **ATP-binding cassette (ABC) % solute carrier (SLC)** transporters

About CYPs

- Membrane bound enzymatic proteins
  - Involved in oxidation/reduction and peroxidation metabolism
  - Responsible for >90% of drug transformation
- 57 different *CYP* genes/17 families encoding 50 different proteins
- CYP1, CYP2 and CYP3 are primarily involved in drug metabolism.
- CYP2D6 present mainly in liver and a major player in drug metabolism including antidepressants, antihypertensive drugs

Enzyme	Allele	Mutation	Effect	
CYP2C9	CYP2C9*2	430 C>T	Decreased	8-13% Caucasians PMs
	CYP2C9*3	1075 A>C	Decreased	1-3% Caucasians PMs
	CYP2C9*5	1080 C>G	Decreased	
CYP2C19	CYP2C19*2	Splicing defect	inactive	15-20% Asians PMs
	CYP2C19*3	636 G>A	Inactive	3-5% Caucasians PMs
	CYP2C19*4	1 A>G	inactive	
	CYP2C19*5	1297C>T	inactive	
	CYP2C19*6	395 G>A	inactive	
	CYP2C19*7	Splicing defect	inactive	
	CYP2C19*8	358 T>C	inactive	
CYP2D6	CYP2D6*3A	2549 A>deletion	inactive	5-10% Caucasians PMs
	CYP2D6*4A	1846G>A	inactive	
	CYP2D6*4B	Splicing defect	inactive	
	CYP2D6*5	CYP2D6 deletion	inactive	

PM
Poor
Metabolism

*CYP2D6*1 : wild type allele*

family, *subfamily*, *individual gene*

http://www.cypalleles.ki.se/

Successful Examples of Applying Pharmacogenomics into Personalized Medicine

Abacavir (Ziagen)

- Nucleoside analog **reverse transcriptase inhibitor** used to treat AIDS patients, approved in 1998

- Subsequent studies showed patients who carry the HLA-B*5701 allele were at high risk for hypersensitivity to this drug

- **The label was changed to recommended pre-therapy screening for the HLA-B*5701 allele**

- Incidence of hypersensitivity has diminished worldwide.

Human Epidermal Growth Factor 2 positive (HER2+) Breast Cancer: Targeted Therapies Affecting Tumor Growth

- Aggressive form of breast cancer associated with genetic variation leading to overproduction of protein called HER2

- If tumor tested for high levels of HER2, then Herceptin (Trastuzumab) is indicated

Trastuzumab (Herceptin)

- HER2 positive tumors comprise 20-25% of all breast cancers are associated with worse clinical outcomes

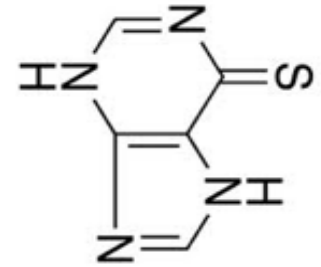
- Trastuzumab is a humanized monoclonal antibody designed to target the HER2 receptor, and utilized today as the foundation therapy for many HER2 positive breast cancers patients

1. Slamon et al., Science 1987;235:177-82; 2. Saini KS et al., Breast. 2011 Oct;20 Suppl

Thiopurine methyltransferase (TPMT)

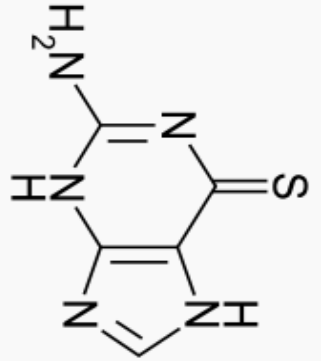
- Main metabolizer of **Purine Analog** chemotherapeutic agents

6-mercaptopurine



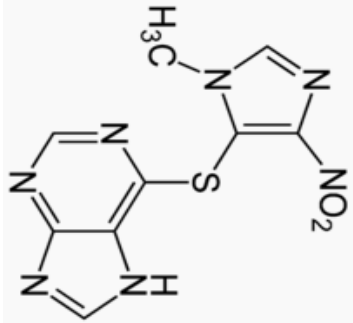
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, and after organ transplantation

6-thioguanine



- TPMT deficiency leads to severe treatment toxicity with potential mortality

azathioprine



Anticoagulant Drug (Warfarin):

- Ranks #1 in total deaths caused by drug adverse events
- Ranks among top drugs associated hospital **ER** visits for **bleeding**
- In 2007, FDA approved label changes to Warfarin with precautions for patients with genetic variations in two genes, **CYP2C9** and **Vitamin K Epoxide Reductase Complex-1** (**VKORC1**).
- Persons with at least one copy of either CYP2C9*2 or CYP2C9*3 influence warfarin metabolism, and require less warfarin dosage for an effective anticoagulation than the general population.
- Hemorrhagic complications are more common in persons who carry these alleles.

Warfarin: Factors Affecting Dose/Response

- **Age; Increased age = decreased dose**
- **Height and Weight**
  - **taller and/or weight more = higher warfarin dose**
- **Ethnicity**
  - **Ancestry plays an important role**
    - **Asians: may need lower doses than Caucasians**
    - **African Americans: may need higher doses.**
- **Diet**
  - **Warfarin works by inhibiting vitamin K.**
    - **Consuming large amounts of vitamin K (through foods or supplements) = higher warfarin doses.**

Codeine and Cytochrome P450 CYP2D6

- Codeine is a commonly used opioid
  - Codeine is a prodrug
  - It must be metabolized into morphine for activity

- Cytochrome P450 allele CYP2D6 is the metabolizing enzyme of codeine in the liver

- 7% of Caucasians are missing one copy of the Cytochrome P450 CYP2D6 gene
  - codeine does not work effectively in these individuals

FDA Approvals with Companion Diagnostics

Vemurafenib/BRAF V600E:

In 2011, FDA simultaneously approved the drug vemurafenib (Zelboraf) along with its companion diagnostic, the Cobas 4800 BRAF V600E mutation test, for use in treating metastatic or **unresectable melanoma**. Vemurafenib inhibits BRAF V600E mutation that is found in approximately 50% of melanoma patients.

FDA Requires Genetic Tests for Certain Therapies

List of FDA Required or Recommended Biomarker Tests in Drug Labels

Biomarker	Test[13]	Drug Example	User Prevalence (%) (n=36.1 million)
CYP2C9	Recommended	Warfarin	2.0896
EGFR	Required	Cetuximab	0.0001
G6PD deficiency	Recommended	Dapsone	0.0257
G6PD deficiency	Recommended	Rasburicase	0.0000
HER2/neu overexpression	Required	Trastuzumab	0.0003
TPMT variants	Recommended	Azathioprine	0.1168
TPMT variants	Recommended	Mercaptopurine	0.0541
TPMT variants	Recommended	Thioguanine	0.0012
UGT1A1 variants	Recommended	Irinotecan	0.0002
Urea cycle enzyme deficiency	Recommended	Valproic acid	0.48
Total			2.768

CYP = cytochrome P450; EGFR = human epidermal growth factor receptor; G6PD = glucose-6-phosphate dehydrogenase; HER2/neu = human epidermal growth factor receptor 2; TPMT = thiopurine S-methyltransferase.

- **2011**
  - *TPMT* – thiopurines
  - *CYP2C19*– clopidogrel
  - *CYP2C9, VKORC*1 – warfarin
- **2012**
  - *CYP2D6* – codeine
  - *HLA-B* – abacavir
  - *SLCO1B1* – simvastatin
- **2013**
  - *HLA-B* – allopurinol
  - *CYP2D6, CYP2C19* – TCAs
  - *HLA-B* – carbamazepine
  - *DPYD* -- 5FU / capecitabine
  - *TPMT* – thiopurines—UPDATE
  - *CYP2C19* – clopidogrel--UPDATE
    - https://cpicpgx.org/guidelines/
- **2014**
  - *IL28B* -- PEG interferon α
  - *CFTR* -- Ivacaftor
  - *G6PD* -- Rasburicase
  - *CYP2C9, HLA-B* -- Phenytoin
  - *CYP2D6* – codeine--UPDATE
  - *HLA-B* – abacavir--UPDATE
  - *SLCO1B1* – simvastatin—UPDATE
- **2015**
  - *CYP3A5* – tacrolimus
  - *CYP2D6*, *CYP2C19*– SSRIs
  - *UGT1A1* – atazanavir
  - *HLA-B* – allopurinol—UPDATE
- **2016**
  - *CYP2C19* – voriconazole
  - *CYP2D6* – ondansetron
  - *CYP2C9, VKORC*1 – warfarin--UPDATE
  - *CYP2D6, CYP2C19* – TCAs--UPDATE
- **2017**
  - *CYP2D6* – tamoxifen
  - *HLA-B* – carbamazepine—UPDATE
  - *DPYD* -- 5FU / capecitabine—UPDATE-in review
- **2018 (in progress)**
  - *RYR1*– inhaled anesthetics
  - *CYP2B6*—efavirenz
  - *TPMT/NUDT15* – thiopurines--UPDATE
  - *CYP2D6*—atomoxetine
  - *CYP2C19*/PPI
  - *CYP2C9*/HLA-phenytoin—UPDATE
  - *CYP2C9*/celecoxib