UNC
CENTER FOR
PHARMACOGENOMICS AND
INDIVIDUALIZED THERAPY

Precision Medicine Call to Action: Deciphering the Genetic Code in Clinical Practice

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Disclosure

- No conflicts of interest to report

Objectives

- Describe precision medicine and pharmacogenomics
- Evaluate the significance of pharmacogenomics on current and future clinical practice
- Apply pharmacogenomics guidelines and additional resources to clinical scenarios
- Describe how personal pharmacogenomics testing will likely affect the future of clinician education
- Discuss the need for patient advocacy in regards to precision medicine

What is Precision Medicine?

- Approach for disease treatment and prevention
- Individual variability in genes, environment, and lifestyle
- Significant advances in cancer
- Minor progress in other disease states

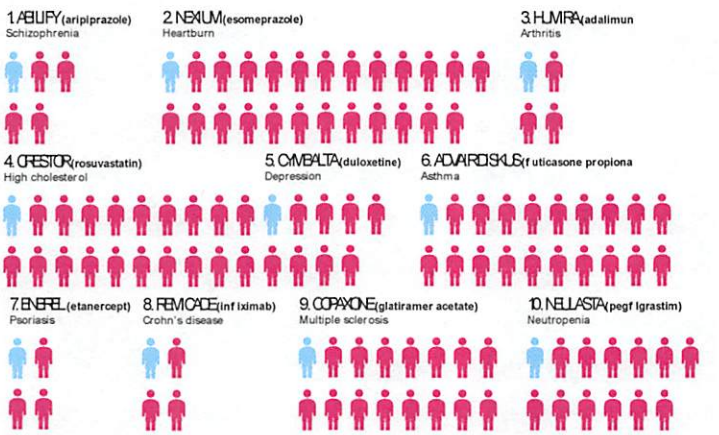
The White House. PMI privacy and trust principles. July 2015. www.whitehouse.gov.

Opportunities for Precision Medicine

	2004	2014
Cost of sequencing a human genome	$22,000,000	$1000
Time to sequence a human genome	2 years	<1 day
Number of smart phones in the United States	1 million (<2% of population)	160 million (58% of population)
Health providers using electronic records	20% to 30%	>90%
Computing power	n	n x 16

Kaiser J. *Science* 2015;347:817.

Current Model: Imprecision Medicine



Blue = Treatment Success

Red = Treatment Failure

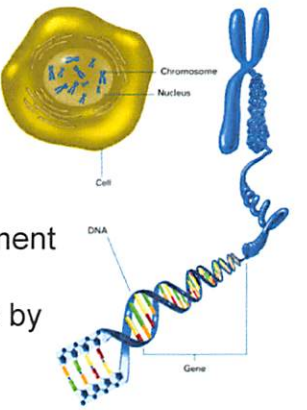
Schork NJ. *Nature* 2015;520:609-611.

What is Pharmacogenomics?

- Study of how genetic variations affect a patient's response to drugs
- Individualize therapy based on genetics
  - Identify responders and non-responders
  - Optimize dose
  - Prevent adverse drug reactions (ADRs)
- Our goal (RIGHT Protocol):
  - The **right** dose of
  - the **right** drug for
  - the **right** patient at
  - the **right** time

Variation in the Human Genome

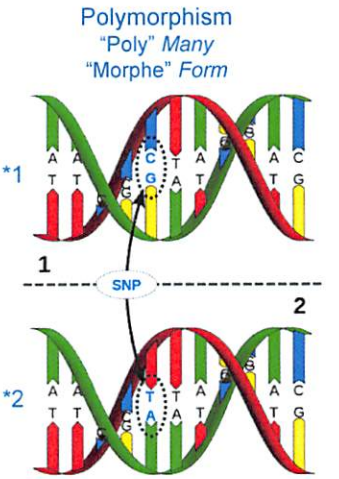
- Our genome contains 3 billion base pairs of DNA
- Between 2 people, there are approximately 3 million base pair differences
- Understanding variation has shown promise for improving disease treatment and outcomes
- Variation can change drug response by affecting pharmacokinetics or pharmacodynamics



National Institute of General Medical Sciences

Variation in the Human Genome

- Single nucleotide polymorphism (SNP)
  - Most common cause of genetic variation
  - Example: *VKORC1* 1173 C>T
- Other polymorphisms:
  - Insertions
  - Deletions
  - Duplications

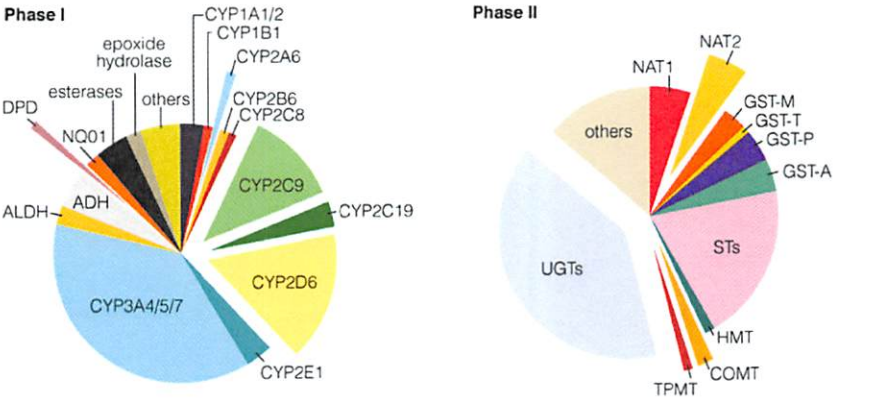


Variation in the Human Genome

- Different versions of a gene are called alleles
  Example: *CYP2C19* *1/*2

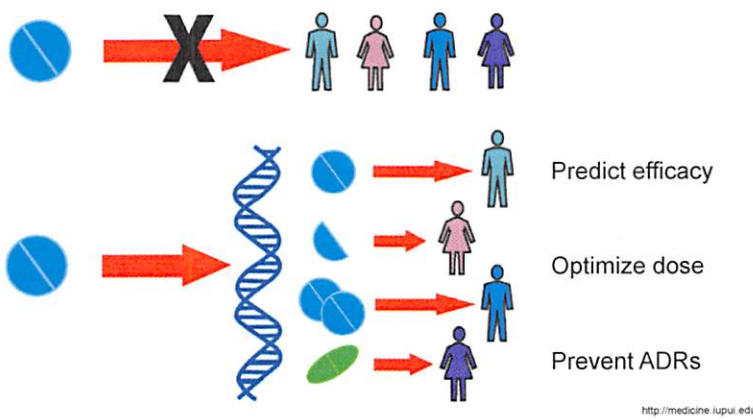
Allele	Function	Frequency of CYP2C19 Variants (%)	
		Caucasian/African American	Asian
*1	Wild-Type	-	-
*2	Loss	10-15	30-35
*3	Loss	<1	5-10
*17	Gain	16-22	1-3

Polymorphic Metabolizing Enzymes



Evans WE and Relling MV. Science 1999;286:487-491.

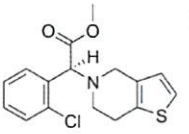
Utilizing Genotype Data



http://medicine.iupui.edu/IIPM

Predicting Efficacy

- Approximately 25% of patients on clopidogrel experience a sub-therapeutic response

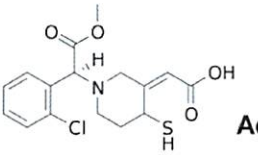


Clopidogrel (Prodrug)

↓

Cytochrome P450
1A2
2B6
X **2C19**

Intermediate Metabolite
Decrease



Cytochrome P450
3A4
3A5
2B6
2C9
X **2C19**

↓

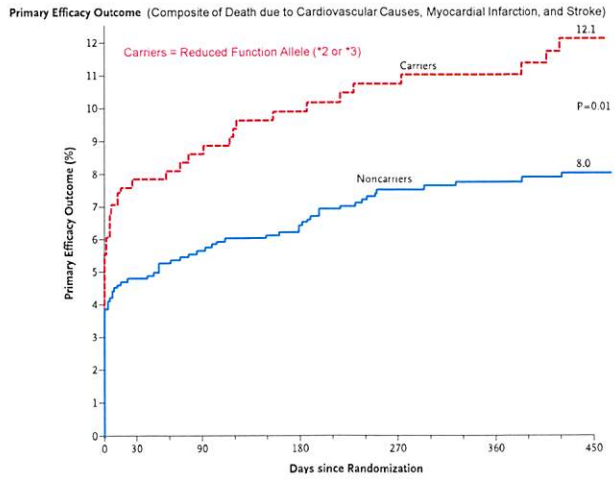
Active Metabolite
Decrease

Therapeutic Failure

Interpreting Results

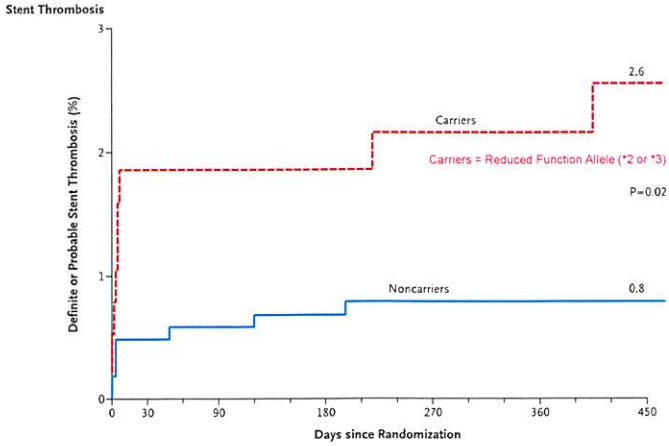
Metabolizer Phenotype	*CYP2C19* Genotype	US (%)
Ultra-rapid	*17/*17	1-5%
Rapid	*1/*17	20-30%
Extensive	*1/*1	35-50%
Intermediate	*1/*2 or *1/*3 or *2/*17 or *3/*17	20-30%
Poor	*2/*2 or *2/*3 or *3/*3	1-5%

CYP2C19 Status and Clinical Outcomes



Mega JL, et al. New England Journal of Medicine 2009;360:354-362.

CYP2C19 Status and Clinical Outcomes



Mega JL, et al. New England Journal of Medicine 2009;360:354-362.

Pharmacogenomics Knowledgebase (PharmGKB)

- https://www.pharmgkb.org/index.jsp
- Offers various levels of information
  - Variant annotations
  - Drug-centered pathway
  - Very important pharmacogenes
  - Clinical annotations
  - Pharmacogenomics-based drug-dosing guidelines
  - Drug labels with pharmacogenomic information

Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Purpose is to translate genetic information into clinical actions
- Prioritizes measurable and interpretable information based on community input, including CPIC members, American Society for Clinical Pharmacology and Therapeutics members (ASCPT), and the Food and Drug Administration (FDA)
- Makes clear recommendations on clinically actionable pharmacogenomic variants

Table 1 Example of assignment of likely _____ [gene] phenotypes based on genotypes

Likely phenotype	Genotype	Examples of diplotypes (alleles, one from each parent)
Homozygous wild type or normal, high activity (~__% of patients)	An individual carrying two or more functional (*1) alleles	*1/*1
Heterozygote or intermediate activity (~__% of patients)	An individual carrying one functional allele (*1) plus one non-functional allele (*2, *___, ___)	*1/*2, *1/*3A, *1/*3B, *1/*3C, *1/*4
Homozygous variant or deficient activity (~__% of patients)	An individual carrying two non-functional alleles (*2, *3A, *___, ___)	*3A/*3A, *2/*3A, *3C/*3A, *3C/*4, *3C/*2, *3A/*4
Ultrarapid....	Add rows as needed	

Relling MV and Klein TE. Clinical Pharmacology and Experimental Therapeutics 2011;89:464-467.

CPIC Guidelines

- https://www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC

Table 1: Recommended therapeutic use of abacavir based on *HLA-B* genotype

Adapted from Tables 1 and 2 of the 2012 guideline manuscript.

Likely phenotype	Genotypes	Examples of diplotypes	Implications for phenotypic measures	Recommendations for abacavir therapy	Classification of recommendation for abacavir therapy [a]
Very low risk of hypersensitivity (constitutes ~94% [b] of patients)	Absence of **57:01* alleles (reported as "negative" on a genotyping test)	*X/*X [c]	Low or reduced risk of abacavir hypersensitivity	Use abacavir per standard dosing guidelines	Strong
High risk of hypersensitivity (~6% of patients)	Presence of at least one **57:01* allele (reported as "positive" on a genotyping test)	*57:01/*X [c] **57:01/*57:01*	Significantly increased risk of abacavir hypersensitivity	Abacavir is not recommended	Strong

[a] Rating scheme described in the 2012 Supplement

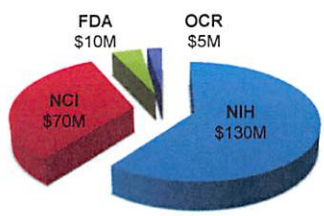
[b] See the 2012 Supplement for estimates of genotype frequencies among different ethnic/geographic groups

[c] **X* = any *HLA-B* genotype other than **57:01*.
HLA-B = human leukocyte antigen B

Importance of Pharmacogenomics

- Precision Medicine Initiative launched during the 2015 State of the Union address

  http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative



Importance of Pharmacogenomics

- 878 pharmacogenomics studies and 210 precision medicine studies as of August 2015
  - http://clinicaltrials.gov
- 380 drugs included in PharmGKB as of August 2015
  - https://www.pharmgkb.org/index.jsp

Importance of Pharmacogenomics

- FDA Guidance for Industry for Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling (2013)
- Over 100 drugs have FDA-recommended pharmacogenomic information on the drugs' labels
  - Table of Pharmacogenomic Biomarkers in Drug Labeling
  - http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm

Drug Labeling

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY

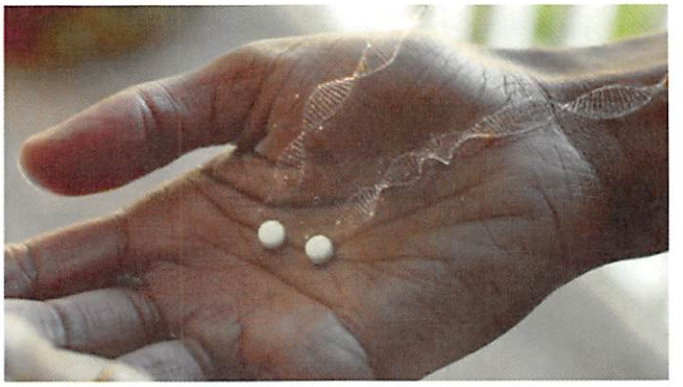
Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown HLA-B*5701 status who have previously tolerated abacavir. HLA-B*5701-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in HLA-B*5701-positive patients.

Malpractice to not test for HLA-B*5701 before administering therapy

Limitations in Clinical Practice

- Medical record implementation
- Health system logistics
- Turnaround time
- Cost and insurance coverage
- Privacy and trust
- Clinician education
- Gene-gene interactions
- Clear medical recommendations

Brace Yourselves, Personal Genome Testing is Coming…



https://www.youtube.com/watch?v=mC19N3e7-G4

Direct to Consumer Advertising (DTCA) of Genetic Testing

- Reduced cost for a panel of genes compared to obtaining multiple single gene tests
- Several vendors available
- Advise caution!

https://www.23andme.com/

http://genesight.com/

American College of Clinical Pharmacology (ACCP) Position Statement

- Verify, in consultation with a knowledgeable and trusted professional, the information presented in DTCA of genetic testing.
- Seek professional advice from a trusted healthcare source trained in genetics.
- Recognize the scientific limitations of each test. *They are not medical crystal balls.*
- Realize that many companies that sell DTC genetic testing services do not provide interpretation of test results.

Ameer B and Krivoy N. *Journal of Clinical Pharmacology* 2009;49:886-888.

Genetic Test Interpretation

Patient Genotypes and Phenotypes		
CYP2D6	Ultrarapid Metabolizer	*2A/*2A
CYP2C19	Intermediate Metabolizer	*1/*1
CYP1A2	Ultrarapid Metabolizer	-163C>A-A/A
CYP2C9	Extensive Metabolizer	*1/*1
SLC6A4	High Activity	L/L
HTR2A	Reduced Activity	G/G

USE AS DIRECTED	USE WITH CAUTION	USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
bupropion (Wellbutrin®)	amitriptyline (Elavil®)	desipramine (Norpramine®)
desvenlafaxine (Pristiq®)	citalopram (Celexa®)	duloxetine (Cymbalta®)
selegiline (Emsam®)	clomipramine (Anafranil®)	fluoxetine (Prozac®)
vilazodone (Vibryd®)	doxepin (Sinequan®)	fluvoxamine (Luvox®)
	escitalopram (Lexapro®)	mirtazapine (Remeron®)
	imipramine (Tofranil®)	nortriptyline (Pamelor®)
	sertraline (Zoloft®)	paroxetine (Paxil®)
	trazodone (Desyrel®)	venlafaxine (Effexor®)

Winner JG, et al. *Discovery Medicine* 2013;16:219-227.

"Here's my sequence…"

Pre-emptive Pharmacogenomics at UNC

- No perfect platform for obtaining pharmacogenomics information
- Using multiplex targeted sequencing to determine polymorphisms for actionable genes involved in pharmacotherapy
- High coverage and accuracy when determining polymorphisms
- Relatively inexpensive
- Seeking Clinical Laboratory Improvement Amendments (CLIA) validation

American Society of Health System Pharmacists (ASHP) Statement

- Advocate for the rational and routine use of pharmacogenomic testing.
- Provide test result interpretation and clinical guidance for return of results to providers and patients in collaboration with other health care professionals (e.g., physicians, laboratory professionals, and genetic counselors).
- Optimize medication therapy based on pharmacogenomic test results.
- Support and participate in research, consortia, and networks that guide and accelerate the application of pharmacogenomics to clinical practice.
- Educate and provide information on the clinical application of pharmacogenomics to health professionals, patients, and members of the public.

http://www.ashp.org/DocLibrary/Policy/HOD/StPharmacogenomicsPrepress.aspx

Accreditation Council for Pharmaceutical Education Standards for 2016

- Pharmacogenomics/genetics

  Genetic basis for disease and individual differences in metabolizing enzymes, transporters, and other biochemicals impacting drug disposition and action that underpin the practice of personalized medicine.
- Pharmacotherapy

  Evidence-based clinical decision making, therapeutic treatment planning, and medication therapy management strategy development for patients with specific diseases and conditions that complicate care and/or put patients at high risk for adverse events. Emphasis on patient safety, clinical efficacy, pharmacogenomic and pharmacoeconomic considerations, and treatment of patients across the lifespan.

https://www.acpe-accredit.org/pdf/Standards2016FINAL.pdf

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- Discuss the need for patient advocacy in regards to precision medicine

Information for Pharmacogenomics is available through the UNC Eshelman School of Pharmacy, Center for Pharmacogenomics and Individualized Therapy (CPIT)

PGXatUNC@unc.edu

https://pharmacy.unc.edu/research/centers/cpit

Questions?