Community Pharmacy & Pharmacogenomics: What's in the DNA Kit?

(& what does it mean?)

Todd A. Thompson, Ph.D.
Associate Professor of Pharmacogenomics
University of New Mexico
College of Pharmacy

DISCLOSURES

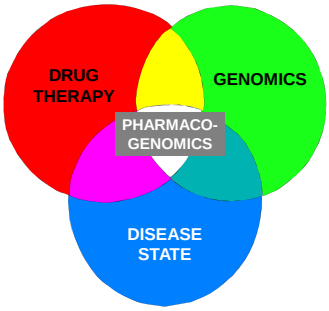
- **Associate Professor – UNM College of Pharmacy**
- **I have no financial affiliations to disclose.**
- **All brand names referenced to in this presentation are intended as educational references only.**

OBJECTIVES

- **Be able to define pharmacogenomics.**
- **Explain how you as a community pharmacist can utilize information from a PGx DNA testing kit to improve patient drug therapy.**
- **Be able to explain the key way in which genetic variants can affect drug response.**
- **Discuss how pharmacokinetic pharmaco-genomic considerations for different types of metabolizers can impact drug therapy.**
- **Using warfarin as an example, describe how PGx algorithms can be used to alter drug dosing based on a patient's PGx information.**
- **Know the groups affected by laws protecting personal genetic information (e.g., GINA).**

What is PHARMACOGENOMICS?

Pharmacogenomics is the study of how genes affect a patient's response to a drug (APhA FOUNDATION).

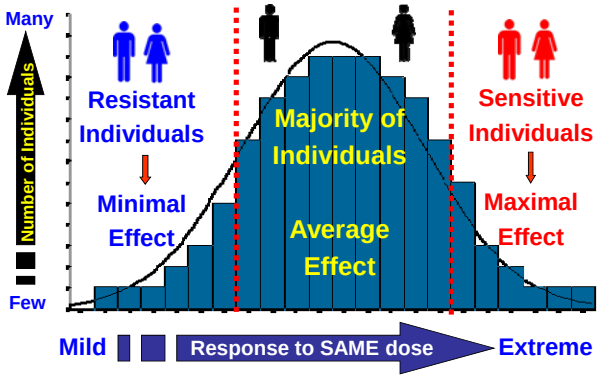


Why Community Pharmacists should know pharmacogenomics:

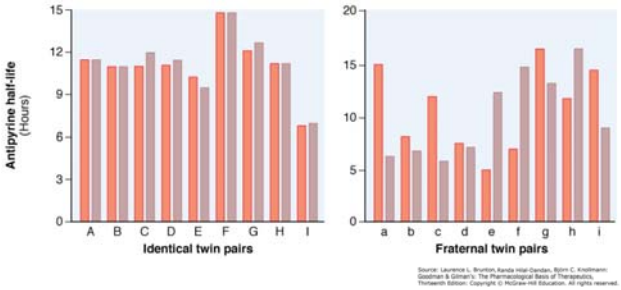
- **Knowing a patient's genetically coded response to a drug before they take it helps avoid adverse drug events by customizing the medication selection and dose to meet the individual patient's needs.**
- **Pharmacists are medication experts - they understand how drugs work in the body and how the body works on the drug.**
- **This makes pharmacists the ideal healthcare provider to interpret pharmacogenomic results and consult with the patient and other providers to personalize medication therapy.**

APhA FOUNDATION

Evidence Prompting the use of PGx



PGx – Genotype Meets Phenotype



Pharmacogenetic contribution to pharmacokinetic parameters. Antipyrine (i.e., phenazone) is a NSAID. The t½ of antipyrine is more concordant in identical twins in comparison to fraternal twin pairs. Bars show the t½ of anitpyrine in identical (monozygotic) and fraternal (dizygotic) twin pairs. (Redrawn from data in Vesell and Page, 1968.)

CLINICAL CONSEQUENCES OF VARIATION IN RESPONSE TO DRUGS

- Therapeutic failure (e.g., not active)
- Increased adverse side effects
- Increased toxicity
- Fatal adverse reactions

- What can pharmacists do?

How PGx Might be Utilized in a Community Pharmacy

- Collect samples for delivery to DNA analysis company.
- Inform patient on results of DNA analysis useful for optimizing drug therapy.
- Describe why a genetic test has resulted in the prescription of a particular medication.
- Explain why, based on a genetic analysis, a drug is administered at a particular dose or in a particular dosage form.
- Provide information about potential drug side-effects that may be suggested from results of a genetic test.
- Increased dispensing of drugs for disease prevention (i.e., chemopreventive agents).

Examples of DNA Testing Kits:

(not necessarily pharmacogenomics)

- **23andMe® – Personal Genetic Service**
- **HomeDNA®**
  - **Healthy Weight**
  - **Ancestry**
  - **Paternity**
- **myDNA® - wellness and nutrition**
- **Color Genomics® – genetic risk test for health, med response, & traits**
- **24 Genetics 5-in-1 DNA Test for Ancestry, Health, Nutrigenetics, Skin Care, and Sports**
- **$R_x$ight® DNA Testing Kit**
- **GeneSight® Psychotropic Test**
- **GENOMIND® PROFESSIONAL PGx**
- **PGxOne® Pharmacogenomics Test**
- **Many, many more …**

23andMe has multiple kits available:

- **Genealogy (Ancestry)**
- **Health (genetic diseases; may include PGx)**
- **Combined ancestry and health**
- **FDA approved PGx kit:**
  - **33 gene variants:**

Gene	Variant(s)
CYP2C19	*2, *3, *17
CYP2C9	*2, *3, *5, *6, rs7089580
CYP3A5	*3
UGT1A1	*6, *28
DPYD	*2A, rs67376798
TPMT	*2, *3C
SLCO1B1	*5
CYP2D6	*2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *15, *17, *20, *29, *35, *40, *41

What a DNA kit might include:

- **DNA collection method – for example, Oragene® saliva collection tube with funnel lid and cap – sample number and barcode**
- **Tube container**
- **Instructions**
- **Specimen bag**
- **Mailer box with label**

Example: 23andMe® Saliva Collection Kit

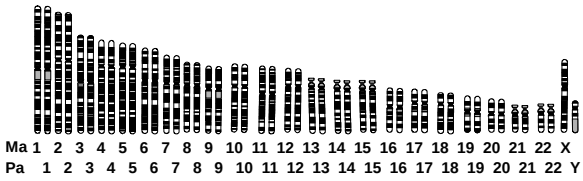
23andMe®

The Big Question:

How does DNA provide information that is useful for determining whether or not a drug will have a specific response in a specific person?

DNA is contained in HUMAN CHROMOSOMES

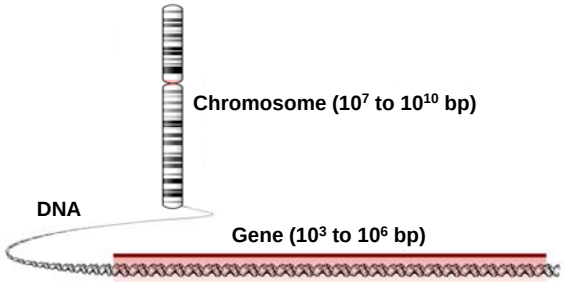
(mostly in the cell nucleus with a wee bit in mitochondria)



Each chromosome contains 100s to 1,000s of genes – the keys to PGx

What is a Gene?

(the science of pharmacogenomics)



A gene is a segment of DNA that encodes function. A chromosome consists of a long strand of DNA containing many genes. A human chromosome can have up to 500 million base pairs of DNA with thousands of genes. (Wikipedia – Gene)

THE HUMAN GENOME

- **DNA is made up 4 different bases that pair (A:T and G:C)**
- **6 billion basepairs** (diploid genome present in each cell of the body – except germ cells)
- **Approximately 25,000 genes**
- **Extensive interindividual variation in genomic structure**
  - Approximately 1 basepair variation every 1,000 basepairs
  - Any 2 people on average are 99.9% genetically identical (on average a 6 million basepair difference)

TYPES OF GENETIC VARIANTS

(POLYMORPHISMS – NOT Mutations)

- everybody in the room is a genetic variant.

Genetic differences in appearance extend to your liver, etc!

Types of Variants:

- Insertions
- Deletions

} Indels

- **Copy number variants**
  - e.g. duplications
- **Single Nucleotide Polymorphisms**

How do we name all these genetic variants?

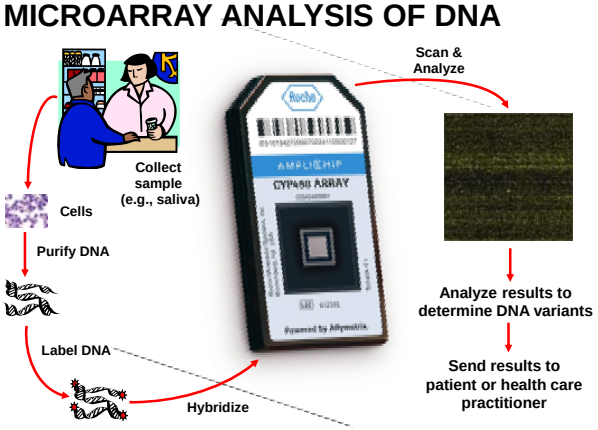
- **Many different ways to name genetic variants – it can be very confusing!**
- **One of the first and still commonly used is star (*) nomenclature.**
  - Example – Commonly used with cytochrome P450 variants – for example:
    - CYP2C9*2
    - CYP2C9*3
- **Many others:**
  - Reference SNP number
  - Allele numeric / alphabetic, Genotype, Haplotype, …

Possible Consequences of Genetic Variations on Gene Product Activity

- Coding Region SNPs may result in:
  - Reduced protein (enzyme) activity compared to common variant
  - Increased enzyme activity
  - No change in enzyme activity
  - Must do functional assay to determine effect
- Non-coding region variants – changes in enzyme levels
  - Reduced levels of gene expression, hence ↓ enzyme activity
  - Increased levels of gene expression, hence ↑ enzyme activity
- Copy number variants
  - More copies = increased activity (& vise versa)

Sophisticated methods are used to analyze the genome:

MICROARRAY ANALYSIS OF DNA



Three Major Divisions of Pharmacogenomics

- Pharmacokinetics (PK) of pharmacogenomics
  - The action of the body on the drug
  - ADME
    - Metabolic enzymes
    - Drug transporters
- Pharmacodynamics (PD) of PGx
  - The action of the drug on the body
  - Drug target pharmacogenomics
- Non-PK, non-PD - pharmacogenomics
  - Adverse drug reactions

INDIVIDUAL VARIATIONS IN DRUG METABOLISM

Cytochrome P450 (CYP) genes metabolize more than 90% of commercially available drugs

"PIEU"
P – poor metabolizer
I – intermediate metabolizer
E – extensive metabolizer
U – ultrarapid metabolizer

Metabolizer Groups

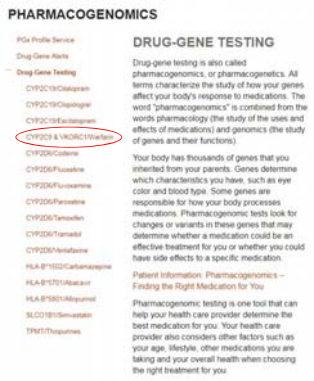
Poor Metabolizers
- Two variant alleles
- No enzyme activity

Intermediate Metabolizers
- One reduced activity allele
- One null allele

Extensive Metabolizers
- At least one normal allele

Ultrarapid Metabolizers
- Multiple functional alleles
- Excess enzymatic activity

Example of PGx Testing
Mayo Clinic: Center for Individualized Medicine



Warfarin Pharmacogenomics (Background)

- **A widely prescribed oral anticoagulant**
- **High incidence of adverse events** **(Wysowski et al 2007)**
  - **Among the top 10 drugs with the largest number of serious adverse events reports in FDA's Adverse Event Reporting System**
  - **Associated with about 29,000 emergency room visits per year for bleeding complications**
- **High inter-individual variability (~ 16-fold) in its dose requirements**
- **Both PK and PD PGx considerations – excellent example to understand general principles of PGx**

Warfarin Pharmacogenomics

1. **Pharmacokinetics of Pharmacogenomics**
   - Warfarin metabolism
     - Cytochrome P-450 variants
     - CYP2C9 (& CYP4F2)
2. **Pharmacodynamics of Pharmacogenomics**
   - Target of warfarin activity – VKORC1
3. **Warfarin Dosing Based on Genotype**
   - WarfarinDosing.org

Package Insert Information - Warfarin

Bristol-Myers Squibb Company

Anticoagulant

COUMADIN® TABLETS
(Warfarin Sodium Tablets, USP) Crystalline

COUMADIN® FOR INJECTION
(Warfarin Sodium for Injection, USP)

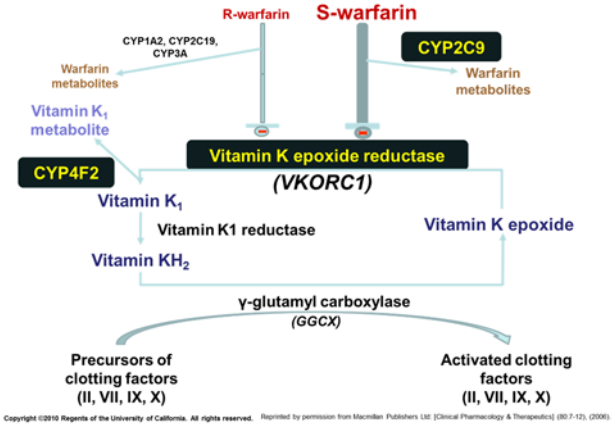
Table 1. Relationship Between S-Warfarin Clearance and CYP2C9 Genotype in Caucasian Patients

CYP2C9 Genotype	N	S-Warfarin Clearance/Lean Body Weight (mL/min/kg) Mean (SD)[a]
*1/*1	118	0.065 (0.025)[b]
*1/*2 or *1/*3	59	0.041 (0.021)[b]
*2/*2, *2/*3 or *3/*3	11	0.029 (0.011)[b]
Total	188	

[a]SD=standard deviation.
[b] $p<0.001$. Pairwise comparisons indicated significant differences among all 3 genotypes.

- **Major pathway for termination of pharmacologic effect is through metabolism of S-warfarin in the liver by CYP2C9**
- **CYP2C9 SNPs alter warfarin metabolism:**
  - **CYP2C9*1 (WT) – normal**
  - **CYP2C9*2 (Arg144Cys) - intermediate activity**
  - **CYP2C9*3 (Ile359Leu) - poor activty**
- **Also, VKORC1 -1639/3673 AA haplotype variant**

Pharmacology of Warfarin

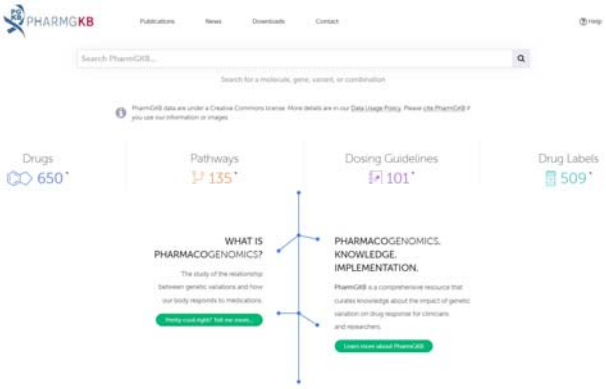


Programs to Help PGx Decision Making

- **e.g., www.WarfarinDosing.org**

– **A publicly available warfarin dosing algorithm**
– **Based on data from over 1,000 patients** (Gage et al 2008)
– **May be used to adjust warfarin dose in patients whose genotype information is available before the 6th dose of warfarin**

Pharmacogenomics Knowledge Base (PharmGKB)



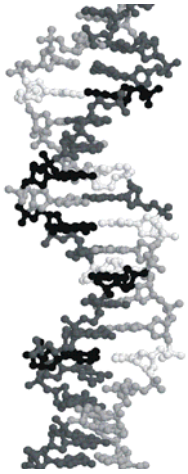
Empowering the Health Care Professional - The Genetic Information Nondiscrimination Act (GINA)

Genetics Day on the Hill 2007: Some of the many people that worked hard to make GINA's signing a reality

- **US legislation designed to prohibit improper use of genetic information by health insurance and employment.**
- **Would prohibit group health plans and health insurers from denying coverage to a healthy individual or charging higher premiums based solely on a genetic predisposition to developing a disease.**
- **Would bar employers from using an individuals' genetic information when making hiring, firing, job placement, or promotion decisions.**

SUMMARY

- **Pharmacogenomics is the study of how genes affect a patient's response to a drug.**
- **Genetic considerations can help in understanding differential drug responses.**
- **Pharmacogenomics in practice will results in new responsibilities for pharmacists.**
- **Community pharmacists can use genetic test information to facilitate personalized drug therapy.**
- **Genetic tests are now available to help determine gene variants that can affect a patient's response to a drug.**
- **Programs have been developed to help pharmacists effectively utilize PGx information.**
- **Laws to protect an individuals private genetic information are in effect.**



Thank You !

Todd A. Thompson, Ph.D.
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