

# The Use of Pharmacogenomics in Mental Health Medication Management

*The study of how genes affect a  
person's response to medication*

# Pharmacogenomics

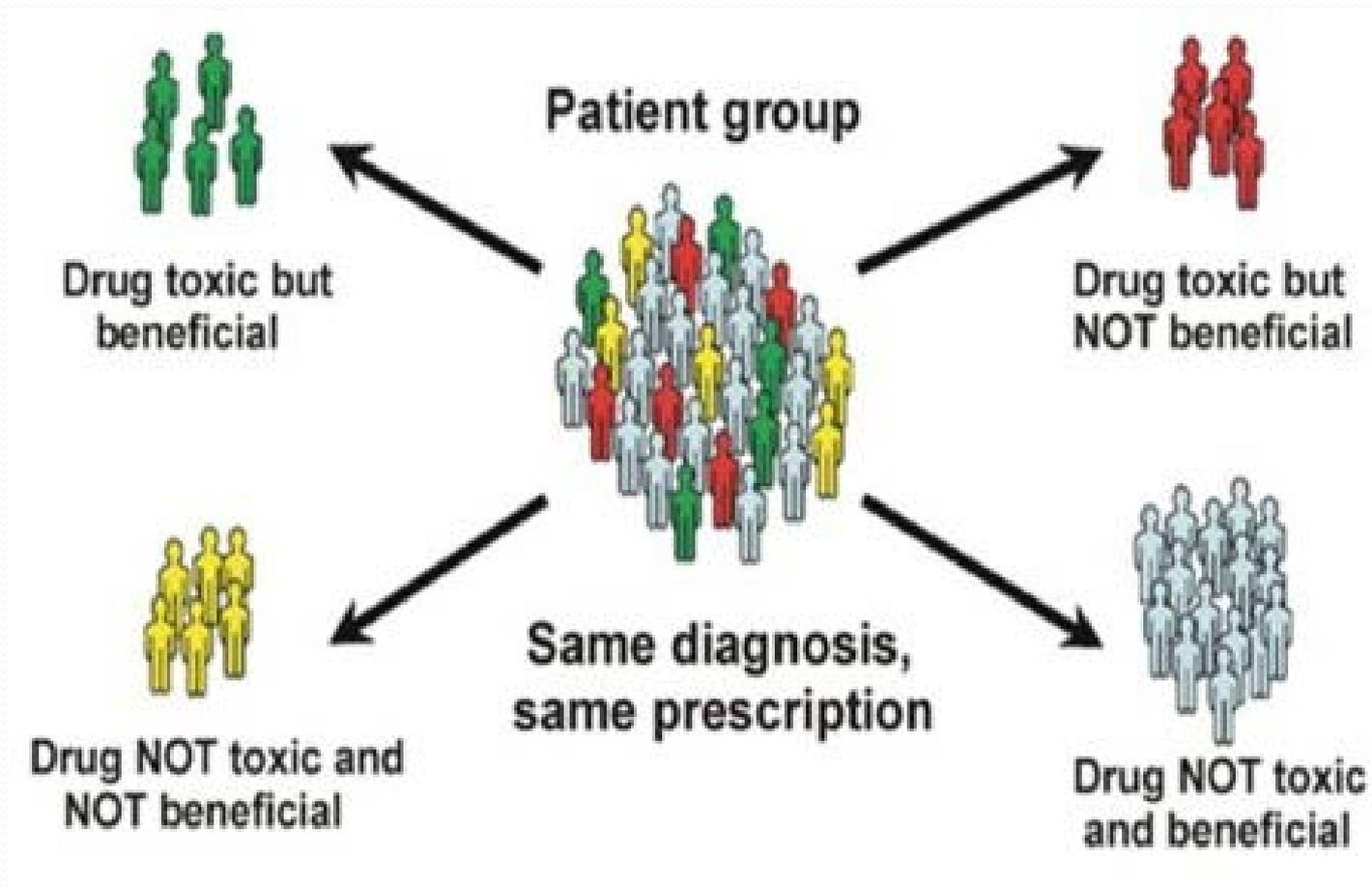
The science that allows us to predict a response to drugs based on an individual's genetic makeup

# Pharmacogenomics and Mental Health Medications

- Pharmacogenomics explains why:
  - One patient has the anticipated response
  - One patient has adverse reactions
  - One patient has no clinical response to the same medication, at similar dosing.
- Pharmacogenomics and genetic testing:
  - Influences clinician decision-making
  - Increases treatment response
  - Increases patient compliance and costs



# Personalized Medicine



**How does this happen?**

# Key Terms

- Pharmacokinetics: how drugs are metabolized, what the body does to the drug.
- Pharmacodynamics: what the drug does to the body.
- Gene: the basic unit of hereditary function
- Phenotype: characteristic that is the result of gene expression (drug metabolism)

~Cytochrome P<sub>450</sub> (CYP<sub>450</sub>) System~



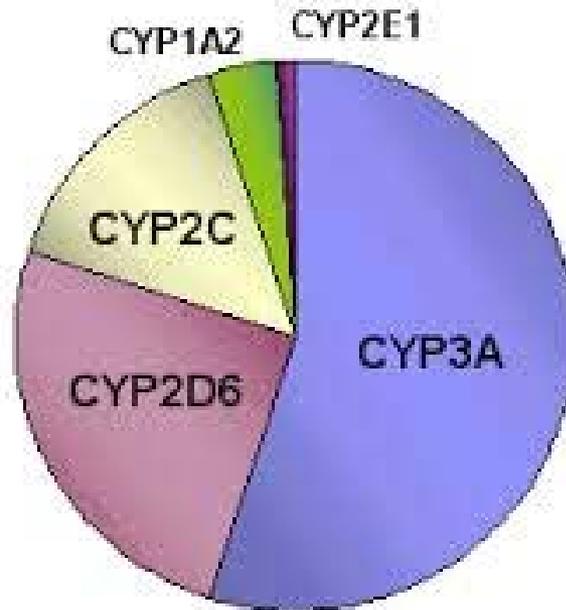
# What is the CYP450 System?

- A collection of enzymes that are responsible for the metabolism of medications.
- These enzyme genes help determine how much of the drug will be available for the body to use.
- The activity of these enzymes is genetically determined.
- These enzymes are highly concentrated in the liver and small intestines.
- 57 enzyme genes have been identified, over 100 subtypes

# Drug Metabolism and CYP450

- Most drugs metabolize via CYP450 enzyme gene systems: CYP 3A4 (47%), CYP 2D6 (25%), CYP 1A2 (15%), CYP 2C9/19 (13%),

Proportion of Drugs Metabolized  
by Major P450 Enzymes



# CYP450 Enzymes and Psychotropic Medications

CLASS	1A2	2B6	2C9/19	2D6	3A4
Antianxiety			Diazepam		Alprazolam Clonazepam Diazepam
Dementia				Donepezil Galantapine	Donepezil Galantapine
Antidepressant	Amitriptyline Duloxetine Fluvoxamine	Bupropion Sertraline	Amitriptyline Citalopram Fluoxetine	Paroxetine Venlafaxine Mirtazapine	Citalopram Sertraline Mirtazapine
Antipsychotic	Clozapine Haloperidol Olanzapine			Aripiprazole Risperidone Iloperidone	
Hypnotic	Melatonin			Doxepin	Trazadone Zolpidem Eszopiclone
Mood Stabilizer					Carbamazepine
Stimulant				Atomoxetine Dextroamphetamine	Modafinil
Other	Propranolol		Benztropine	Clonidine	Guanfacine

# 14 Genes involved in Psychotropic Medication Metabolism

- CYP<sub>2D6</sub>
- CYP<sub>2C19</sub>
- CYP<sub>2C9</sub>
- CYP<sub>1A2</sub>
- Catecholamine-O-methyltransferase gene
- Norepinephrine transporter gene
- Dopamine transporter gene
- Serotonin Transporter gene
- Serotonin 1A receptor gene
- Serotonin 2A receptor gene
- Serotonin 2C receptor gene
- D<sub>2</sub> dopamine receptor gene
- D<sub>3</sub> dopamine receptor gene
- D<sub>4</sub> dopamine receptor gene

# Genes and Metabolism

- Drug metabolism is determined by the pair of genes inherited from one's parents.
- Play an important role in either the pharmacokinetic availability or pharmacodynamic effect of mental health medications.
- 4 inherited metabolism categories: extensive metabolizer, intermediate metabolizer, poor metabolizer, ultra-rapid metabolizer

# Pharmacogenomics: Types of Metabolizers

- Extensive Metabolizer
  - Normal drug doses are metabolized at a normal rate
- Intermediate Metabolizer
  - Reduced rate of metabolism
  - Drug may not be tolerated
  - May required decreased dosage, slower titration
  - CYP2D6 variation: 7-12% of the population
  - Variations in CYP450 2C19:
    - 30% European ancestry
    - 40% African American ancestry
    - 55% Asian ancestry

# Pharmacogenomics: Types of Metabolizers-con't

- Poor Metabolizers
  - Drug is not tolerated, potentially harmful
  - Slow rate of metabolism
  - Alternate treatment should be used
  - CYP2D6 variation: up to 35% of the population
    - Variations in CYP450 2C19
      - 2% European ancestry
      - 4% African American ancestry
      - Up to 20% Asian ancestry

# Pharmacogenomics

## Types of Metabolizers-con't

- Ultra-rapid Metabolizers
  - Rapid metabolism with loss of therapeutic effect.
  - May require an increase dose
  - CYP<sub>2D6</sub> variation: up to 29% of Asian population

# Inducers and Inhibitors

- Inducers: drugs that *stimulate* CYP450 synthesis

If a drug is a CYP450 inducer of another drug...

- the rate of drug metabolism is increased
- = less drug bioavailability (less effect)

- Inhibitors: drugs that *reduce* CYP450 synthesis

If a drug is a CYP450 inhibitor of another drug...

- The rate of drug metabolism is decreased
- = more bioavailability (potential toxicity)

- Important inducers to know:
  - Steroids
  - Anticonvulsant/Antiepileptics (AEDs)
  
- Important inhibitors to know:
  - Macrolide antibiotics
  - Azole antifungals
  - Antivirals
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Isoniazid (INH)
  - H<sub>2</sub> blocker Cimetidine
  - Grapefruit juice
  - Cigarettes

# Pharmacogenomic Testing

- Genetic profile is obtained
- Data analyzed and genotype is determined (ie. 2D6)
- Phenotype is assigned (ie. extensive metabolizer)
- Provider utilizes report to make medication decisions
  - Drug selection
  - Dosing
  - Drug to drug interactions

## Patient, Sample

DOB: 7/22/1984

 Reference: 1456CIP  
 Clinician: Sample Clinician

 Order Number: 9299  
 Report Date: 6/13/2013

### Antidepressants

#### USE AS DIRECTED

**bupropion** (Wellbutrin®)  
**desvenlafaxine** (Pristiq®)  
**selegiline** (Emsam®)  
**vilazodone** (Viibryd®)

#### USE WITH CAUTION

**amitriptyline** (Elavil®) [2]  
**citalopram** (Celexa®) [3]  
**clomipramine** (Anafranil®) [2,7]  
**doxepin** (Sinequan®) [2]  
**escitalopram** (Lexapro®) [3]  
**imipramine** (Tofranil®) [3]  
**sertraline** (Zoloft®) [3]  
**trazodone** (Desyrel®) [2]

#### USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

**desipramine** (Norpramin®) [2]  
**duloxetine** (Cymbalta®) [2,7]  
**fluoxetine** (Prozac®) [2]  
**fluvoxamine** (Luvox®) [2,7]  
**mirtazapine** (Remeron®) [2,7]  
**nortriptyline** (Pamelor®) [2]  
**paroxetine** (Paxil®) [2,4,6]  
**venlafaxine** (Effexor®) [3]

### Antipsychotics

#### USE AS DIRECTED

**fluphenazine** (Prolixin®)  
**lurasidone** (Latuda®)  
**paliperidone** (Invega®)  
**ziprasidone** (Geodon®)

#### USE WITH CAUTION

**asenapine** (Saphris®) [2,7]  
**quetiapine** (Seroquel®) [2]  
**thiothixene** (Navane®) [2,7]

#### USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING

**aripiprazole** (Abilify®) [2]  
**chlorpromazine** (Thorazine®) [2,7]  
**clozapine** (Clozaril®) [2,7]  
**haloperidol** (Haldol®) [2]  
**iloperidone** (Fanapt®) [2]  
**olanzapine** (Zyprexa®) [2,7]  
**perphenazine** (Trilafon®) [2,7]  
**risperidone** (Risperdal®) [2]  
**thioridazine** (Mellaril®) [2,7]

[2]: Serum level may be too low, higher doses may be required.  
 [3]: Difficult to predict dose adjustments due to conflicting variations in metabolism.  
 [4]: Genotype may impact drug mechanism of action and result in reduced efficacy.

[6]: Use of this drug may increase risk of side effects.  
 [7]: Serum level may be too low in smokers.

#### All psychotropic medications require clinical monitoring.

Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed.

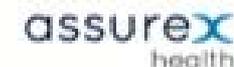
### Patient Genotypes and Phenotypes

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



## GeneSight® Psychotropic Results

### Patient Genotypes and Phenotypes



<b>CYP2D6</b>		<b>Poor Metabolizer</b>	<b>*4/*4</b>
CYP2D6 *4:	This allele produces no enzyme activity.		
CYP2D6 *4:	This allele produces no enzyme activity.		
Comment:	This genotype is most consistent with the poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.		

<b>CYP2C19</b>		<b>Intermediate Metabolizer</b>	<b>*1/*2</b>
CYP2C19 *1:	This allele produces normal enzyme activity.		
CYP2C19 *2:	This allele produces no enzyme activity.		
Comment:	This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.		

<b>CYP2C9</b>		<b>Intermediate Metabolizer</b>	<b>*1/*2</b>
CYP2C9 *1:	This allele produces normal enzyme activity.		
CYP2C9 *2:	This allele produces reduced enzyme activity.		
Comment:	This genotype is most consistent with the intermediate metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal phenotype.		

<b>CYP3A4</b>		<b>Extensive Metabolizer</b>	<b>*1/*1</b>
CYP3A4 *1:	This allele produces normal enzyme activity.		
CYP3A4 *1:	This allele produces normal enzyme activity.		
Comment:	This genotype is most consistent with the extensive metabolizer (normal) phenotype.		

**SPECIMEN INFORMATION**

AIB 11-1112-0000006



Date Collected: 01/29/2014 0:03  
Date Received: 01/23/2014  
Date Reported: 01/26/2014 14:50  
Specimen Type: Buccal Swab

**PATIENT INFORMATION**

Name: Jack Tripper Sex: Male  
SSN: 521-45-8866 Age: 30  
Date of Birth: 8/17/81 Chart#: 123  
Registration #: KA20113023AJI  
Phone: 804.562.4587

**PHYSICIAN INFORMATION**

Mary D. Dupont M.D.  
Dupont Center  
15825 Shady Grove Road, Suite 60  
Rockville MD 20850  
Phone: 301.869.5211  
Fax: 301.869.5212

**CLINICAL HISTORY**

Provided ICD-9 Codes:  
414.00 Coronary Atherosclerosis of unspecified site

**PersonaGene™ Patient Medication Report**

	Gene*	Implications*	Therapeutic Recommendations*
Clopidogrel (Plavix®)	CYP2C19	Normal Metabolizer of Clopidogrel	Start Clopidogrel at 300 mg (loading dose) and continue with 75 mg daily (maintenance dose). Avoid using Clopidogrel with omeprazole, a CYP2C19 inhibitor.
<b>1</b> Methadone (Dolophine®)	<b>2</b> CYP3A4	<b>3</b> Poor Metabolizer of Methadone	May need lower doses <b>4</b> of Methadone. <b>5</b> Usual of Methadone.
Methadone (Dolophine®)	CYP3A4	Normal metabolizers are at no increased risk for adverse effects.	Follow label dosing and administration information. No change needed.
Citalopram (Celexa®)	CYP2C19	Intermediate Metabolizer of Citalopram	Monitor for adverse effects.
	CYP2C8	Reduced Metabolism/ Increased Levels of NSAIDs. Increased Risk of Gastrointestinal Bleeding.	Administer with caution. Consider alternative. Monitor for gastrointestinal bleeding.

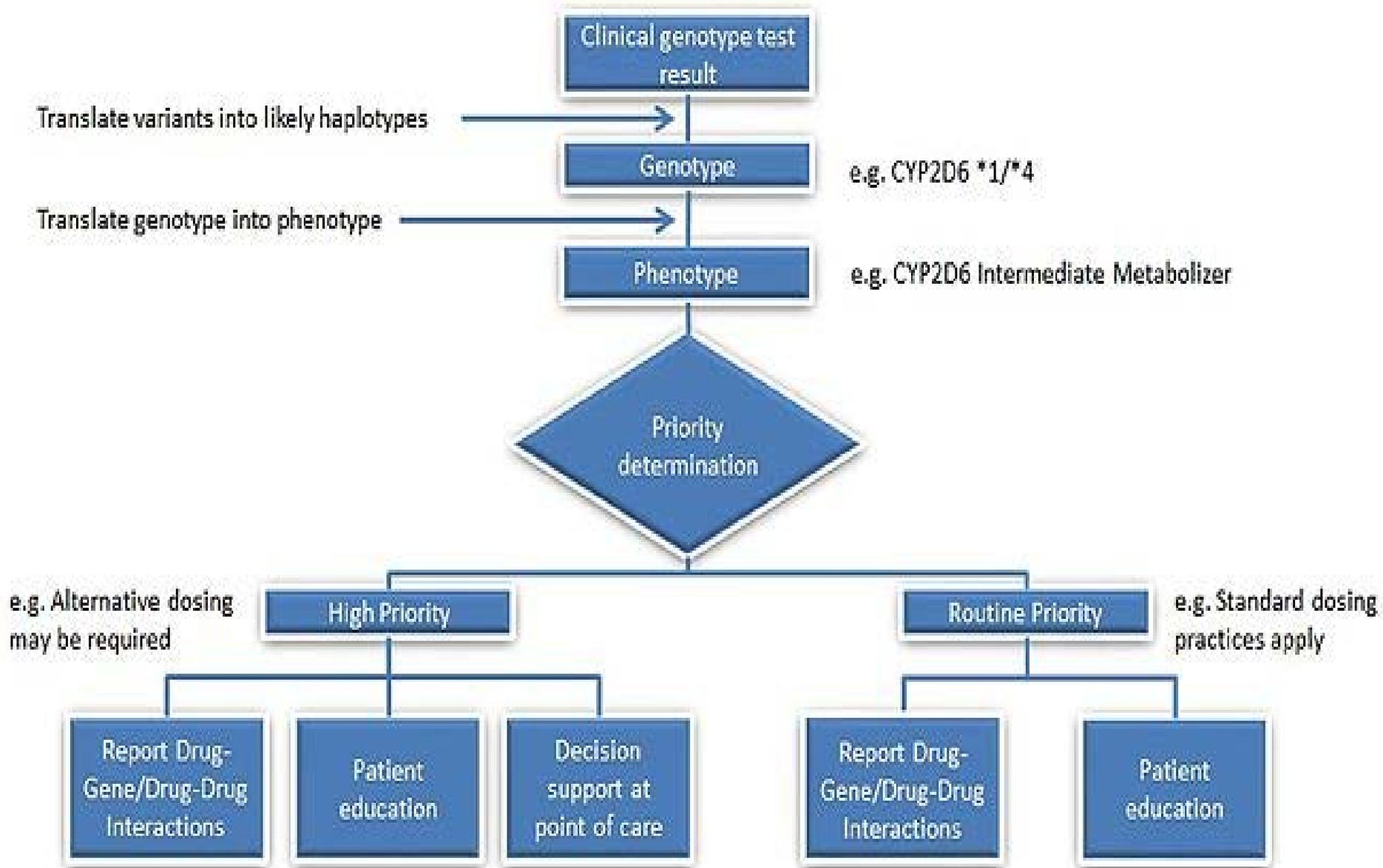
**Legend**

- Use with increased caution and/or consider alternative therapy
- Use with caution
- Use as directed

\* For additional information, please refer to <http://www.aibiotek.com/reports-normative>

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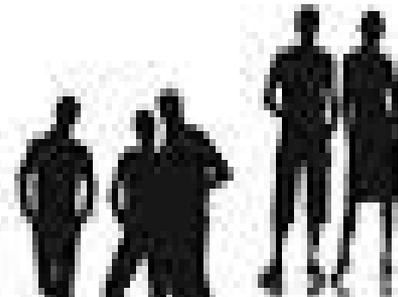
THIS REPORT DOES NOT TAKE INTO CONSIDERATION DRUG TO DRUG INTERACTIONS, DRUG SENSITIVITY, PATIENT HISTORY, AND/OR ALLERGIES. IT IS THE RESPONSIBILITY OF THE PHYSICIAN TO DETERMINE APPROPRIATE DRUG AND DOSING CHOICES BASED ON ALL AVAILABLE DATA.





## Medicine Today

Reactive, population-based,  
one-size-fits-all model of care



## Personalized Medicine

Predictive, preventive, patient-  
centric model of care



# References

- Mrazek DA. Psychiatric Pharmacogenomics . New York, NY Oxford University Press. 2010
- Caley, C, F. (2011). *Interpreting and applying CYP<sub>450</sub> genomic test results to psychotropic medications.* Journal of Pharmacy Practice 24(5) 439-46.



# Questions