



# Pharmacogenetics 101

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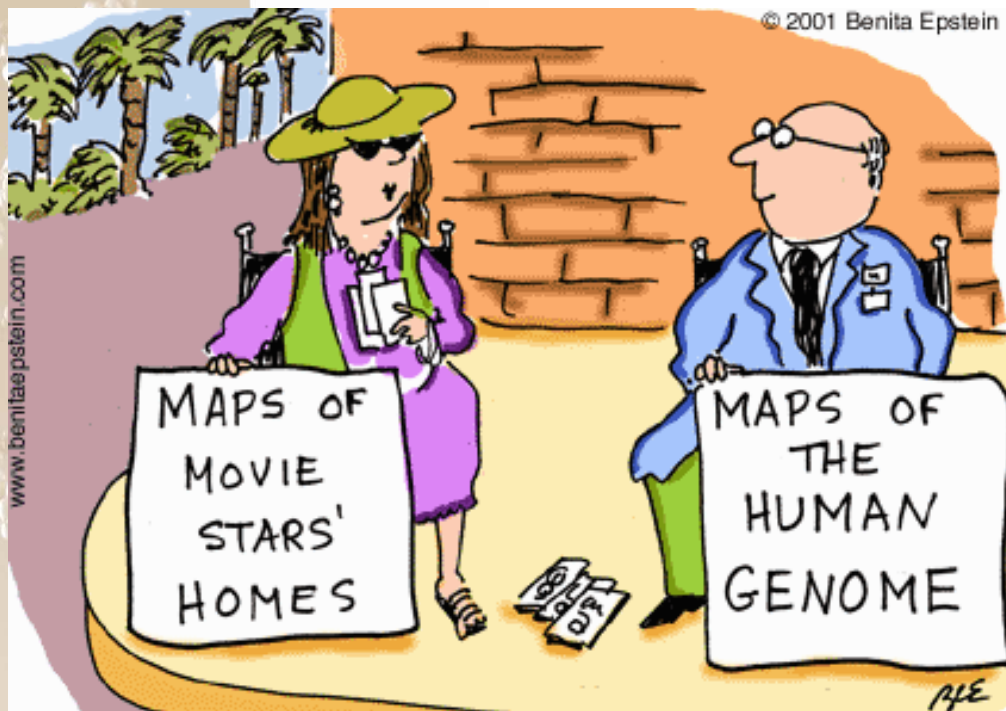
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*No conflicts of interest to disclose*



# Overview of clinical pharmacogenetics



- Each gene and drug we discuss today could be an entire lecture unto itself
- Diseases & drug responses are very often multi-factorial
- Field is extremely plastic and new knowledge is being obtained and incorporated very rapidly



# Pharmacogenetics is not a new concept in medicine

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- Anecdotal evidence that subpopulation of patients will not respond to drug therapies
- Advances in genetics and molecular biology now allow for association of genetic traits with patient outcomes



“If it were not for the great variability between individuals, medicine might as well be a science, not an art.”

– Sir William Osler, pathologist, 1892

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# Personalized Medicine

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- Right drug, right dose, right patient, ideally at the right time
- Based upon individual patient metabolic status
- Metabolic status determined by changes in key genes



# Overview

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- Why use pharmacogenetics in clinical practice?
- Fundamentals
  - Drug metabolizing enzymes
  - Why do small genetic changes matter?
- Clinical pharmacogenetics
  - What are the basic principles?
  - How can we use this genetic information to guide medication management?
- Examples of clinical utility
- Public policy impact



# Adverse Drug Reactions (ADR)

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- Over 2 MILLION serious ADRs yearly
- 100,000 DEATHS yearly
- Non-hospitalized patient ADR rate - unknown
- Nursing home patients ADR rate - 350,000 yearly
- ADRs 4th leading cause of death
  - Pulmonary disease
  - Diabetes
  - AIDS
  - Pneumonia
  - Accidents and automobile deaths

Institute of Medicine, National Academy Press, 2000  
Lazarou J et al. *JAMA* 1998;279(15):1200–1205  
Gurwitz JH et al. *Am J Med* 2000;109(2):87–94

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# Cost of ADRs

- ADRs were examined in over 8 million hospitalized Medicare patients (1998); study population = patients who experienced an ADR (1.73%; 141,398 patients)
- In patients who experienced an ADR
  - death rates 19.18% higher (odds ratio 1.208)
  - length of hospital stay 8.25% higher (77,769 excess days)
- Charges for patients with an ADR were increased as follows:
  - total Medicare 19.86% (\$339,496,598)
  - drugs 9.15% (\$24,744,650)
  - laboratory charges 2.82% (\$6,221,512)
- Frequent drug classes associated with ADRs were commonly prescribed medications (cardiotonic glycosides, adrenal corticosteroids, antineoplastic agents, anticoagulants, and analgesics)



# Advocates of PGx have stressed its potential to:

- Select optimal therapy & reduce "trial-and-error" medicine
- Reduce adverse drug reactions
- Improve the selection of drug targets
- Increase patient compliance with therapy
- Reduce the time, cost, and failure rate of clinical trials
- Revive drugs that failed clinical trials or were withdrawn from the market
- Avoid withdrawal of marketed drugs
- Shift the emphasis in medicine from reaction to prevention
- Reduce the overall cost of healthcare

"The Case For Personalized Medicine,"  
<http://www.personalizedmedicinecoalition.org>

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# Clinical goals of PGx

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Avoid adverse drug reactions

Maximize drug efficacy

Select responsive patients



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# What's an enzyme?

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- Molecular machine with a specific function
- Made of protein
- Proteins are encoded by specific DNA sequences (genes)
- Genes contain the directions for making enzymes
  - Changes in these genes can result in decreased or no enzyme metabolism
  - Extra copies can result in enzyme overproduction, leading to abnormally high levels of metabolism



# Drug metabolism enzymes



- **Cytochrome P450 enzymes** chemically modify drugs (Phase I reactions)
- **Conjugation enzymes** link one chemical to another, generally making them more water soluble and allowing elimination in the urine (Phase II reactions)



# Cytochrome P450

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- Family of Phase I liver enzymes
- Responsible for drug metabolism
  - CYP2D6 – over 65 compounds
  - Everything from amoxicillin to zidovudine
- Predictable consequences of gene polymorphisms have been previously identified
  - Effects on individual drug metabolism rates (*in vitro*)
  - With deleterious effects (*in vivo*, patient case studies)



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# Changes in genes can impact function

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- Analysis of DNA sequences identified changes in key drug metabolizing enzyme genes
- Research demonstrated that some of these changes resulted in
  - Complete loss of enzyme function
  - Lower rates of enzyme metabolism
  - Increased or decreased levels of enzyme in liver
- Also observed in patients with ADRs and in forensics



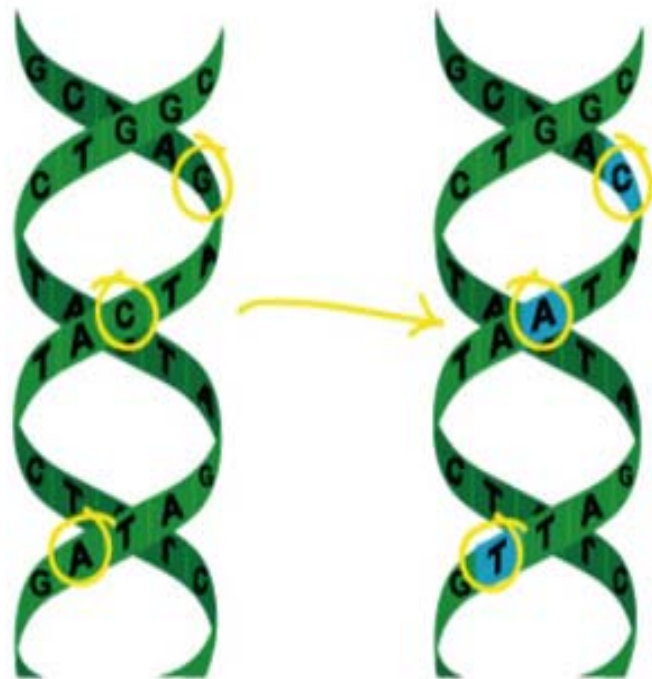
# Single Nucleotide Polymorphisms (SNPs)

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- Naturally occurring genetic variations present in a percentage of a given population (>1%)
- Frequency of the polymorphism often varies with race
- Not all result in non-functional variants
  - Silent or conservative changes
  - Reduced or enhanced protein function

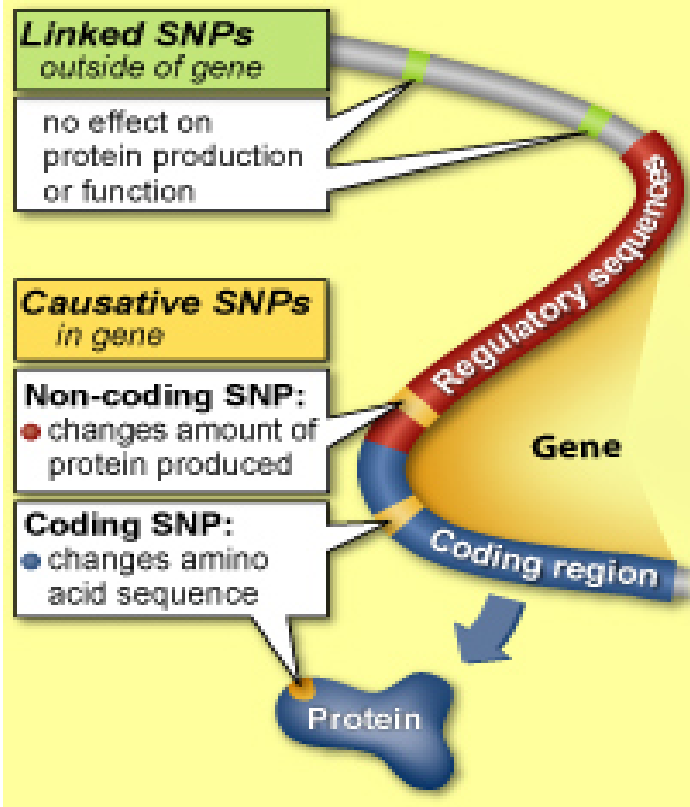


# Types of SNPs



## SNP Statistics

- Estimated SNPs in human genome: 10 million
- Number that have been seen twice: about two million



# CYP450 SNPs with clinical utility to predict drug-drug interactions

CYP2D6			CYP2C9			CYP2C19		
Variant	Alleles	Activity	Variant	Alleles	Activity	Variant	Alleles	Activity
Wild type	*1	Normal	Wild type	*1	Normal	Wild type	*1	Normal
Duplication of *1	Dupl.	Ultra	430C>T	*2	Decr.	681G>A	*2	Null
Deletion	*5	Null	1075A>C	*3	Decr.	636G>A	*3	Null
-1584C>G	*2A Promoter	Decr.	1076T>C	*4	Decr.	1A>G	*4	Null
100C>T	*4, *10	Decr.	1080C>G	*5	Decr.	1297C>T	*5	Null
124G>A	*12	Null	818delA	*6	Null	395G>A	*6	Null
883G>C	*11	Null				IVS5+2T>A	*7	Null
1023C>T	*17	Decr.				358T>C	*8	Null
1707T>del	*6	Null				-806C>T	*17	Ultra
1758G>T	*8	Decr.						
1846G>A	*4	Null						
2549A>del	*3	Null						
2613-2615 del AGA	*9	Decr.						
2850C>T	*2, *17	Decr.						
2935A>C	*7	Null						

**Table.** Alleles of clinical reference for CYP2D6, CYP2C9, and CYP2C19.



# Clinical testing for CYP450 SNPs

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- Patient provides sample for DNA extraction
  - Blood
  - Buccal swab
  - Tissue sample
- Multiple platforms available to detect clinically relevant subset of CYP450 gene SNPs
  - AmpliChip (Roche) is FDA approved
  - TM Biosciences / Luminex (FDA submission in progress)
  - Others
- Commercially available



# Patient classifications based upon CYP450 genotypes (SNPs)

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- **Extensive metabolizers (EM) = 2 good copies**
  - Represent the norm for metabolic capacity
- **Intermediate metabolizers (IM) = 1 defective copy**
  - May require lower than average drug dosages for optimal therapeutic response
  - Multiple drug therapy should be monitored closely
- **Poor metabolizers (PM) = 2 defective copies**
  - Increased risk of drug-induced side effects
  - Diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug
- **Ultra-rapid metabolizers (UM) = 3+ good copies**
  - Higher than normal rates of drug metabolism
  - Require increased dosage or simultaneous treatment w/ inhibitors to achieve desired results



# Population frequency of CYP450 genotypes

Gene	PM	IM	EM	UM
<b>CYP2D6</b>	10%	35%	48%	7%
<b>CYP2C9</b>	4%	38%	58%	N/A
<b>CYP2C19</b>	3-21%	N/A	79-97%	N/A

<http://www.healthanddna.com/professional/pharmacogenetics.html>

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# How do you select a good PGx candidate?

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- Drug
  - Narrow therapeutic range
  - High variability in inter-individual response
  - Problems in monitoring ADR or treatment response
  - Few alternative treatment options
- Gene with a polymorphism
  - Genetic change that alters function of key processes in target drug metabolism
  - Relatively common in population using the target drug





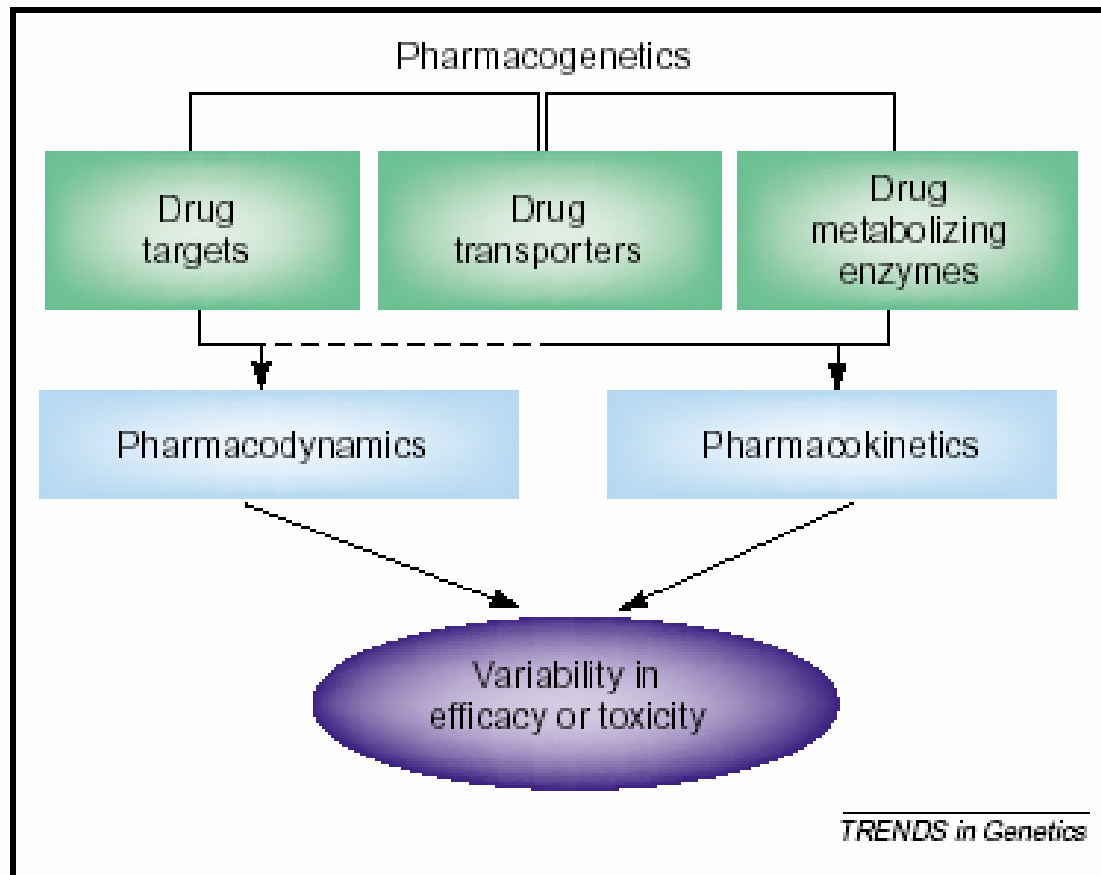
# PGx: Two essential concepts

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- Pharmacokinetics: how a drug gets in and out of the body (kinetics = movement of the drug)
- Pharmacodynamics: how the drug acts on the body to produce good effects (as well as bad effects)



# The big picture



Johnson, *Trends In Genetics*, 2003

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# PGx testing augments medication management

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- Can help identify why a patient is having problems with a particular medication
  - Explanation of an ADR
  - Identification of increased drug levels during routine therapeutic drug monitoring
  - Apparent non-response to typical dosing
- Can provide rationale for modifying therapies
  - Decreased or increased doses of current drugs
  - Change of medication to avoid particular enzyme pathway
  - Addition of TDM to clinical management



# Case Based Example

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- A 47-year-old male taxi driver experienced multiple ADRs during therapy with clomipramine (CMI) and quetiapine for major depressive disorder, after having been unsuccessfully treated with adequate doses of mirtazapine and venlafaxine
- Drug serum concentrations of CMI and quetiapine were significantly increased




# Case Based Example

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- Pharmacogenetic test results
  - CYP2D6 poor metabolizer
  - low CYP3A4/5 activity
  - normal CYP2C19 genotype
- After reduction of the CMI dose and discontinuation of quetiapine, all ADR subsided except for the increase in liver enzymes.





# Clinical reality of PGx testing?

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- Microarray approach to identifying polymorphisms in the drug metabolism genes
- Variations in these genes affect drug clearance and dose-response
- Blood sample for DNA analysis
- Reasonable turn-around-times for results
- Commercially available test platforms



# PGx as a “reactive” diagnostic tool

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- Applied when there is a medical condition for which pharmacogenetic information may provide an explanation (e.g. ADR)
  - Evidence to support clinical decisions
  - Provide proof to third party payers
    - higher medication doses
    - drug changes to potentially more expensive or non-standard options
  - Provide a potential explanation to the compliant patient for the trouble they've been having
- Forensics (overdoses)



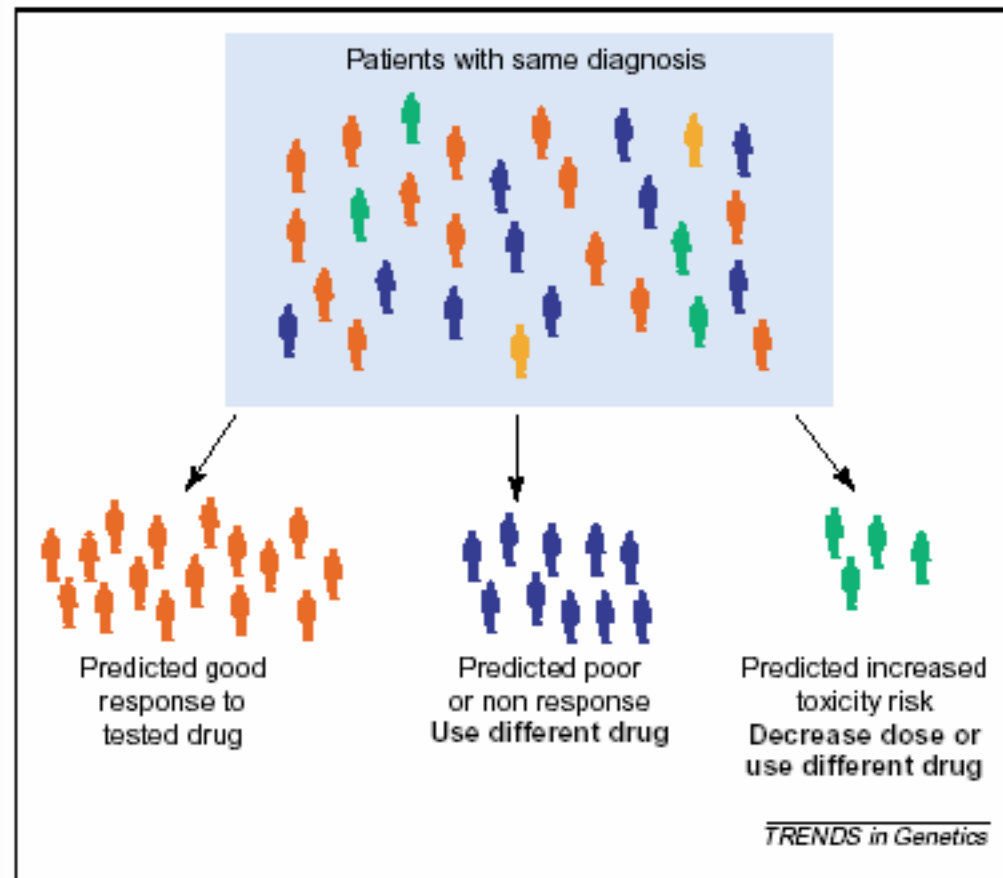
# PGx can also be used as a prospective screening tool

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- Carried out in the absence of a pre-existing medical condition
- Used to identify potential future problems in the hopes of preventing them from occurring
  - Screening family members of patients known to have had an ADR
  - Testing patients who have a history of therapeutic failure, but need to receive the problem drug again



# Prospective incorporation of PGx into clinical practice



*Johnson, 2003*

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# Pharmacogenetics testing will NOT replace

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- Need for clinical monitoring of the patient for desired response
- Necessity to monitor
  - Drug levels
  - Metabolite levels
  - Other biomarkers



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# Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

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- **Gene variants**

- *CYP2C9*
- *CYP2D6*
- *CYP2C19*
- N-acetyltransferase (*NAT*)
- *TPMT*
- *UGT1A1*

- **Gene expression**

- *C-KIT*
- *EGFR*
- *Her2/neu*
- *PML/RAR alpha*

- **Deficiencies**

- Dihydropyrimidine dehydrogenase (*DPD*)
- Glucose-6-phosphate dehydrogenase (*G-6-PD*)
- Protein C
- Philadelphia chromosome

[http://www.fda.gov/cder/genomics/genomic\\_biomarkers\\_table.htm](http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm)

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# Personalized medicine examples

Therapy	Biomarker/Test	Indication
anti-retroviral drugs	TruGene HIV1	therapy selection, resistant HIV genotypes
irinotecan (Camptosar)	UGT1A1	colon cancer; ADR avoidance
imatinib mesylate (Gleevec)	BCR-ABL	CML; therapy selection
trastuzumab (Herceptin)	HER-2/neu receptor	breast cancer; therapy selection
immunosuppressive drugs	AlloMap gene profile	monitor immune response post-transplant
mercaptopurine (Purinethol)	TPMT	ALL; ADR avoidance
tamoxifen	estrogen receptor	breast cancer; therapy selection
CYP450 metabolized drugs	CYP450 enzymes	therapy selection, ADR avoidance

“The Case For Personalized Medicine,”  
<http://www.personalizedmedicinecoalition.org>

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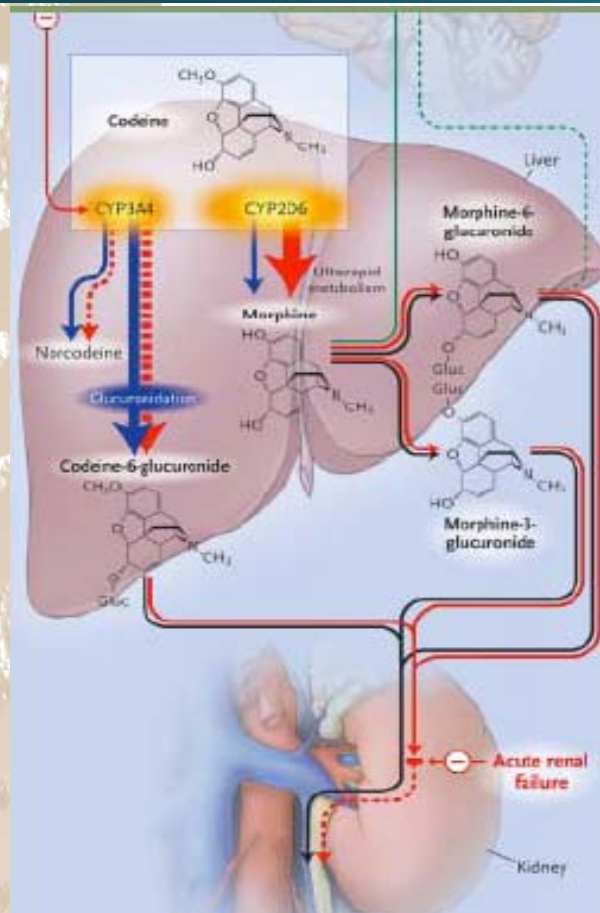
# CYP450 Testing Applications

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- Psychiatry – antidepressants, antipsychotics
- Anticoagulation therapy - warfarin
- Transplant - azathioprine
- Oncology – tamoxifen, chemotherapeutic drugs
- Drug addiction – nicotine
- Pain management – codeine
- Cardiology – beta-blockers



# Codeine toxicity case report



- 62 y.o. man hospitalized for pneumonia
- Treated with “standard” doses of codeine as a cough suppressant
- Coma; morphine levels 20x expected levels

***CYP2D6***  
***ultrarapid metabolizer***



# Atomoxetine (Strattera)

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- Treats ADHD in children
- Product insert label has significant CYP2D6 guidelines
  - PMs plasma drug levels 5x higher than in EMs
  - Drug half life increases from 5 to 20 hours in PMs
  - Lists side effects – undesirable hyperactivity, appetite loss, suicidal ideations
  - “Laboratory tests are available to identify CYP2D6 poor metabolizers.”



# Atomoxetine (Strattera) guidelines

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- Extreme caution for PMs
- Precautionary assessment of drug interactions for IMs, CYP2D6 inhibitors (paroxetine, fluoxetine) may phenocopy PM
- Reduce initial dosage for pediatric PMs, using the algorithm specified in the drug label
  - <70 kg body weight
    - EM 1.2 mg/kg/day
    - PM 0.5 mg/kg/day
  - >70 kg body weight
    - EM 80 mg/day
    - PM 40 mg/day



# Warfarin

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- Anticoagulant, used in atrial fibrillation, heart valve replacement, deep vein thrombosis
- Narrow therapeutic range
  - Ratio of the dose required to produce the desired therapeutic effect and the toxic dose
  - Overdose – uncontrolled bleeding, can be fatal
  - Underdose – clotting rapidly, can be fatal
- Laboratory methods to measure
  - PT - prothrombin time to clot, around 7-10 seconds
  - INR - International Normalized Ratio, standardized version of PT test against reference sample



# Aithal *et al*, Lancet 1998

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- Seminal work - demonstrated that CYP2C9 variants affected outcomes not just dose requirements
- Individuals with CYP2C9 variants had greater chance of bleeding incident
- Also consider public health aspects
  - Reduce time stabilizing patient dose at onset of treatment
  - Reduce cost of hospitalization
  - Improve patient compliance with therapy



# Dosage recommendations by genotype for warfarin sodium

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\*1/\*1 (WT) – 100%

\*1/\*2 – 87%

\*2/\*2 – 82%

\*1/\*3 – 68%

\*2/\*3 – 57% \*\*

\*3/\*3 – 33% \*\*

\*\* *Consider alternatives*



# Multi-factorial PGx: CYP2C9 and Vitamin K epoxide reductase complex (VKORC1)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Effect of *VKORC1* Haplotypes on Transcriptional Regulation and Warfarin Dose

Mark J. Rieder, Ph.D., Alexander P. Reiner, M.D., M.P.H.,  
Brian F. Gage, M.D., M.Sc., Deborah A. Nickerson, Ph.D., Charles S. Eby, M.D.,  
Howard L. McLeod, Pharm.D., David K. Blough, Ph.D.,  
Kenneth E. Thummel, Ph.D., David L. Veenstra, Pharm.D., Ph.D.,  
and Allan E. Rettie, Ph.D.

- Drug target for warfarin
- Haplotypes associated with warfarin dosing identified
- 25% variance explained by *VKORC1* haplotype
- Polymorphisms identified from 2 patients
- Functional polymorphisms led to decreased *VKOR* activity *in vitro*

### letters to nature

*Nature* 427, 537 - 541 (05 February 2004); doi:10.1038/nature02214

## Mutations in *VKORC1* cause warfarin resistance and multiple coagulation factor deficiency type 2

SIMONE ROST<sup>1,2,\*</sup>, ANDREAS FREGIN<sup>1,\*</sup>, VYTAUTAS IVASKEVICIUS<sup>3</sup>, ERNST CONZELMANN<sup>4</sup>,  
KONSTANZE HÖRTNAGEL<sup>2</sup>, HANS-JOACHIM PELZ<sup>5</sup>, KNUT LAPPEGARD<sup>6</sup>, ERHARD SEIFRIED<sup>3</sup>, INGE SCHARRER<sup>7</sup>,  
EDWARD G. D. TUDDENHAM<sup>8</sup>, CLEMENS R. MÜLLER<sup>1</sup>, TIM M. STROM<sup>2,9</sup> & JOHANNES OLDENBURG<sup>1,3</sup>

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# CYP2C9 and VKORC1 (-1639G>A)

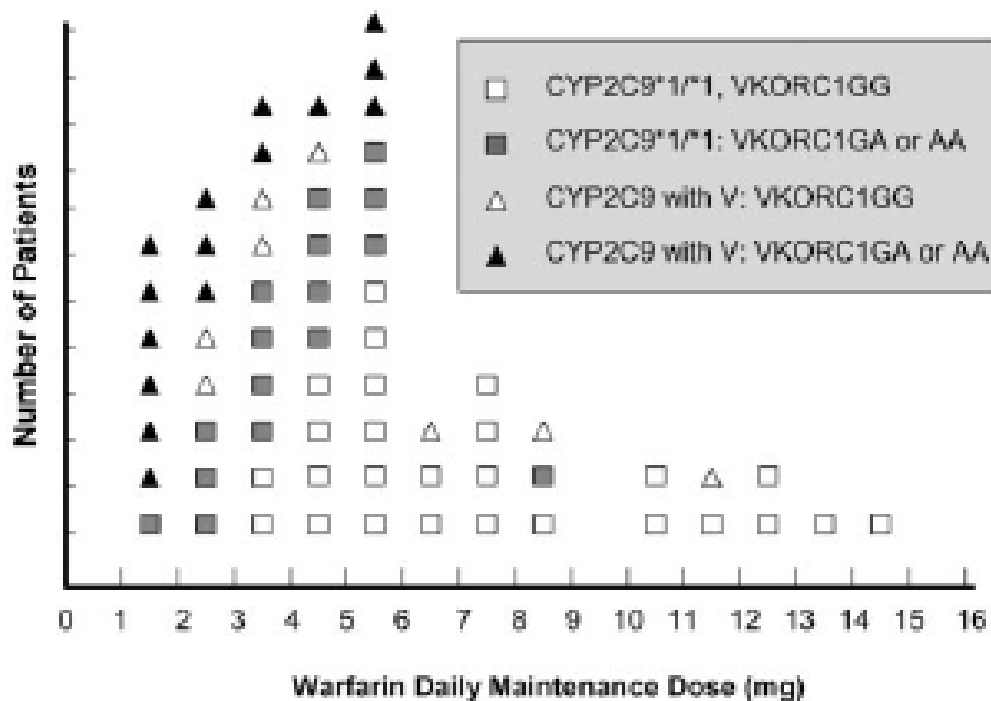


Fig. 1. Histogram representing the *CYP2C9* and *VKORC1* genotypes and warfarin maintenance dose requirements of the study population.

- *VKORC1* (-1639G>A) can result in warfarin sensitivity even without a *CYP2C9* variant
- Model including *VKORC1* and *CYP2C9* genotypes, age, sex, and body weight accounted for 61% of the variance in warfarin daily maintenance dose





# Not simple “if-then” results

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- Impact of any individual SNP on drug metabolism can be over or underestimated
- Other as yet unknown/untested influences on specific drug’s metabolism may be important
- Non-genetic factors must be accounted for as well (age, weight, kidney & liver disease, etc.)
- Even the relatively accepted examples (based upon FDA biomarker table) are not so easy to implement (non-specific dosage adjustment advice, etc.)
- Controlled, randomized, multi-center clinical trials are needed to further establish utility and clinical validity



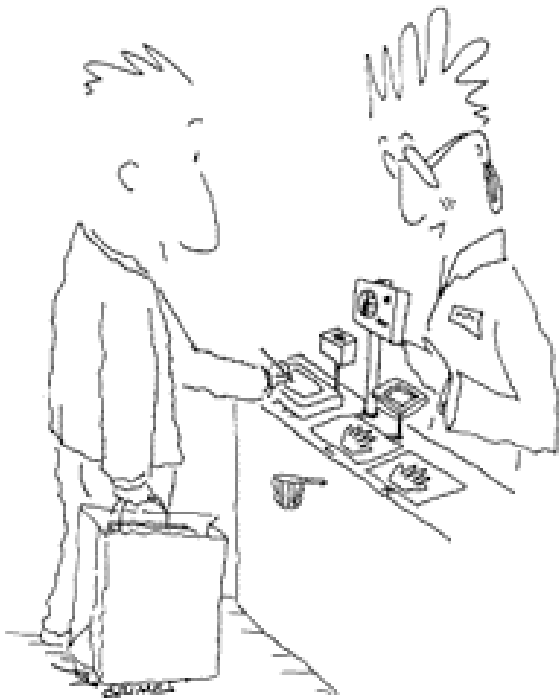
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# PGx has many areas of public policy impact



*"SIGN HERE, BREATHE  
HERE, THUMBPRINT  
HERE, LOCK OF HAIR  
HERE, SALIVA HERE,  
SPECIMEN HERE,  
SAY CHEESE!"*

- Regulation
- Reimbursement policies
- Legislative protections against misuse of genetic information
- Healthcare information technology infrastructure
- Education of healthcare professionals

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# Who are the impacted groups?

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- Patients
- Providers
- Pharmaceutical industry
- Insurers
- Government
- Society

***Interest, utility, ethical impact and implementation varies for each group***



## 3 general uses for PGx testing

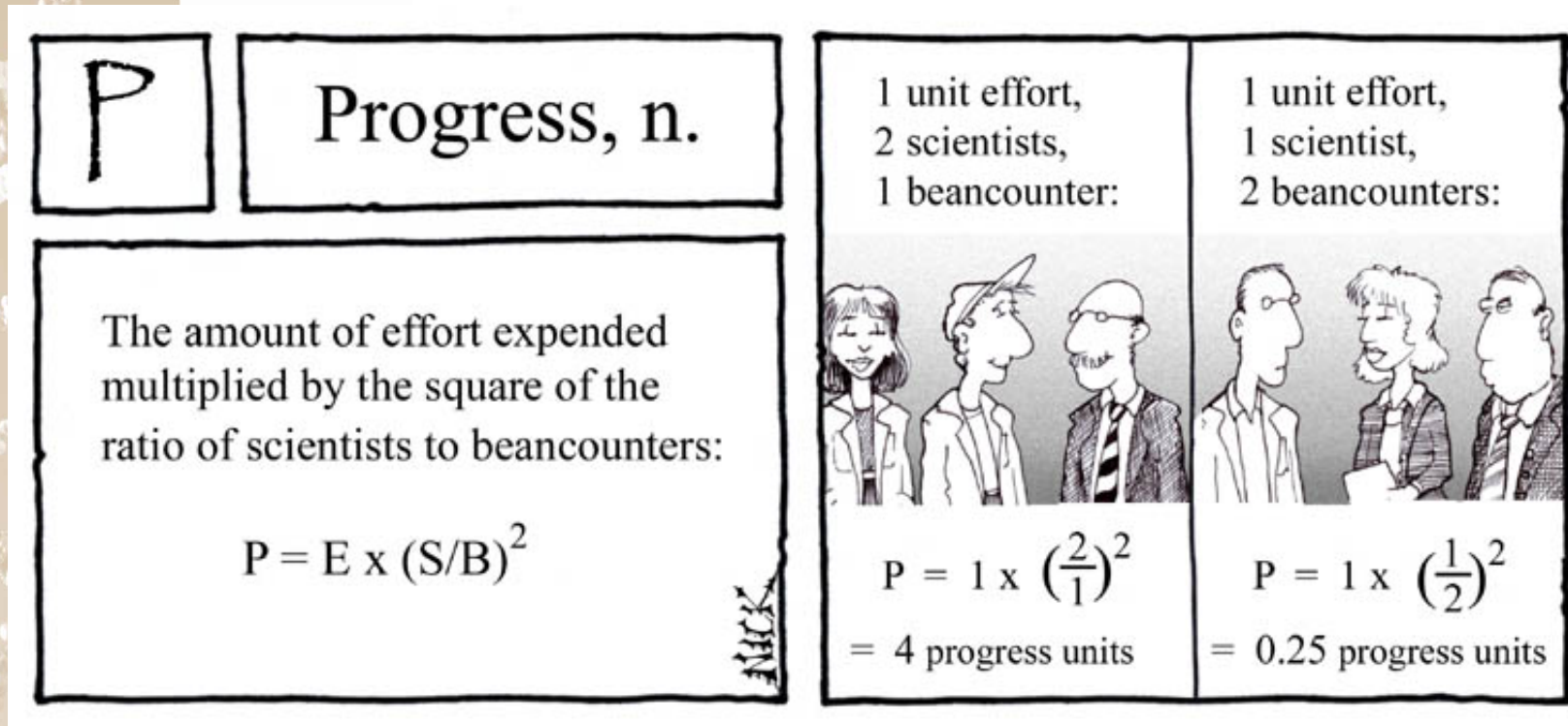
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- Predict disease risk
- Target drug therapies based on genetic variation of **disease**
- Target drug therapies based on genetic variation of **patient**

*Cost-benefit of each use is also viewed differently by each group*



# Clinical test implementation is never as fast as the discoveries behind it!



# What Is the FDA's Role in Advancing Pharmacogenomics?

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- "It's mission is to advance and protect public health...by helping to speed innovations that make medicines more effective, safer and more affordable." *Dr. Mark McClellan, FDA Commissioner in "Improving Innovation in Medical Technology: Beyond 2002" and reported in the Pink Sheet, February 3, 2003*
- Identify critical path opportunities for PGx and support its translation of research to the bedside
- Committed to a multi-year, multi-dimensional approach to advancing PGx

**L. Lesko, Ph.D., FACP**  
**Center for Drug Evaluation and Research**  
*Pharmacogenomics: A Critical Path Opportunity*  
*Special Grand Rounds March 18, 2004*

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# Reimbursement by insurers

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- Adequate and timely for PGx to gain approval
- Usually follows regulatory approval
- Coverage and payment policies pressed to keep pace with scientific progress
- Realigned to support preventive, proactive approach
- Formulary policy (current one-size-fits-all) will have to be reconsidered



# Take the Long View: The Vision of Medicine Response Profiles

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- By 2007 - 2010 SNP-based pharmacogenomic testing will be standardized for patient populations
- Test results will be routinely available in primary care for targeting an appropriate drug on the basis of sufficient efficacy and individualized safety

**L. Lesko, Ph.D., FACP**  
**Center for Drug Evaluation and Research**  
*Pharmacogenomics: A Critical Path Opportunity*  
*Special Grand Rounds March 18, 2004*

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# Take Home Messages

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- Personalized medicine has begun to pay off
  - Targeted therapies (Herceptin, Gleevec)
  - Risk reduction strategies (HIV resistance testing)
- In the future, multiple opportunities exist to
  - Prevent or predict ADRs
  - Improve medication management
  - Reduce health care costs
  - Improve pace of drug discovery/clinical trials
- Multiple challenges to implementation still remain
  - Clinical science
  - Public policy



# PGx testing at Shodair

## Psychiatric Drugs Metabolized by CYP2D6

### Antidepressants

fluoxetine  
fluvoxamine  
bupropion  
paroxetine  
trazodone  
venlafaxine  
tricyclic antidepressants

### Antipsychotics

chlorpromazine  
haloperidol  
perphenazine  
risperidone  
thioridazine

Source: [http://www.postgradmed.com/issues/1999/11\\_99/cadieux.htm](http://www.postgradmed.com/issues/1999/11_99/cadieux.htm)

- Institutional decision made to offer PGx testing for Shodair patients
- Patient Care Improvement Goals
  - Better medication management
  - Reduced length of stay
  - Reduced time in seclusion and restraint
  - Reduced repeat admissions

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# PGX Testing at Shodair Hospital Psychiatric Inpatient and Residential Units

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- Hypothesis 1: Testing will result in better management—anticipation of drug interactions and side effects, more rational use of medications, fewer ADRs, important information for the patient
- Hypothesis 2: Children admitted to Shodair have failed outpatient therapy and may have a higher frequency of deleterious PGX alleles



RM 13 yo Male

Dx: Bipolar, ADHD, ODD

Problems: Suicidal (depression)

Current Meds	Med History	PGX Results	Implications
Buspar Concerta Zyprexa	Strattera Ativan Prozac (agitation)	1A2: EM 2C9: EM 2C19: IM 2D6: IM	1A2: None 2C9: None 2C19: None 2D6: Buspar (tapered, Wellbutrin added) Continue Zyprexa Abilify (sub/inh 2D6) added at low dose



EP 13 yo Male

Dx: Bipolar, Hx of Abuse

Problems: Anger, aggression

Current Meds	Med History	PGX Results	Implications
Buspar Ativan	Seroquel (sedation) Depakote	1A2: Hyperinducer 2C9: IM 2C19: IM 2D6: IM	1A2: No inducers 2C9: None 2C19: None 2D6: Started low dose Abilify, did well DC Ativan Continue Buspar(3A4) Test helpful

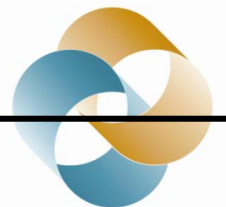


DP 8yo Male

Dx: PTSD (abuse), ADHD, Borderline IQ,  
Bipolar -> Schizoaffective DO

Problems: Aggression

Current Meds	Med History	PGX Results	Implications
Wellbutrin Depakote Metadate Zyprexa	Concerta Risperdal Buspar Clonidine Effexor Seroquel- <b>EPS</b> (3A4, minor 2D6) Paxil Klonopin	<b>1A2: Hyperinducer</b> 2C9: EM <b>2C19: PM</b> <b>2D6: PM</b>	<b>1A2:</b> Zyprexa, no inducers 2C9: None, Depakote <b>2C19:</b> None <b>2D6:</b> Zyprexa 60% dose Metadate, Wellbutrin inhibitors



KC 14 yo Female

Dx: PTSD (abuse, P and S)

Problems: Aggression, anxiety

Current Meds	Med History	PGX Results	Implications
Cymbalta Concerta	Ritalin Zoloft (GI, fatigue) Seroquel Wellbutrin Lexapro Prozac (sedation)	1A2: Hyperinducer 2C9: EM 2C19: EM 2D6: IM	1A2: No inducers 2C9: None 2C19: None 2D6: Cymbalta DC (?psychosis), Risperdal (96%) and Desyrel (3A4) started—both inhibit as does Concerta; Desyrel 2D6 metabolite anxiogenic



KJ 10 yo Male

Dx: Bipolar/Mood DO, ADHD, PDD-NOS

Problems: Aggression, Hallucinations

Current Meds	Med History	PGX Results	Implications
Risperdal Focalin Klonopin Paxil ?Versed for surgery ?add Prozac or Wellbutrin	Ritalin (tics) Seroquel (EPS) Abilify (agitation) Geodon Zoloft Effexor Zyprexa (not tolerated)	1A2: Hyperinducer 2C9: EM 2C19: IM 2D6: EM	1A2: No inducers 2C9: None 2C19: Prozac 2D6: None Started Lithium, Seroquel, Tenex, Metadate, Klonopin cont'd, Wellbutrin better choice



# The 3 Variables that Determine Drug Response

Site of Action	Drug Concentration at Site of Action	Underlying Biology of Patient
Affinity for site Intrinsic activity at site	Absorption (compliance) Distribution Metabolism Elimination (ADME)	Genetics Age Disease Environment (GADE)

Preskorn SH. Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors. Caddo, OK: Professional Communications, Inc; 1996.  
<http://www.preskorn.com>.



# PGX Testing at Shodair Hospital Psychiatric Inpatient and Residential Units n=5

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- Hypothesis: Testing will result in better management—anticipation of drug interactions and side effects, more rational use of medications, **information for the patient FOR THE MINORITY**
- Hypothesis: Children admitted to Shodair have failed outpatient therapy and may have a higher frequency of deleterious PGX alleles **MAYBE**

