

# Pharmacogenomic testing: What should a family medicine MD know?

Lisa B. Namerow, MD  
Assistant Professor of Pediatrics and Psychiatry  
University of Connecticut School of Medicine  
Medical Director, Consultation service to Pediatrics  
Attending, Child and Adolescent Psychiatry, Institute of  
Living  
October 18, 2018

# Disclosures

- QA grant from hartford hospital
- Auxilliary grant from hartford hospital
- No commercial conflicts of interest
- Any commercial results reviewed are for educational purposes only; not to endorse any particular company or product

# Why is pharmacogenomics suddenly so popular?

- How many of you have experienced a patient who had unusual or concerning side effects to medications you prescribed?
- How many of you have found that your patients have not responded to evidence-based medications?
- Trial-and error prescribing....Doesn't feel so good...☹️
- But we need to be careful and understand what pharmacogenomics can and cannot do

## So is pharmacogenomics the answer? Editorials are clearly mixed

- Initial hope: would become part of standard practice by 2020 (Phillips et al., NEJM, 2001)
- *Non validated pharmacogenomic tests: Confessions of a Professor, Part I*, (de Leon, Psychiatric Times, October, 2016)
- *When Genetic Testing Is Unproven: The Case of Depression Treatments* (NEJM Journal Watch, 2017)
- “Antidepressant Pharmacogenomics” (Singh et al., American Journal of Psychiatry, May 2017)

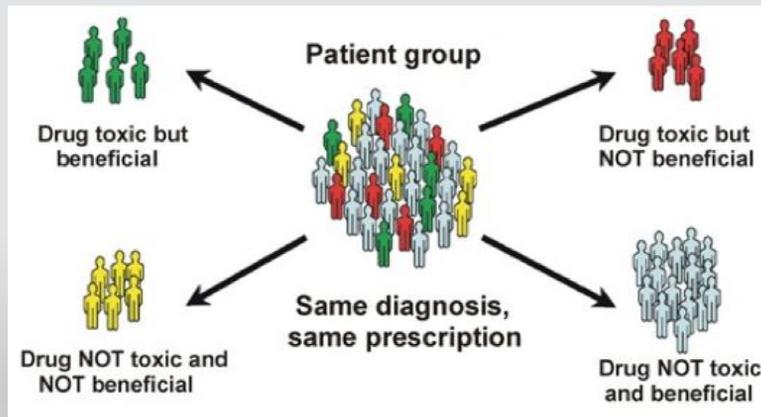
# So where do we begin.....?

- At the beginning.....
- A look at 10 important points involving pharmacogenomics



# #1 What is the hope of pharmacogenomics?

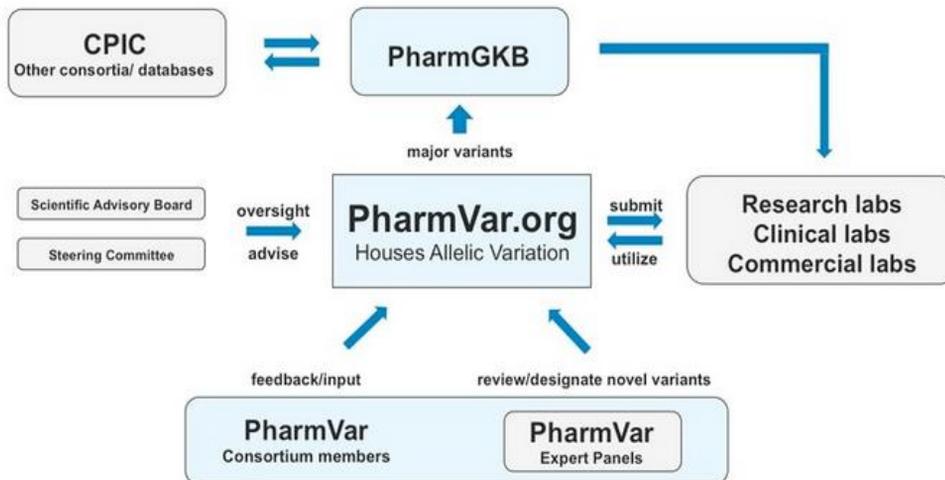
- Minimize potential side effects
- Maximize probability for the chosen drug to be effective



## #2: What is the basis for this testing and can it be trusted?

- Molecular biologists have determined multiple problem alleles in the genes that are involved with drug metabolism and drug action
- These alleles code for proteins/enzymes that are altered in some way
- These alterations impact their activity or change the molecules that are target sites of medications (receptors, transporter genes)
- It is the impact on treatment outcome that is being debated

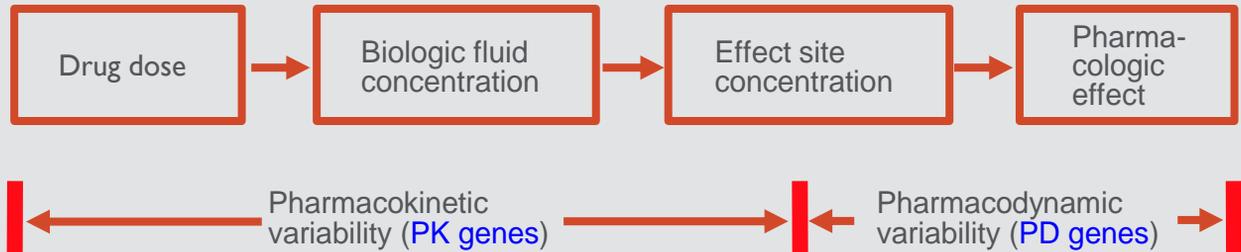
# PharmVar Consortium and Database



## #3 Where might genes play a role in psychopharmacotherapy?

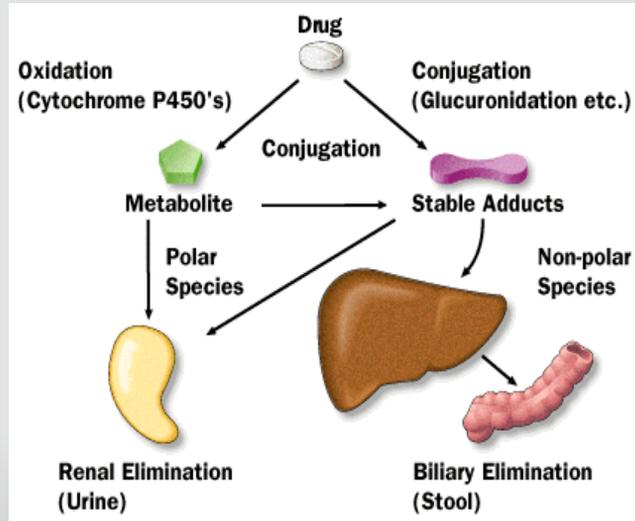
- In coding for the enzymes that metabolize medications: pharmacokinetic genes (PK)
- In coding for the targets of medication activity: pharmacodynamic genes (PD)

## Genetically susceptible factors from drug administration to clinical effects



# #4 What are the PK genes that have been the most studied?

- **CYP3A4**
- **CYP2D6**
- **CYP2C9**
- **CYP2C19**



# Cytochrome P450 Nomenclature

- **CYP2D6**
- CYP=Cytochrome P450
- 2=Genetic family
- D=Genetic subfamily
- 6=specific gene
- Involved in metabolism of over 70 medications

## #5 What do allelic variants do to the p450 (PK) genes in terms of the proteins they produce?

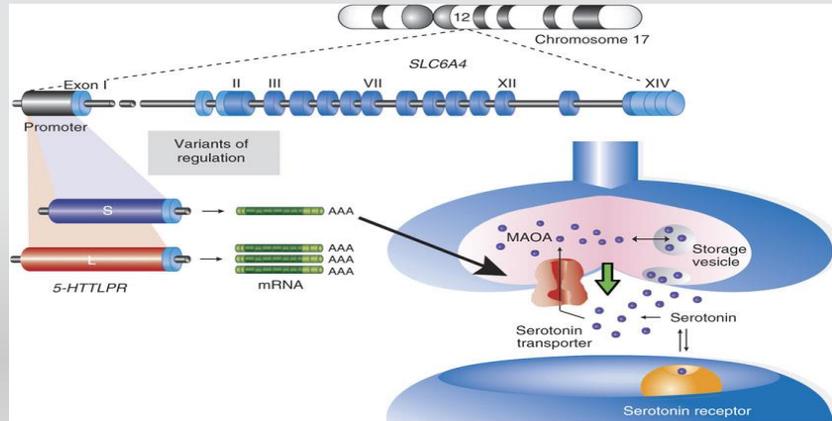
- Create enzymes that have poor/null activity
- Create enzymes that have deficient activity
- Create enzymes that have normal activity
- Create enzymes that have ultrarapid activity

## #6 What are the relevant PD genes?

- For depression: serotonin transporter gene, serotonin receptor gene, norepinephrine transporter gene (not yet commercially available), possibly COMT
- For ADHD: COMT, adrenergic receptor gene
- Let's talk a closer look at why.....

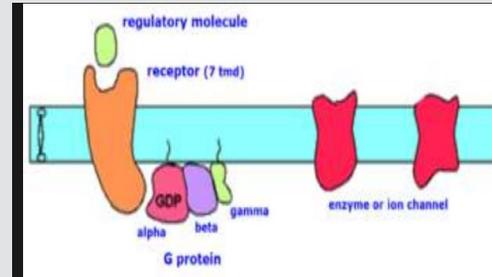
## SLC6A4 Serotonin Transporter Gene

- Located on chromosome 17
- Structure: contains 14 exons (21 kb)
- Function: gene codes for the Serotonin Transporter which is responsible for reuptake of serotonin from the synapse
- Altered SLC6A4 expression leads to reduced serotonin reuptake
- Most clinical studies focused on 5-HTTLPR
- Length variation polymorphism generates 2 alleles:
  - Long form (L)
  - Short form (S)



## 5-HTR2A Serotonin Receptor Gene

- The main serotonin Receptor:
  - post-synaptic excitatory
  - coupled with G-protein signaling cascades
- Polymorphisms result in tendency for variable responses to some SSRIs and SNRIs (e.g. citalopram – most studied)
- SNP rs7997012 G>A and rs6313 T>C
  - AA or CC genotype → tendency for increased response
    - especially in Caucasians,
    - but not as significant in Asians



*(review by Reyes-Barron et al, Clin Depress 2016, 2:2)*

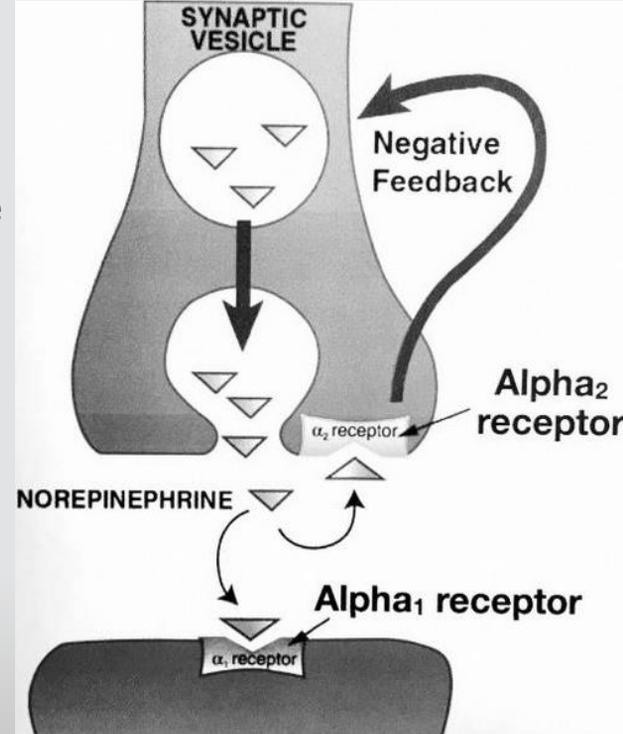
# ADHD related: COMT-Catechol- O- Methyl Transferase

- Enzyme responsible for the degradation of dopamine in the prefrontal cortex
- **Val/Val Genotype-**
  - Faster than normal COMT genotype
  - Lower dopamine in the synapse-
  - May use Dopaminergic agents
- **Val/Met-Intermediate Activity**
- **Met/Met Genotype-**
  - Slower than normal COMT genotype
  - Large amounts of dopamine in the synapse
  - Caution with Dopaminergic agents
  
- 1. Hamidovic, A., et al., *Psychiatric Genetics*, 2010
- 2. Shield, A.J., et al., *Molecular Psychiatry*, 2004

# ADRA2A- Alpha-2A Adrenergic Receptor

- This gene codes for the ADRA2A which binds pre-synaptically norepinephrine in the prefrontal cortex
- Receptor involved in neurotransmitter release
- 1291G>C
  - C/C Reduce response to Methylphenidate
  - G alleles carriers had greater improvement of inattentive symptoms with Methylphenidate treatment compared with C-allele

(1. Polanczyk G et al., Arch Gen Psychiatry, 2007  
2. da silva TL et al, Journal of neural transmission, 2008)



# #7 Do genes tell the whole story in terms of medication metabolism and efficacy?

- NO...and therein lies part of the problem....

## Environmental (non-genetic) factors involved with drug response

- Individual health variables
  - liver function, renal function, age, weight
- Behavioral variables
  - compliance, alcohol use, tobacco, diet
- Additional variables
  - Co-administration of other medications which alter pH, or cause interactions due to inducing or inhibiting enzyme activity

## And epigenetic factors also determine gene outcome and pharmacogenomic testing cannot address those

- Huntington's gene
- BRCA2 testing
- Ex., the BRCA1 : increases risk 12 percent to 55-65%
- BRCA2: increases risk to 45% by age 70
- IN men, increases risk by 10%
- But its not 100%
- Gene testing often confers vulnerability rather than outcome

## #8 What do results look like and how do you best interpret and apply the results?

- Most commercially available gene panels are categorized by disorder (e.g., ADHD panel, depression panel, pain panel)
- The report will contain the specifics on which genes are being tested, what is the finding for each gene, and what is the possible clinical implication
- Then relevant medications will be listed in categories of green, yellow, red based on a summation of risk from the gene findings
- REMEMBER that genes tell you about vulnerability and possible risk
- They do NOT predict outcome
- It is important to review that with patients and families

# Case 1

- 12 year old male with symptoms of ADHD currently in 6th grade
  - Diagnosis supported by Vanderbilt results
  - 504 in place
  - No other stressors noted
  - Symptoms significantly affecting school performance and self-esteem
- Medication trials
  - Lisdexamfetamine 30 mg
    - Irritability, insomnia, and anxiety
  - Atomoxetine 60 mg
    - Headache, fatigue, palpitations, tremor, dizziness

Report Date:  
Clinician:  
Reference:



Questions? Call 855.891.9415 or  
email [medinfo@assurexhealth.com](mailto:medinfo@assurexhealth.com)

## PATIENT GENOTYPES AND PHENOTYPES

### PHARMACODYNAMIC GENES PD

COMT VAL/VAL	High Activity	ADRA2A G/G	Typical Response
This patient is homozygous for the Val allele of the Val158Met polymorphism in the catechol-o-methyltransferase gene. Carriers of this genotype are more likely to have a typical response to stimulant medications.		This patient is homozygous for the G allele of the -1291G>C polymorphism in the adrenergic alpha-2A receptor gene. This genotype suggests a typical response to certain ADHD medications.	

### PHARMACOKINETIC GENES PK

<b>CYP2D6</b> *4/*17		<b>Poor Metabolizer</b>
CYP2D6*4 allele enzyme activity: None CYP2D6*17 allele enzyme activity: Reduced		
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.		

Report Date:  
Clinician:  
Reference:



Questions? Call 855.891.9415 or  
email [medinfo@assurexhealth.com](mailto:medinfo@assurexhealth.com)

### USE AS DIRECTED

**dexamethylphenidate** (Focalin®)  
**guanfacine** (Intuniv®)  
**methylphenidate** (Ritalin®,  
Concerta®, Metadate®, Daytrana®)

### MODERATE GENE-DRUG INTERACTION

**amphetamine salts** (Adderall®) 1  
**dextroamphetamine** 1  
(Dexedrine®)  
**lisdexamfetamine** (Vyvanse®) 1

### SIGNIFICANT GENE-DRUG INTERACTION

**clonidine** (Kapvay®) 1  
**atomoxetine** (Strattera®) 1,5

### CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required

5: CYP2D6 genotype indicates that this patient may experience increased side effects, but also increased efficacy

# Outcome

- Patient placed on methylphenidate with good effects
- 504 plan in place
- Therapy in place

# Atomoxetine: an example of a medication with FDA labeling about PK gene activity

- Concomitant Use with Strong CYP450 2D6 Inhibitor or in CYP450 2D6 Poor Metabolizers (PMs):
  - 70 kg or Less: 0.5 mg/kg/day; only increase dose to 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well-tolerated.
  - Over 70 kg: 40 mg/day; only increase dose to 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well-tolerated.

## Case #2

- 15 year old who presents with a 6 month history, gradual worsening of the following symptoms
  - Excessive Worry
  - Depressed mood with poor motivation
  - Poor sleep, energy and concentration
  - Social and academic worry and decline
  - Anhedonia
  - School Avoidance
  - Irritability
- Due to parents request for testing, PRIOR to any medication prescribed, genomic testing was ordered
- IEP requested and referral to therapy also done

DOB:  
Order Number:  
Report Date:

Clinician:  
Reference:

Questions? Call 855.891.9415 or  
email [medinfo@assurexhealth.com](mailto:medinfo@assurexhealth.com)

## PATIENT GENOTYPES AND PHENOTYPES



### PHARMACOKINETIC GENES

PK

#### CYP1A2 Extensive (Normal) Metabolizer

-163C>A - C/A, 5347C>T - C/T

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### CYP2B6 Intermediate Metabolizer

\*1/\*6

CYP2B6\*1 allele enzyme activity: Normal  
CYP2B6\*6 allele enzyme activity: Reduced

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.

#### CYP2C19 Extensive (Normal) Metabolizer

\*1/\*1

CYP2C19\*1 allele enzyme activity: Normal  
CYP2C19\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### CYP2C9 Intermediate Metabolizer

\*1/\*2

CYP2C9\*1 allele enzyme activity: Normal  
CYP2C9\*2 allele enzyme activity: Reduced

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.

#### CYP3A4 Extensive (Normal) Metabolizer

\*1/\*1

CYP3A4\*1 allele enzyme activity: Normal  
CYP3A4\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### CYP2D6 Extensive (Normal) Metabolizer

\*2A/\*9

CYP2D6\*2A allele enzyme activity: Increased  
CYP2D6\*9 allele enzyme activity: Reduced

This genotype is most consistent with the extensive (normal) metabolizer phenotype.

#### UGT1A4 Extensive (Normal) Metabolizer

\*1/\*1

UGT1A4\*1 allele enzyme activity: Normal  
UGT1A4\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

#### UGT2B15 Extensive (Normal) Metabolizer

\*1/\*1

UGT2B15\*1 allele enzyme activity: Normal  
UGT2B15\*1 allele enzyme activity: Normal

This genotype is most consistent with the extensive (normal) metabolizer phenotype. The patient is expected to have normal enzyme activity.

DOB:  
Order Number:  
Report Date:

Clinician:  
Reference:



Questions? Call 855.891.9415 or  
email [medinfo@assurexhealth.com](mailto:medinfo@assurexhealth.com)

## PATIENT GENOTYPES AND PHENOTYPES



### PHARMACODYNAMIC GENES

PD

<b>SLC6A4</b> L/L <p>This patient is homozygous for the long promoter polymorphism of the serotonin transporter gene. The long promoter allele is reported to express normal levels of the serotonin transporter. The patient is predicted to have a normal response to selective serotonin reuptake inhibitors.</p>	<b>Normal Response</b>	<b>HLA-B*1502</b> Not Present <p>This patient does not carry the HLA-B*1502 allele or a closely related *15 allele. Absence of HLA-B*1502 and the closely related *15 alleles suggests lower risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.</p>	<b>Lower Risk</b>
<b>HTR2A</b> G/A <p>This individual is heterozygous for the G allele and A allele of the -1438G&gt;A polymorphism for the Serotonin Receptor Type 2A. They have one copy of the G allele. This genotype is not predictive of adverse drug reactions with selective serotonin reuptake inhibitors.</p>	<b>Normal Sensitivity</b>	<b>HLA-A*3101</b> A/A <p>This patient is homozygous for the A allele of the rs1061235 A&gt;T polymorphism indicating absence of the HLA-A*3101 allele. This genotype suggests a lower risk of serious hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms when taking certain mood stabilizers.</p>	<b>Lower Risk</b>

DOB:  
Order Number:  
Report Date:

Clinician:  
Reference:



Questions? Call 855.891.9415 or  
email [medinfo@assurexhealth.com](mailto:medinfo@assurexhealth.com)

## ANTIDEPRESSANTS

### USE AS DIRECTED

**amitriptyline** (Elavil®)  
**citalopram** (Celexa®)  
**clomipramine** (Anafranil®)  
**desipramine** (Norpramin®)  
**desvenlafaxine** (Pristiq®)  
**doxepin** (Sinequan®)  
**duloxetine** (Cymbalta®)  
**escitalopram** (Lexapro®)  
**fluvoxamine** (Luvox®)  
**imipramine** (Tofranil®)  
**levomilnacipran** (Fetzima®)  
**mirtazapine** (Remeron®)  
**nortriptyline** (Pamelor®)  
**paroxetine** (Paxil®)  
**sertraline** (Zoloft®)  
**trazodone** (Desyrel®)  
**venlafaxine** (Effexor®)  
**vilazodone** (Viibryd®)  
**vortioxetine** (Trintellix®)

### MODERATE GENE-DRUG INTERACTION

**bupropion** (Wellbutrin®) 1  
**fluoxetine** (Prozac®) 1  
**selegiline** (Emsam®) 1

### SIGNIFICANT GENE-DRUG INTERACTION

## CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.

## *Treatment Course*

- Adequate tolerated trials with limited efficacy
  - Escitalopram
  - Fluoxetine
  - Sertraline
  - Venlafaxine
- Continued to refuse individual therapy.
- Mother refused in home services and did not want him in a clinical day school
- Patient refused IOP
- Frequent cancellations
- Sometimes a lack of efficacy it NOT related to genomics

## #9 How do the labs know which medication is metabolized by which enzymes?

- FDA requires that information on all medications which come to market; part of the approval process
- Flockhardt chart exists that summarizes all existing medications and the enzyme pathways which metabolize them
- It also includes which medications additionally inhibit or induce the enzyme activity
- Along with the data on the PD genes, and through some internal algorithm, the red, yellow, green categories are generated

# #10 When or should a clinician order this testing?

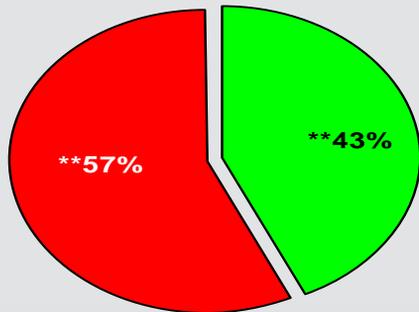
- Depends in part with your comfort on the interpretation of the results
- Remember: it is NOT standard of care to order this testing
- Remember medical school rule: do not order any test if you are not sure how to interpret the results.... 😊
- But families may bring the testing to you...

# A brief look at our experience at the IOL and relevant research

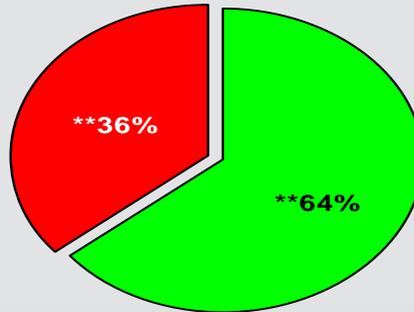
# Combinatorial Carrier Prevalence

## *CYP2C9 + CYP2C19 + CYP2D6*

Institute  
of Living  
A Division of Hartford Hospital



IOL  
*Psych Referrals*



HH  
*Cardiology*

Deficiencies

- 0 or 1 gene
- 2 or 3 genes

Ruaño, Goethe et al, *Personalized Medicine* 2008



# Antidepressant-Induced Mood Dysregulation and Its Association with CYP450 Enzyme Alterations

Lisa Namerow<sup>1</sup>, M.D., Allana Lee<sup>1</sup>, D.O.; David Villagra<sup>2</sup>, B.A.; Andreas Windemuth<sup>2</sup>, Ph.D.; Gualberto Ruaño<sup>2</sup>, M.D., PhD

<sup>1</sup> Institute of Living, Hartford Hospital, Hartford, CT, United States

<sup>2</sup> Genetics Research Center, Hartford Hospital and Genomas Inc., Hartford, CT, United States



Dr. Ruaño, Dr. Windemuth and Mr. Villagra are full-time employees of Genomas Inc. Dr. Namerow and Dr. Lee have no disclosures

**Objective:** To examine the association between cytochrome P450 enzyme deficiencies and the clinical finding of antidepressant-induced mood dysregulation in patients treated for major depressive disorder (MDD) or Depressive Disorder, NOS. We hypothesized that patients with reduced drug metabolism capacity may be susceptible to higher vulnerability for "bipolar" type responses (i.e., what has been called Bipolar III) when "challenged" with an antidepressant secondary to ineffective CYP450 activity altering antidepressant or endogenous neurotransmitter metabolism.

**Background:** Bipolar III, although not a DSM-IV recognized term, has been used both in children and adults to convey the presence of a state of mood dysregulation, induced by antidepressant therapy. The progress of genomic technologies have enabled clinicians to assess for polymorphisms relevant to drug metabolism in the CYP450 enzyme system (Figure 3). Given that most antidepressants are metabolized through one of the main CYP450 isoenzymes, we sought to determine whether children and adolescents in our practice who developed mood dysregulation when treated with an antidepressant (Bipolar III) were genotypically more likely to have CYP450 enzyme irregularities than patients who tolerated antidepressants without any induction of mood dysregulation. If found, this association between genotype and phenotype would have significant clinical implications for pharmacotherapy in child and adolescent psychiatric patients.

**Method:** Sixty-nine (69) patients who were referred to our outpatient child and adolescent practice at the Institute of Living were selected to undergo CYP testing either due to psychiatric complexity and/or a history of medication intolerance. DNA samples were extracted from whole blood from each patient and genotyped to detect 34 allelic variations in the genes CYP2C9, CYP2C19, and CYP2D6. Without knowing the CYP450 findings, we identified 13 patients of that group who were referred for this testing primarily because they had exhibited an exacerbation of mood dysregulation in response to an antidepressant trial. None of these patients carried a bipolar diagnosis prior to being treated with an antidepressant. We identified those patients as "Bipolar III" and compared their 2450 findings with the other patients of the P450-tested group who had not exhibited mood dysregulation symptoms and had been referred for the testing due to other reasons. Thus, 13 patients were in the Bipolar III group and 56 patients were in the Non Bipolar III, control group. Using a case control approach, we tested for differences between the groups with respect to quantitative drug metabolism status as defined by individual gene alterations and by a combined Gene Alteration Index (cumulative deviation from functional status across the 3 genes).

**Results:** After correcting for covariates, we found that patients with an alteration index of 2 or 3 compared to those with an index of 0 or 1 were disproportionately represented in the mood dysregulation or Bipolar III group versus the Non Bipolar III group (77% vs. 36%,  $p = 0.017$ ). Among the 3 genes, CYP2C9 evidenced the most contrast, with 77% altered in the symptom group versus 34% functional in the group without the symptom ( $p = 0.012$ ). In particular, the CYP2C9\*2 and CYP2C9\*3 allele frequencies were 31% and 12% in the diagnosed group as opposed to 11% and 7% in the non-diagnosed group, respectively ( $p < 0.001$ ). Figure 1 highlights the marked difference in CYP2C9 gene functionality between the diagnosed and non-diagnosed populations. Figure 2 illustrates the differences in the combinatorial gene alterations between the bipolar III group (77% 2 or 3 genes altered as shown in yellow and red) vs. the non-bipolar III group (36% 2 or 3 non-functional genes). Figure 4 represents the specific combinatorial gene alterations, demonstrating the CYP2C9 and CYP2D6 combination to be particularly elevated in the Bipolar III group ( $p < 0.001$ ).

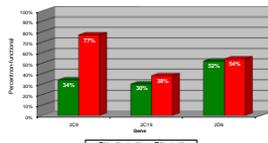


Figure 1: Percent non-functional CYP450 genes (CYP2C9, CYP2C19, CYP2D6) across two cohorts. Notice elevated CYP2C9 deficiencies.

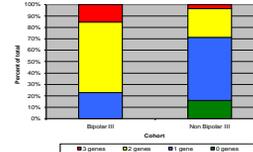


Figure 2: Combinatorial percent of non-functional CYP450 (CYP2C9, CYP2C19, CYP2D6) genes across two cohorts.

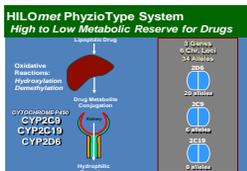


Figure 3: Biochemical rationale and molecular summary for the HiLOmer PhysioType System used for CYP450 DNA typing in this study.

**Conclusions:** Altered CYP450 combinatorial genotypes are significantly enriched in patients evidencing mood dysregulation in child and adolescent psychiatric patients treated for depression. In adult studies, there has been an indication that CYP2C9 is associated with mood severity and our study seems to provide further evidence of that significant association. The results also suggest that high-resolution combinatorial CYP450 genotyping can be utilized to benchmark the innate hepatic drug metabolism reserve of the patient and also provide a potential marker for severity of mood disorder and antidepressant-induced mood dysregulation in children and adolescent psychiatric patients.

#### References:

Aiskal HS, Hantouche EG, Alliaire JF, et al: Validating antidepressant-associated hypomania (bipolar III): a systematic comparison with spontaneous hypomania (bipolar II). *J Affect Disord* 2003; Jan;73(1-2):65-74

Ruaño G, Villagra D, Rahim US, Windemuth A, Kocherik M, Bower B, Szarek BL, Goethy JW. Increased Carrier Prevalence of Deficient CYP2C9, CYP2C19 and CYP2D6 Alleles in Depressed Patients Referred to a Tertiary Psychiatric Hospital. *Personalized Medicine* 5 (6): 579-587, 2008

Hindset M, Møldén E, Refsum H, Herrmann M: Impact of CYP2D6 Genotype on Steady-State Serum Concentrations of Risperidone and 9-Hydroxyrisperidone in Patients Using Long-Acting Injectable Risperidone. *Journal of Clinical Psychopharmacology*, 29 (6): 537-541, 2009

Llerena A, Berezic R, Dorado P, Gonzalez AP, Penas-Llado EM, De La RA: CYP2C9 gene and susceptibility to major depressive disorder. *Pharmacogenomics* J, 9, 300-2 (2008).

Lalka B, Leucht S, Heres S, Steimer W: Intermediate metabolizer: increased side effects in psychotropic drug therapy. The key to cost-effectiveness of pretestament CYP2D6 screening? *Pharmacogenomics* J, 9, 395-403 (2009).

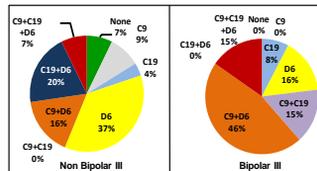
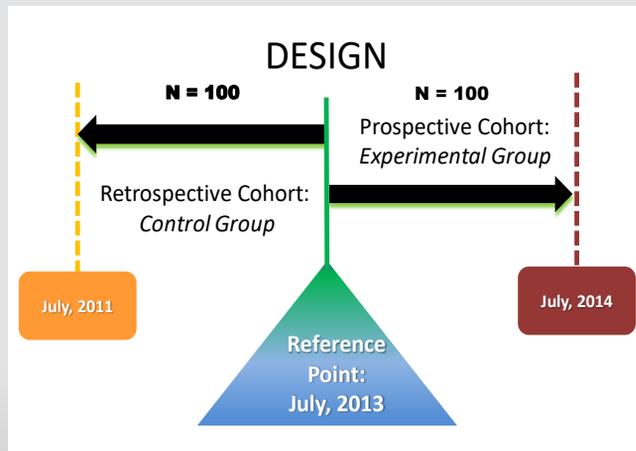


Figure 4: Differences in combinatorial gene deficiencies between the two cohorts. Notice elevated CYP2C9/CYP2D6 combined deficiencies in Bipolar III patients.

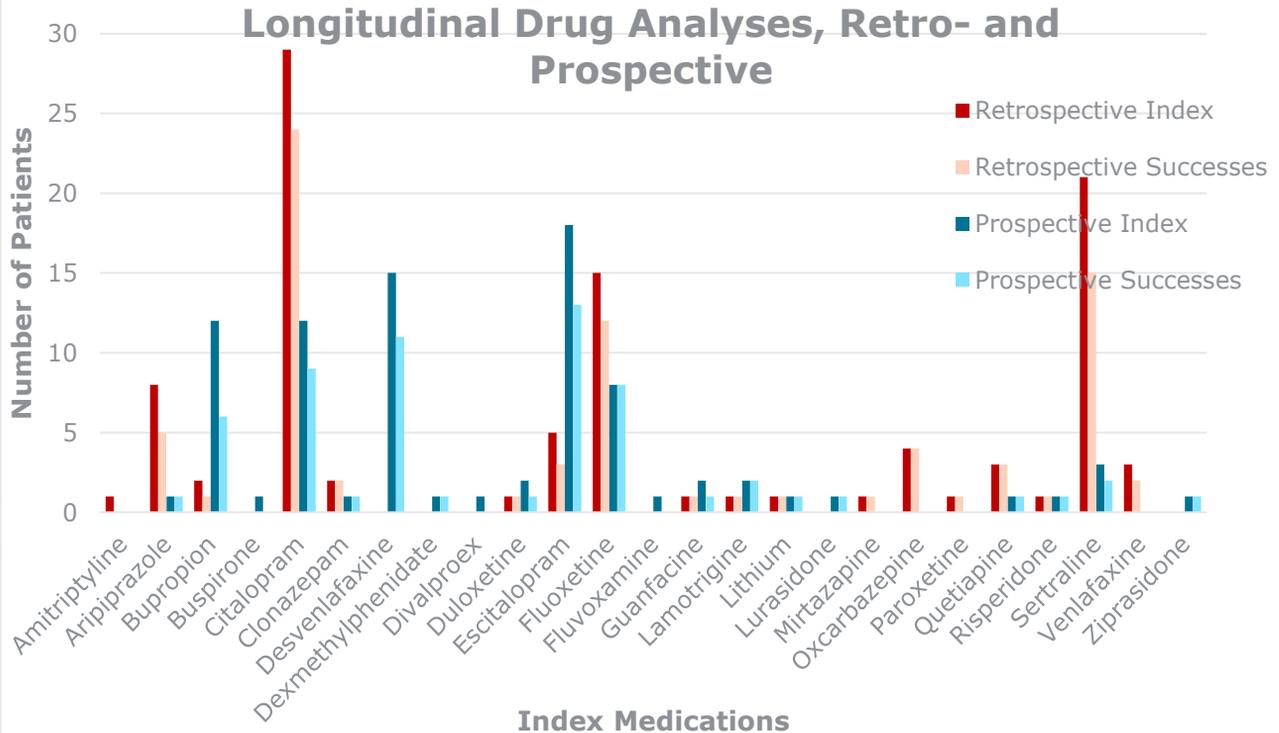
# Enhancing Pediatric Depression treatment Using p450 guidance (Namerow, Ruano, Stevens, Kesten, 2016)



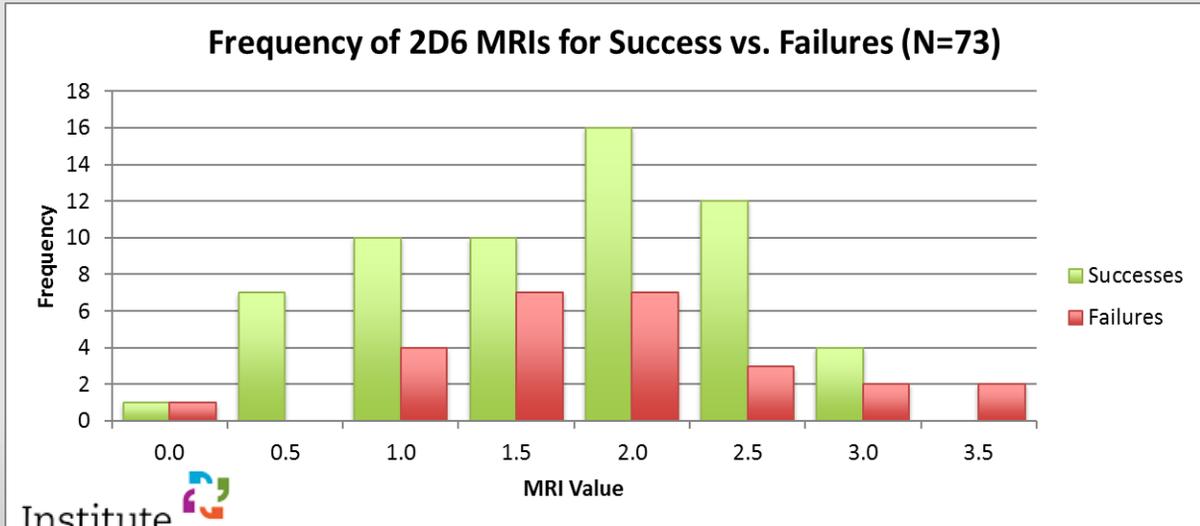
# A brief look at the results

- No significant difference between the retrospective and prospective group in primary outcome variable, medication discontinuation
- Retrospective group: 20% discontinuation
- Prospective group: 17%
- We took “On index med at 4 months” to be an indicator of both tolerance and efficacy so our overall discontinuation rate seemed very low for both groups
- Important to note: patients in the retrospective group had a history of medication intolerance which then might have guided medication selection even without genomic guidance
- We did find a couple other interesting things....

# Medication retention and impact of guidance on medication selection



# The greater the 2D6 vulnerability, the greater the impact of p450 guidance



Institute  
of Living



A Division of Hartford Hospital

# Evidence for pharmacokinetic genes guiding dosing and selection of SSRIs

- Clinical Pharmacogenetics Implementation Consortium CPIC guidelines (Clinical Pharmacology and Therapeutics, May, 2015)
- Paxil (2D6), Fluvoxamine (2D6)
- Celexa (2C19), Zoloft (2C19)

# Dosing recommendations from the CPIC guidelines (2C19)

Likely phenotype	Genotypes	Examples of CYP2C19 diplotypes	Implications for citalopram/escitalopram metabolism	Therapeutic Recommendations	Classification of recommendations <sup>a</sup>
Ultrarapid metabolizer <sup>b</sup> (~5-30% of patients)	An individual carrying two increased function alleles or one normal function allele and one increased function allele	*17/*17, *1/*17	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19. <sup>c</sup>	Moderate
Extensive metabolizer (~35-50% of patients)	An individual carrying two normal function alleles	*1/*1	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
Intermediate metabolizer (~18-45% of patients)	An individual carrying one normal function allele or one increased function allele and one no function allele	*1/*2, *1/*3, *2/*17 <sup>d</sup>	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
Poor metabolizer (~2-15% of patients)	An individual carrying two no function alleles	*2/*2, *2/*3, *3/*3	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction <sup>e,f</sup> of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19. <sup>c</sup>	Moderate

## How does a clinician possibly review the literature?: A look at the 3 major research designs

- Looking at impact of combined panel of PK and PD genes on depression treatment outcome
- Within depression studies, looking genome wide to see if any genes are relevant to treatment outcome (GWS studies)
- Pairing polymorphisms to medication/treatment outcome

## Clinical Validity: Combinatorial pharmacogenomics predicts antidepressant response and health utilization better than single gene phenotypes (Altar et al, 2015)

- Panel included 3 pharmacokinetic genes 2D6, 2C19, CYP2D6 and other two molecules are SLC6A4 (the serotonin transporter gene) and HTR2A (the serotonin 2A receptor gene).
- Ham-D outcomes
- Hamm clinic
- Pine Rest
- Internal algorithm that drives the relative contribution of each finding and provides the clinician with a red-yellow-green outcome for relevant medications

## Carlat report concerns (Carlat, 2015)

- Industry open label studies are vulnerable to bias
- Patients were not assigned to groups randomly
- Patients who knew their treatment was guided, might have had an increased placebo effect
- Prescribers knew which patients were being guided by the test, potentially leading to the “cheerleader effect.
- Raters knew which patients were in which group, potentially leading to biased ratings
- Conclusion: possible role for patients with a history of unusual side effects

## Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: randomized double blind clinical trial (Perez et al., 2017)

- N=280 (PGx guided-136; unguided-144)
- Higher responder rate among PGx guided group
- Lower FIBSER scores (side effect scale)
- Genes studied: 30 PK and PD genes
- Ham-D outcomes measured
- CGI-I (primary variable): patient reported
- Again, Industry-supported

## Evidence for pharmacodynamic genes and medication response

- Meta-analysis association of 5-HTTLPR (s/s and s/l) (serotonin transporter gene) with SSRI efficacy measured by response rate within 4 weeks (Seretti et al., Molecular Psychiatry, 2007)
- Clinical validity of P450 and serotonin gene variants in psychiatric pharmacotherapy (extensive review by Altar et al., 2013)
- Common Genetic Variation and Antidepressant Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Genome-Wide Pharmacogenetic Studies (Am Journal of Psychiatry, 2013)

Institute  
of Living

A Division of Hartford Hospital

## Genome-wide studies (GSW): Common Genetic Variation and Antidepressant Efficacy in Major Depressive Disorder: A Meta-Analysis of Three Genome-Wide Pharmacogenetic Studies (Am Journal of Psychiatry, 2013)

- GENDEP (Genome-Based Therapeutic Drugs for Depression): 12-week multicenter pharmacogenetic trial of escitalopram vs. nortriptyline (N=706)
- MARS (Munich Antidepressant Response Signature): naturalistic inpatient study study (n=604)
- STAR\*D (Sequenced Treatment Alternatives to Relieve Depression): pragmatic trial of protocol guided outpatient treatment study

## GWS studies (cont'd)

- Limited the analysis to citalopram and escitalopram looking at gene associations with outcomes
- No significant findings were reported
- Often cited as evidence that there are “no reliable predictors of antidepressant outcome”
- In GWS, the detection of complicated polymorphisms may be compromised

## Take home points

- KEY: Be discerning and know what you are ordering
- Know what panels include which genes
- Remember that pharmacokinetic genes are most likely to determine tolerance whereas pharmacodynamic genes have the potential to confer response/efficacy
- Even though the results might be conveyed in terms of which medications are green, yellow, or red, consider looking at each gene result individually to familiarize yourself with how the medications have been placed into each category

## Take home points: Consider the concept of vulnerability/risk

- Do not oversell impact of testing to patients and families
- Remember that genetic contribution to medication tolerance/response/efficacy is about 42%
- Consider the following script: “This testing does NOT tell me which medication your child will respond to but it may, in conjunction with evidence based recommendations, help me to select a medication that reduces the chance of untoward side effects and increases the chance of response”.

## Consider possible screening questions to determine need for testing: seeking reactions to 2D6 substrates

- Has your child ever had a negative reaction to a pain medication? If so, which one?
- Has your child ever had a negative or strange reaction to a medication used for psychiatric conditions?
- Has your child every had a bad reaction to cold or cough medication? If so which one? (?DXM)
- Has any parent or first degree family member had any usual or strange reaction to either pain or psychiatric medications?

## Lots to learn and consider

- Over the next decade: need more pediatric studies
- Adult data data does not suggest that everyone should be tested: high expense and low yield
- However, any patient presenting with a history suggest of medication intolerance and a positive family history of such, pharmacogenomic testing might play a role
- The challenge for clinicians is how to know enough about the testing to be able to best apply the results

# Thoughts/comments/questions?



[This Photo](#) by Unknown Author is licensed under [CC BY](#)