Pharmacogenomic Testing: Utility for Psychotropic Medication Management

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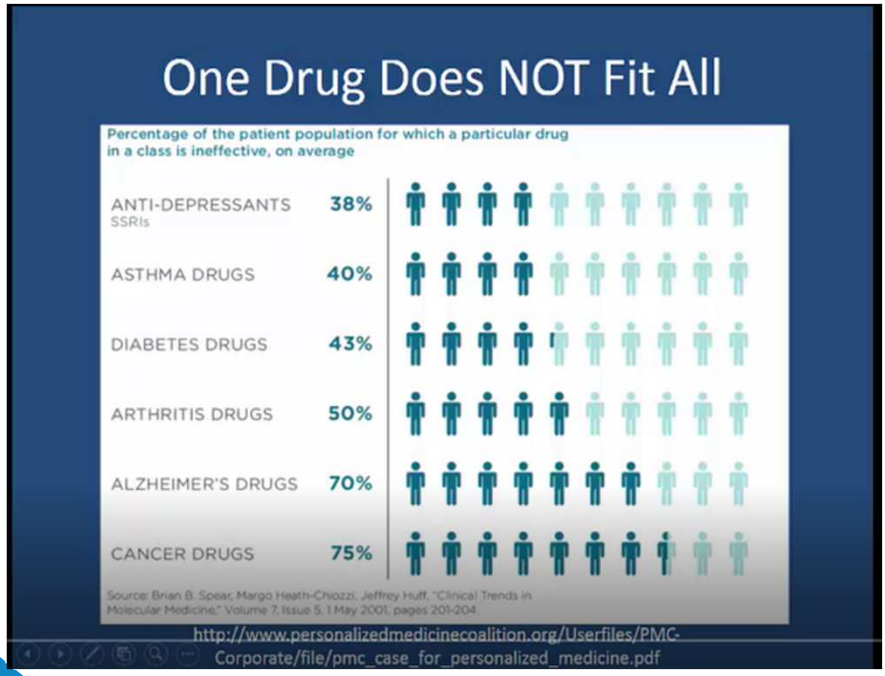
Objectives

1. Review the Fundamentals of Pharmacogenomics
2. Navigate Evidence-Based Pharmacogenomic References for Psychotropic Medication Classes
3. Use evidence-based PGx information to guide medication changes/dosing for psychiatric cases

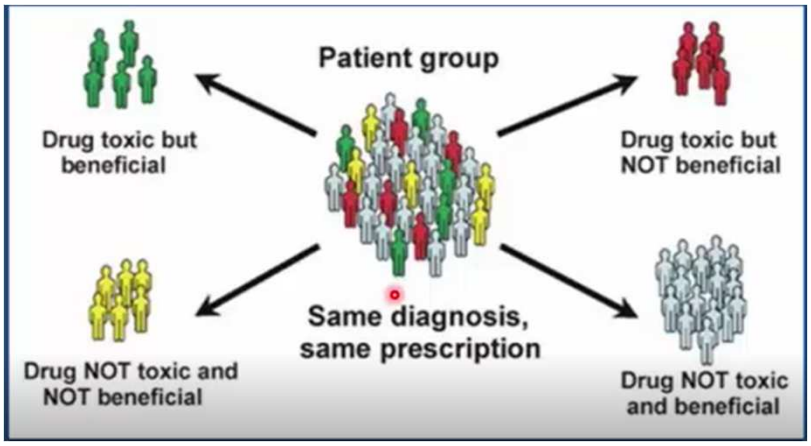
Era of Precision Medicine

- Tailor medical treatments to individual needs , characteristics, and patient preferences
- **Pharmacogenomics:** using genetic information to guide drug dosing and selection
  - Goals: Maximize Efficacy Reduce Adverse Events
  - Studies of whole genomes and variations (SNPs > 1% pop) vs pharmacogenetics (single genes)
- Another tool for treatment success
  - **Patient specific factors, concurrent medications MUST be taken into consideration**

AHRQ, publication 01-0020, 9/24/2013;www.uptodate.com

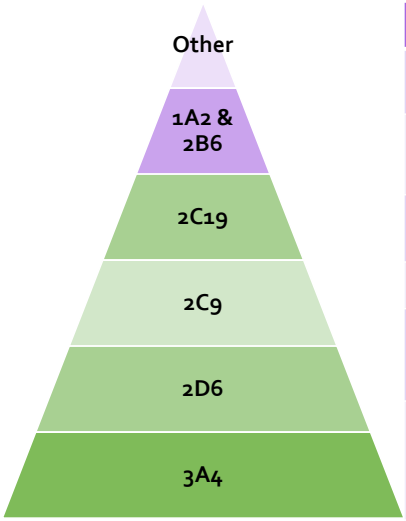


PGX FUNDAMENTALS



http://pharmainfo.net/role-pharmacogenetics

CYP450 Enzymes: major system for oxidative metabolism of medications. Currently 58 different human CYP genes with various isoenzymes



Enzyme	Drug Classes
Other	Acetaminophen, anesthetics, chemotherapy
1A2 & 2B6	Antipsychotics, bupropion, caffeine, chemotherapy, naproxen
2C19 (10%)	Antidepressants, chemotherapy, clopidogrel, phenytoin, PPIs
2C9 (10%)	ARBs, diabetic agents, NSAIDs, warfarin
2D6 (25-30%)	Analgesics, antidepressants, antipsychotics, beta blockers, metoclopramide, ondansetron, tamoxifen
3A4 (50%)	Analgesics, antibiotics, anti-emetics, antipsychotics, benzodiazepines, calcium channel blockers, HIV medications, statins, steroids

Zhou SF et al. CurrDrug Metab2008;9(8):738.

Major Pharmacogenetic Changes

Decreased/Increased metabolizing enzyme function

- Decreased/Increased enzyme efficiency
- Decreased/Increased enzyme affinity
- Non-functional enzymes
- Multiple copies of the gene (duplications xN)

- **Reduced/increased binding of the drug to its receptor**
  - ADHD, depression, pain, neurology, chemo targets

- **Effects on idiosyncratic reactions, such as the likelihood of a hypersensitivity reaction to a certain drug.**
  - i.e. HLA hypersensitivity for neuroleptic agents

Other Factors Associated with Drug-Gene Response

Intrinsic Factors

- Age
- Sex
- Genetics
- Organ Function
- Disease States

Extrinsic Factors

- Smoking
- Alcohol
- Phenoconversion: Drug-Drug-Gene Interaction

Considerations for Drug-Drug-Gene Interactions

Strong CYP2D6 Inhibitors	Strong CYP2D6 Inducers
Fluoxetine, paroxetine, bupropion, duloxetine (moderate), sertraline (moderate)	Carbamazepine, phenytoin
Strong CYP2C19 Inhibitors	**Strong CYP2C19 Inducers**
Fluoxetine, fluvoxamine, fluconazole, proton pump inhibitors	Rifampin, phenobarbital, primidone
Strong CYP3A4 Inhibitors	**Strong CYP3A4 Inducers**
Antifungals (fluconazole), anti-retrovirals , nefazodone, amiodarone, diltiazem, verapamil	Phenytoin, rifampin, phenobarbital, primidone

Examples of CYP2D6 Allele Frequencies in Different Populations

Variant Allele	Consequence	Allele Frequency Caucasians	Allele Frequency Asians	Allele Frequency Africans
CYP2D6*2xN	Increased activity	1-5%	0-2%	2%
CYP2D6*4	Nonfunctional	12-21%	1%	2%
CYP2D6*5	Nonfunctional	27%	6%	4%
CYP2D6*10	Reduced function	1-2%	51%	6%
CYP2D6*17	Reduced function	0%	0%	20-35%
CYP2D6*41	Reduced function	8-10%	0-2%	11-14%

Frequency of poor metabolizer phenotype: Caucasians (5-10%), African (5%), Asian (1%)

Clin Pharmacol Ther 2013; 94:317-323

Examples of CYP2C19 Allele Frequencies in Different Populations

Variant Allele	Consequence	Frequency Caucasians	Frequency Asians	Frequency Africans
CYP2C19*2	Loss-of-function	12-15%	29-35%	15%
CYP2C19*3	Loss-of-function	<1%	2-8%	<1%
CYP2C19*17	Gain-of-function	18-21%	3%	16%

- Frequency of poor metabolizer phenotype: Caucasians (2%), Africans (4%), Asians (14%)
- Frequency of ultrarapid metabolizer phenotype: Caucasians (40%), Africans (45%), Asians (<5%)

Clin Pharmacol Ther 2013; 94:317-323

CPIC Term Standardization Project

Final Term	Function Definition	Genetic Definition	Examples of Diplotypes
Ultra-Rapid Metabolizer	Increase activity compared to rapid	2 increased function alleles or duplicate copies	CYP2C19*17*17 CYP2D6*1*1xN
Rapid Metabolizer	Increased activity	Combo of normal and increased function	CYP2C19*1*17
Normal Metabolizer	Fully Functional	Combo of normal and reduced function	CYP2D6*1*1 CYP2C9*1*1
Intermediate Metabolizer	Decreased activity	Combo of normal, decreased, or non-functional	CYP2C19*1*2 CYP2D6*1*41
Poor Metabolizer	Little to no activity	Combo of non-functional and/or decreased function	CYP2D6*3*4

CYP2D6—Clinical Example

- Codeine is a prodrug, codeine→morphine (active metabolite).
- CYP2D6 UMs rapidly metabolize codeine to morphine. Therefore, CYP2D6 UMs may have _____ efficacy and an _____ risk of adverse effects following codeine administration.

Slide Courtesy of Chris Aquilante

CYP2C19—Clinical Example

- Clopidogrel is a prodrug, clopidogrel→active metabolite.
- CYP2C19 PMs have an increased risk of adverse cardiovascular events and stent thrombosis versus EMs after clopidogrel administration.
  - WHY?
- Some data suggest CYP2C19 UMs have an increased risk of bleeding after clopidogrel administration.
  - WHY?

Slide Courtesy of Chris Aquilante

Studies have shown that CYP2C19 poor metabolizers have higher *H. pylori* cure rates than extensive metabolizers following omeprazole therapy. Provide a reason for this observation.

A. Reduced metabolism decreases the half-life of omeprazole resulting in better acid suppression
B. Reduced metabolism increases AUC (exposure) to the PPI resulting in better acid suppression
C. Omeprazole is a pro-drug
D. None of the above, there are not studies showing better cure rates of H. pylori based on pharmacogenomic data

Pharmacogenetic Psychotropic Panel:

- Categories of enzymes/receptors/transporters and associated medication classes for Depression, Anxiety, ADHD, Antipsychotics, Mood Stabilizers
- Categorizes medications into the Green , Yellow, Red
- Contains subscript text for further (minimal) information on the drug-gene interaction, FDA labelling. Does not give what dosing to use (CONSULT GUIDELINES)
- Does not take into account concurrent medications and drug-drug interactions or past med trials or smoking status
- Do not list Guideline LOA or SOR but does follow CPIC and PharmVAR guidelines

Reporting Variations

Green: (no significant drug-drug-gene interactions)

Yellow : (moderate drug-drug-gene interactions)

Red: (significant drug-drug-gene interactions)

Not always this simple. Often have to re-evaluate based on CPIC as well as concurrent medications and past trials

https://www.vectorstock.com/royalty-free-vector/stoplight-sign-vector-15452447

Example PGx Report

Antidepressants

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
desvenlafaxine (Pristiq®)	**levomilnacipran** (Fetzima®)	1	**bupropion** (Wellbutrin®)	1,6
selegiline (Emsam®)	**vilazodone** (Viibryd®)	1	**citalopram** (Celexa®)	1,6
sertraline (Zoloft®)			**escitalopram** (Lexapro®)	1,6
			fluoxetine (Prozac®)	1,6
			mirtazapine (Remeron®)	1,6
			trazodone (Desyrel®)	1,6
			venlafaxine (Effexor®)	1,6
			amitriptyline (Elavil®)	1,6,8
			clomipramine (Anafranil®)	1,6,8
			desipramine (Norpramin®)	1,6,8
			doxepin (Sinequan®)	1,6,8
			duloxetine (Cymbalta®)	1,6,8
			fluvoxamine (Luvox®)	1,6,8
			imipramine (Tofranil®)	1,6,8
			nortriptyline (Pamelor®)	1,6,8
			paroxetine (Paxil®)	1,6,8
			vortioxetine (Trintellix®)	1,6,8

Clinical Considerations

1: Serum level may be too high, lower doses may be required.
5: CYP2D6 genotype indicates that this patient may experience increased frequency of side effects but also greater symptom improvement in those who find the treatment tolerable.
6: Use of this drug may increase risk of side effects.
8: FDA label identifies a potential gene-drug interaction for this medication.
9: Per FDA label, this medication is contraindicated for this genotype.
10: While this medication does not have clinically proven genetic markers that allow it to be categorized, it may be an effective choice based on other clinical factors.

Anxiolytics and Hypnotics

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
eszopiclone (Lunesta®)	**alprazolam** (Xanax®)	1	**diazepam** (Valium®)	1,6
lorazepam (Ativan®)	**buspirone** (BuSpar®)	1	**propranolol** (Inderal®)	1,6,8
oxazepam (Serax®)	**chlordiazepoxide** (Librium®)	1		
temazepam (Restoril®)	**clonazepam** (Klonopin®)	1		
	clorazepate (Tranxene®)	1		
	zolpidem (Ambien®)	1		
	lemborexant (Dayvigo®)	1,8		
	suvorexant (Belsomra®)	1,8		

Antipsychotics

Use as Directed	Moderate Gene-drug Interaction		Significant Gene-drug Interaction	
thiothixene (Navane®)	**asenapine** (Saphris®)	1	**cariprazine** (Vraylar®)	1,6
	fluphenazine (Prolixin®)	1	**chlorpromazine** (Thorazine®)	1,6
	olanzapine (Zyprexa®)	1	**quetiapine** (Seroquel®)	1,6
	paliperidone (Invega®)	1	**aripiprazole** (Abilify®)	1,6,8
	ziprasidone (Geodon®)	1	**brexpiprazole** (Rexulti®)	1,6,8
	lumateperone (Caplyta®)	1,8	**clozapine** (Clozaril®)	1,6,8
	lurasidone (Latuda®)	1,8	**haloperidol** (Haldol®)	1,6,8
			iloperidone (Fanapt®)	1,6,8

CES1A1 — **Extensive (Normal) Metabolizer**
GLY/GLY
CES1A1 - Gly allele enzyme activity: Normal
CES1A1 - Gly allele enzyme activity: Normal
This genotype is most consistent with the extensive (normal) metabolizer phenotype. This patient is expected to have normal enzyme activity.

CYP1A2 — **Extensive (Normal) Metabolizer**
-163C>A - C/A, 5347C>T - C/T
This genotype is most consistent with the extensive (normal) metabolizer phenotype.

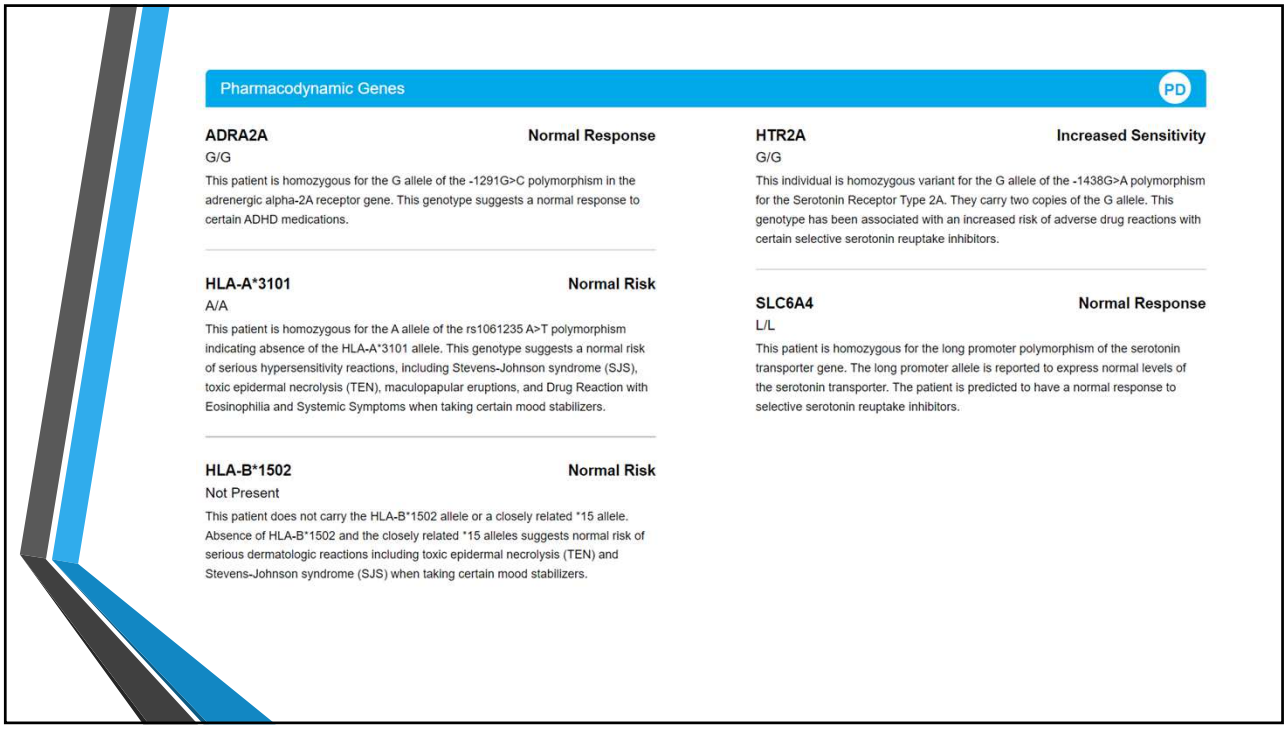
CYP2B6 — **Extensive (Normal) Metabolizer**
*1/*1
CYP2B6*1 allele enzyme activity: Normal
CYP2B6*1 allele enzyme activity: Normal
This genotype is most consistent with the extensive (normal) metabolizer phenotype.

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.

CYP2D6 — **Poor Metabolizer**
*5/*9
CYP2D6*5 allele enzyme activity: None
CYP2D6*9 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.

CYP3A4 — **Intermediate Metabolizer**
*1/*22
CYP3A4*1 allele enzyme activity: Normal
CYP3A4*22 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.

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.


Pharmacodynamic Genes
PD
ADRA2A
Normal Response
G/G
This patient is homozygous for the G allele of the -1291G>C polymorphism in the adrenergic alpha-2A receptor gene. This genotype suggests a normal response to certain ADHD medications.
HLA-A*3101
Normal Risk
A/A
This patient is homozygous for the A allele of the rs1061235 A>T polymorphism indicating absence of the HLA-A*3101 allele. This genotype suggests a normal 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.
HLA-B*1502
Normal Risk
Not Present
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 normal risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.
HTR2A
Increased Sensitivity
G/G
This individual is homozygous variant for the G allele of the -1438G>A polymorphism for the Serotonin Receptor Type 2A. They carry two copies of the G allele. This genotype has been associated with an increased risk of adverse drug reactions with certain selective serotonin reuptake inhibitors.
SLC6A4
Normal Response
L/L
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.


Interpreting the Literature
Evidence and Study Designs

Study Design in Pharmacogenomics

- Different needs and populations; will not typically have RCTs
- Most likely study design: Case-Control or Cohort
  - Observational vs Experimental
  - Identify patients from larger RCTs (parent study) match to control
  - Look at allele frequencies in patients who have the trait/outcome (phenotype) and compare to patients without the phenotype/outcome (control)

Genome-Wide Approach

- Investigate genetic variants across an entire genome and associate with phenotypic traits or disease
- Outcomes: determine if allele frequency is higher in case vs control
- P-values: High chances of false positives, require 100,0oos SNPs
  - Must apply stringent p value correction to minimize changes of false positives
- **Bonterroni Correction**: conventional p/ # SNP testing

  = 0.05/1 million = 5x 10-8 p-value

Limitations to GWAS

- Populations not controlled for different ancestry and SNPs associated with their genetics (confounders)
- Internal vs External Validity for pop variance
- Some difficult to replicate studies
- Selection bias
- Genotyping errors

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines

Gene(s):

- Background
- Genetic Test Interpretation
- Available Genetic Test Options
- Incidental findings
- Other considerations

Drug(s):

- Background
- Linking genetic variability to variability in drug-related phenotypes
- Dosage and/or Therapeutic Recommendations
- Recommendations for Incidental Findings
- Other Considerations

Clinical Pharmacogenetics Implementation Consortium (CPIC)
https://cpicpgx.org

Ex CYP2D6 and 2C19 CPIC Guidelines

CPIC® Guideline for Tricyclic Antidepressants and CYP2D6 and CYP2C19

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC®) for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Tricyclic Antidepressants: 2016 Update (December 2016)

CPIC® Guideline for Selective Serotonin Reuptake Inhibitors and CYP2D6 and CYP2C19

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (August 2015)

Pharmacogenomics Knowledge Base (PharmGKB)

- Comprehensive resource for impact of genetic variations on drug response
- Dosing Guidelines
- FDA and other Drug Labels
- Clinically Actionable Drug-Gene Associations
- Genotype-Phenotype Relationships
- Publishes Guidelines, summaries, and drug-centered pathway

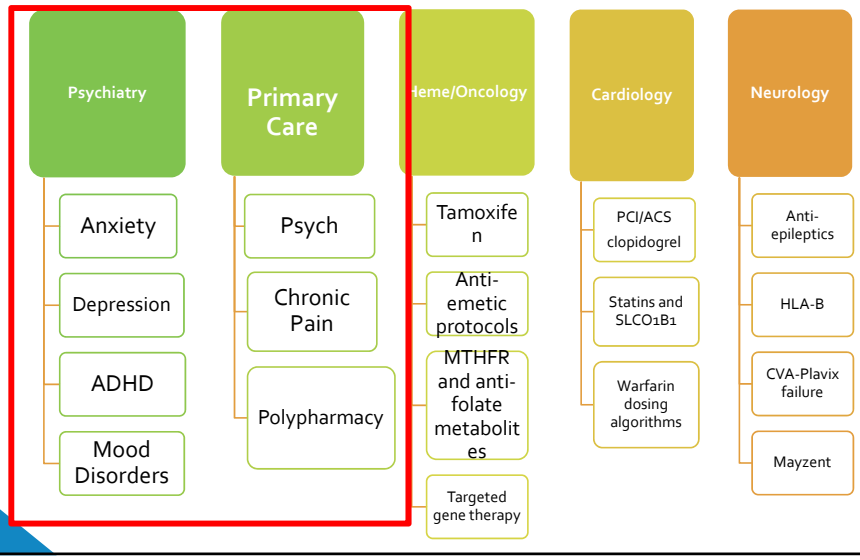
Pharmacogenomics Knowledge Base (PharmGKB)

www.pharmgkb.org

How are we doing ....

Considerations for Pharmacogenomic Testing

Major Classes of Medications Impacted by PGx

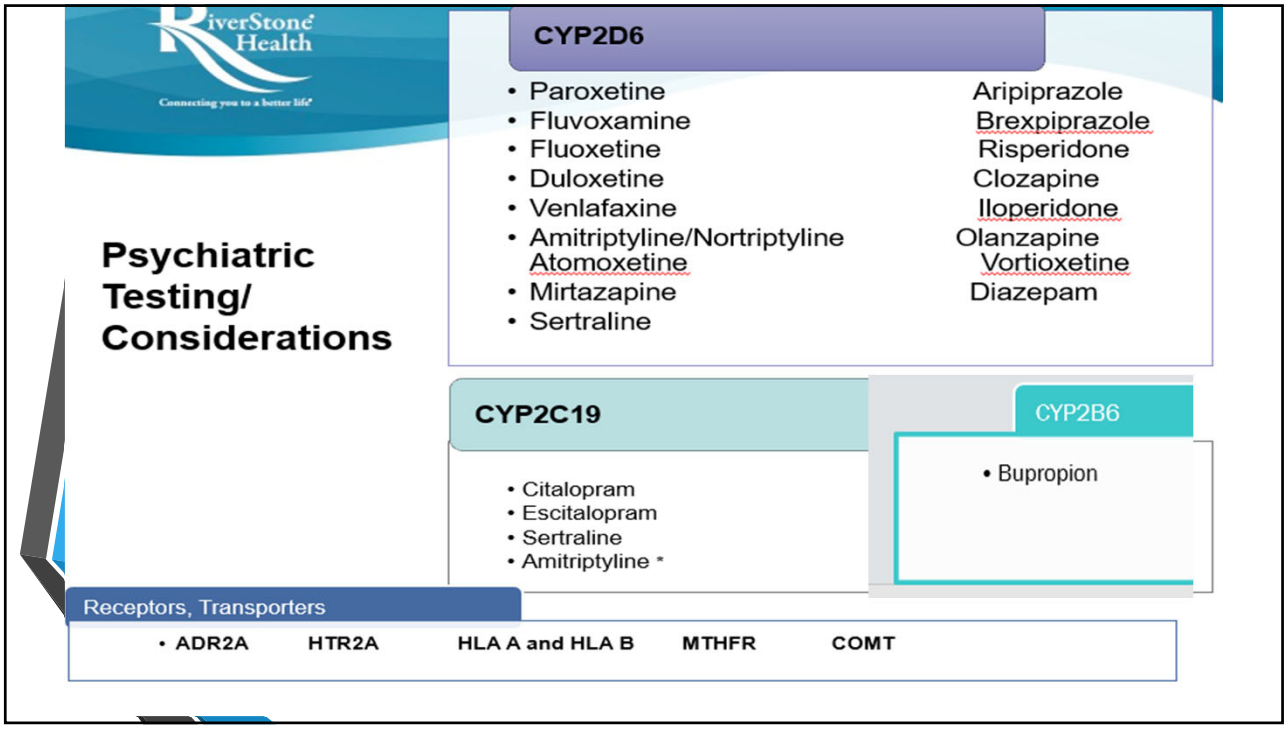


Psychiatric Disorder PGx Selection

- Anxiety
- Depression
- Mood Disorders
- ADHD

- Patient has failed adequate medication trials (ie appropriate dose, frequency, duration) and not met goals of therapy

- Patient experiencing treatment failures or ADRS



GENE	DRUG	CLASS	CPIC/ PHARMGKB LOA	Clinical Recommendations for PGx
CYP2D6	fluvoxamine	SSRI	A/1A	Actionable PGx
CYP2D6	paroxetine	SSRI	A/1A	Consider alt agent for both CYP2D6 UM and CYP2D6 PMs. For CYP2D6 PMs consider reducing the recommended starting dose by 50% . Paroxetine prescribing information-no recs
CYP2D6	venlafaxine	SNRI	AB/1A	Select alt agent for CYP2D6 PM and IM or reduce dose, consider obtaining plasma metabolites; CYP2D6 UM, increase dose to 150% of the normal dose or select an alternate
CYP2D6	vortioxetine	Other AD	B/3	Max recommended dose is 10 mg/day in CYP2D6 PM
CYP2D6/CYP1A2	duloxetine	SNRI	C	Concomitant administration of duloxetine with a potent CYP1A2 inhibitor in patients who are poor CYP2D6 metabolizer (n =14) resulted in a 6-fold increase in duloxetine AUC and Cmax. *Cigarette smoking: Duloxetine bioavailability is reduced by ~33% in smokers
CYP2D6	fluoxetine	SSRI	C/3	CYP2D6 PMs have more than twofold greater AUC of R-fluoxetine than EMs, and more than a 12-fold greater AUC of S-fluoxetine than EMs (statistically significant).
CYP2C19	citalopram	SSRI	A/1A	Consider a 50% reduction or alt agent for CYP2C19 PM (max 20 mg/day); Consider alt agent in CYP2C19 UM.
CYP2C19	escitalopram	SSRI	A/1A	Consider a 50% reduction or alt agent for CYP2C19 PM; Consider alt agent in CYP2C19 UM
CYP2C19	sertraline	SSRI	B/1A	Consider a 50% reduction or alt agent for CYP2C19 PM; Consider alt agent in CYP2C19 UM

Gene	Drug	Category	CPIC/PharmGKB LOA	Clinical Recommendations for PGx
CYP2C19/ CYP2D6	**amitriptyline**	**TCA**	**A/1A**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM 50% reduction in CYP2C19PM
CYP2D6	**nortriptyline**	**TCA**	**A/1A**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM
CYP2C19/ CYP2D6	**clomipramine**	**TCA**	**B/2A**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM 50% reduction in CYP2C19PM
CYP2D6	**desipramine**	**TCA**	**B/1A**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM
CYP2C19/ CYP2D6	**doxepin**	**TCA**	**B/3**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM 50% reduction in CYP2C19PM
CYP2C19/ CYP2D6	**imipramine**	**TCA**	**B/2A**	Alternate agent CYP2D6UM 50% reduction or alternate agent in CYP2D6 PM[37] 50% reduction in CYP2C19PM

Receptor Evidence: Weak

GENE	MED/CLASS	CPIC LOA	PHARMGKB LOA
COMT	SSRIs	C	2B
HTR2A	antidepressants	D	2B
HTR2A	citalopram	D	2B
HTR1A	paroxetine	D	2B

www.cpic.org

Exercise 1

A 42 year old woman is known to have the CYP2C19 *17/*17 (UM) genotype. She was recently diagnosed with depression and you want to start her on escitalopram. Is escitalopram an appropriate medication choice for this patient based only on PGx?

A. Yes
B. No
C. I don't know

The patient is also CYP2D6 *1*1 (WildType). Based only on PGx is paroxetine an appropriate alternative?

A. Yes
B. No
C. I don't know

Exercise 2

An adult patient on your panel comes in with psychotropic testing panel . The patient has a medical history significant for treatment-resistant depression and insomnia. The patient has concerns about her panel and the results showing she should be cautious taking venlafaxine 150 mg XR daily which has been working very well for her. Her CYP2D6 is *10*10 (IM). What do you tell her?

A. Based on her PGx report it would be recommended that we increase her dose to venlafaxine 300 mg XR daily
B. Based on her PGx report we should reduce her dose to venlafaxine 75 mg XR daily
C. Based on her reported efficacy and tolerability regardless of PGx report this is not an actionable result and recommend continue therapy with monitoring

Exercise 3

The same patient presents back to clinic with ongoing issues with insomnia- failed trazodone, mirtazapine gabapentin, hydroxyzine, melatonin. You would like to initiate nortriptyline therapy as an adjunct for her depression and sleep. The patient is known to have the CYP2D6 *5*6 (PM). Why does the CPIC guideline recommend avoiding nortriptyline use in patients with this diplotype?

Due to phenotype of poor metabolizer this patient would have greatly reduced metabolism of TCA and higher serum concentrations which will increase likelihood of ADRs . Recommend avoiding use. Strength of recommendation STRONG

Mood Stabilizers and Antipsychotics

Gene	Drug	Category	CPIC/PharmGKB LOA	Clinical Recommendations for PGx
CYP2D6	aripiprazole	Anti-psychotic	B/3	Reduce dose by 50% in PM. Reduce to 25% dose in PM + CYP3A4 inhibitor IM-reduce to 300 mg monthly for PM; 200 mg monthly PM+ CYP3A4 inh > 14 days
CYP2D6	brexpiprazole	Anti-psychotic	B/3	Reduce dose by 50% in PM. Reduce to 25% dose in PM + CYP3A4 inhibitor
CYP2D6	risperidone	Anti-psychotic	B/3	Consider reducing dose by 33% in PM, with further dose reduction to 50% of the standard dose if CNS side effects occur. In CYP2D6 UM consider alt drug or titrate the dose according to the maximum dose for the active metabolite paliperidone
CYP2D6	iloperidone	Anti-psychotic	B/C	Reduce dose by 50% in PM
CYP2D6	clozapine	Anti-psychotic	C	Consider reducing dose in PM due to higher serum levels
CYP2D6	haloperidol	Anti-psychotic	C/3	Reduce dose by 50% or find alternative not metabolized by CYP2D6
UGT1A4 *3	olanzapine	Anti-psychotic	C/3	Consider closer monitoring of olanzapine therapy in patients who are known carriers of the UGT1A4*3 allele

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CPIC® Guideline for Atomoxetine based on CYP2D6 genotype

Most recent guideline publication:

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* Genotype and Atomoxetine (February 2019)

ADHD

Atomoxetine, Methylphenidate

Atomoxetine in Children – CYP2D6

Phenotype	Activity Score	Therapeutic Recommendation	Strength of Recommendation
Ultra-rapid Normal	> 2	• 0.5 mg/kg/day & titrate to 1.2 mg/kg/day • No response in 2 weeks – consider checking peak plasma levels	Moderate
Normal	1.5-2.0		
Intermediate-Normal	0.5-1.0	• 0.5 mg/kg/day • If no response in 2 weeks consider checking levels if < 200 can increase dose to achieve goal of 400 ng/mL • If unacceptable SE – consider dose reduction	Moderate
Poor	0.0-0.5	• 0.5 mg/kg/day • If no response in 2 weeks consider checking levels if < 200 can increase dose to achieve goal of 400 ng/mL • If unacceptable SE – consider dose reduction	STRONG

Atomoxetine in Adults – CYP2D6

Phenotype	Activity Score	Therapeutic Recommendation	Strength of Recommendation
Ultra-rapid Normal	> 2	• Initiate 40 mg/day and increase to 80 mg/ day after 3 days. • If no clinical response and no ADRs, consider increasing dose to 100 mg/day. • If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. • Dosages > 100 mg/day may be needed to achieve target concentrations.	Moderate
Normal	1.5-2.0		
Intermediate-Normal	0.5-1.0	• Initiate 40 mg/day and if no clinical response and in the absence of adverse events after 2 weeks increase dose to 80 mg/day. • If response is inadequate after 2 weeks consider obtaining a plasma concentration 2–4 hours after dosing. • If concentration is < 200 ng/mL, consider a proportional dose increase to achieve a concentration to approach 400 ng/mL. If unacceptable side effects are present at any time, consider a reduction in dose.	Moderate
Poor	0.0-0.5		

Methylphenidate – ADRA2A

Allele	Phenotype
GG	○ Improved response
CG	○ Intermediate response
CC	○ Poor response

- FDA: None
- CPIC: None
- PharmGKB: LOE 3

Exercise 5

Patient is a 21 year old female who had pharmacogenomic testing via direct to consumer testing for her treatment resistant anxiety, depression when she was 18. She was diagnosed with ADHD this year by BH. She has a history of SUD and you want to initiate Strattera for her. What is the PGx guided recommendations for dosing and titrations based on her CYPD26 genotype of *1*2?

- Initiate 40 mg/day and increase to 80 mg/ day after 3 days. If no clinical response and no ADRs, consider increasing dose to 100 mg/day. If no clinical response observed after 2 weeks, consider obtaining a peak plasma concentration (1–2 hours after dose administered). If < 200 ng/mL, consider a proportional increase in dose to approach 400 ng/mL. Dosages > 100 mg/day may be needed to achieve target concentrations.

CHALLENGES, UTILITY, LIMITATIONS OF PGX

Forms often required for sample submission for patient

- Lab Requisition (Signed by provider)
- Advanced Beneficiary Notification (Medicare)
- Non-Covered Services (Commercial or Clinic Form)
- Face Sheet /Demographics sheet (Insurance information)
- Medication reconciliation, diagnosis codes
- Saliva Sample or Blood Sample w/ patient label and 2 identifiers

- If not all submitted together can delay and cause sample to expire

Test Interpretation

- Direct to Consumer Testing
  - Several options to patients now: Genesight, 23andMe (Personal Genome Service), MayoClinic, Oneome, and others
  - Several facilities across the US off these services to patients and employees
- Clinical evaluation and clinical utility for your patient
  - CPIC, PharmGKB, PGx Expert consensus, labelling
- Drug-Drug-Gene interactions
  - Phenoconversions
  - i.e. Provigil (strong CYP3A4 inducer)
  - Bupropion (strong CYP2D6 inhibitor)

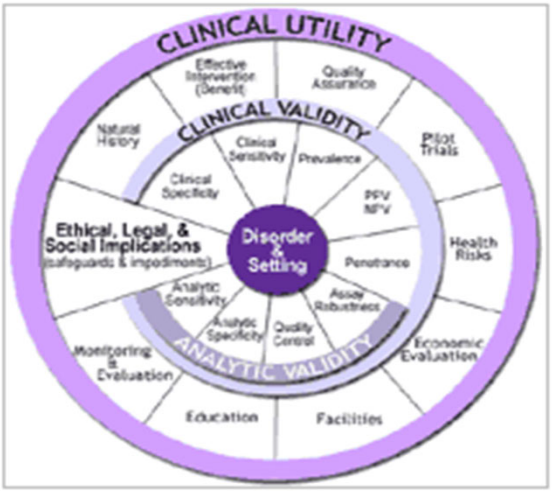
Challenges of PGx Testing

- Limitations in the design of published pharmacogenetic studies (GWAS)
  - lack of RCT showing benefit of genotype-assisted dosing vs conventional dosing
- Regulatory and ethical concerns
- Lack of cost effectiveness
- Limitations in available pharmacogenomic tests and lack of guidelines for test implementation
  - Pre-emptive vs Reactive testing
- A lack of education on the risks and benefits of pharmacogenomic testing, both for patients and providers
- Potential for delay in therapy while awaiting results of genotyping

FDA Statement on PGx

- **Lack of Evidence and Literature to Support**
  - Consult FDA Labelling and evidence-based references
- **Recommendations for Patients**
  - Avoid discontinuing medications
  - Consult a healthcare professional familiar with PGx
- **Recommendations for Providers**
  - Consider lack of evidence for DNA PGx polymorphisms and relationship to medication effects prior to testing
  - Direct to consumer tested patients provide education
  - Understand levels of evidence vs informative PGx

- ***ACCE Framework:***
  - Collect
  - Evaluate
  - Interpret
- Analytical Validity
- Clinical Validity
- Clinical Utility
- Ethical, Legal, Social



http://www.cdc.gov/genomics/gtesting/acce

Clinical Utility

- Likelihood a test will lead to an improved clinical outcome
  - Consider risk vs benefit for patient
  - How will this impact patient's treatment (ie will it delay?)
  - Will it lead to improved outcomes
  - How will the result affect the patient (emotionally)
  - Economic implications (cost/benefit)

Patient Education Pre-Testing

- Purpose of the testing
- Role of genes in drug response
- Risks and Benefits to testing (ie potential delayed therapy) , choosing therapy with reduced ADR risk
- Limitations to this testing (RCTs, etc see previous slide)
- Emphasize this is a DNA sample
  - Most labs only store sample for a short period of time until report is resulted
- Describe for pre-emptive testing ie future benefits

Patient Education Post-Testing

- Inform patient and provider of testing results
- Inform of the absence or presence of variants, specifically focus on variants inquired upon by provider but will also need to address ALL variants and drug-gene interactions
- Avoid saying "metabolizers" Say : Processing, or Slower than normal ability to break this down
- Inform of any changes to medications if made or any recommendations
- Re-emphasize the relevance of the results and importance of sharing the information with future providers
- Will need to re-look at if they have major CYP interactions ie a strong CYP3A4 inhibitor etc
- Use patient friendly language

Pharmacogenomics Competencies

- Genomics/Genetics Competency Center (G2C2)
- Online repository of genomics educational materials
- Peer-reviewed collections for genetic counselors, nurses, pharmacists, physician assistants, and physicians
- Pharmacists: Basic Concepts, Genetics and Disease, Ethical/Legal/Social

http:genomicseducation.net

Other Useful References

- PharmVar: Pharmacogene Variation Consortium
  - https://www.pharmvar.org/genes
- Indiana University SOM: Flockhart Table
  - https://drug-interactions.medicine.iu.edu/Main-Table.aspx
- FDA PGx product labelling
  - https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm
- SparcTool
  - **https://ignite-genomics.org/publications/**

Questions?

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