UW PACC
Psychiatry and Addictions Case Conference
UW Medicine | Psychiatry and Behavioral Sciences

04/18/2019

WELCOME!

Today's Topic:

Pharmacogenetic testing

What is pharmacogenetic testing and should I be using to help with medication selection?

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PANELISTS:

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UW Medicine
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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

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Psychiatry and Addictions Case Conference

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PHARMACOGENETICS TESTING IN PSYCHIATRY

FOCUS ON DEPRESSION AND ANTIDEPRESSANTS

JESSIE WHITFIELD, MD, MPH

APRIL 18, 2019

UW Medicine
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project ECHO

GENERAL DISCLOSURES

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GENERAL DISCLOSURES

UW PACC is also supported by Coordinated Care of Washington

SPEAKER DISCLOSURES

✓ I have no disclosures

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Health & Science

Can genetic testing help doctors better prescribe antidepressants? There's quite a debate.

BUSINESS

In the race to use genetic tests to predict whether antidepressants will work, science might be getting left behind

By REBECCA ROBBINS @rebeccadrobbins / SEPTEMBER 28, 2018

Sept 28, 2018 *Stat News;* March 31, 2019 *Washington Post*

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OBJECTIVES

- Review background of pharmacogenetics
- Evidence base for use in antidepressant guidance
- Current guidelines
- Review logistics of tests available
- Recommendations for practice

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CASE

- A 33 yo male with a history of MDD, recurrent presents to his PCP with a depressive sxs after a 2 year period of stability. He is not currently on medication. His PHQ9 is 20; he denies SI but endorses multiple neurovegetative sxs. He reports multiple prior med trials with various SSRIs (escitalopram, citalopram, fluoxetine, and sertraline), but reports 'none really worked for me'. He comments to you that he's heard that genetic testing can sometimes help inform which medications might work best for him to try now. What do you say?

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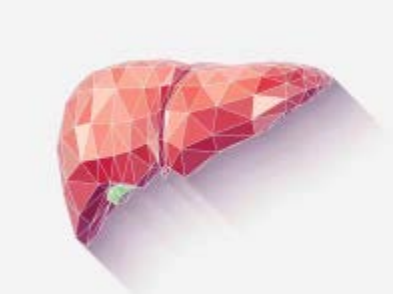
PHARMACOGENETICS

- Pharmacogenetics: study of DNA/gene variations and their effect on drug metabolism, efficacy and tolerability.
- History:
  - 1900, three blood groups → 1956, G6PD deficiency → 1977, cytochrome P450 enzymes
- Currently available for a wide range of health problems
  - >140 FDA-approved drugs with pharmacogenetic information
- Support from policy level:
  - In Jan 2015, the Precision Medicine Initiative was introduced
- Language: decision support tools, 'personalized' or 'precision' medicine, Pgx or Pgen

Baskys 2019, Hess et al 2016, Zeier et al 2018, Butler 2018

DRUG METABOLISM EFFECTS



- Medications metabolized by cytochrome P450 (CYP) enzymes in liver
- ~ 90% of all drugs are metabolized by 7 cytochrome enzymes:
  - CYP1A2, CYP3A4, CYP3A5, CYPC19, CYP2D6 (~25%), CYP2C9 and CYP2B69
- Small changes in genes coding for these enzymes can have large effects
  - Deletions = no or poor enzyme activity
  - Duplications/multiplications = increased or rapid activity

Baskys 2018, Ruano et al 2013, Butler 2018

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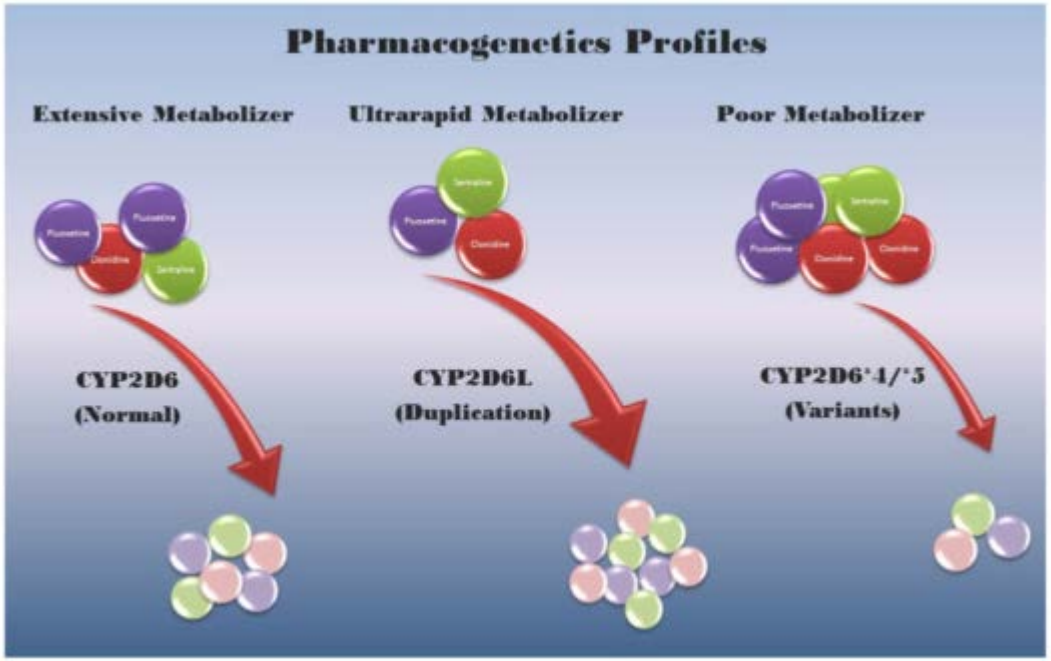
DRUG METABOLISM EFFECTS

- Poor, rapid and ultra-rapid metabolizers
- 5-10% of population
- Changes to drug tolerability, efficacy



Butler 2018

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PHARMACOGENETICS AND DEPRESSION

- Genetic etiology of depression
  - MDD is 40-50% heritable, determined by a large number of genes
- Genes as possible targets:
  - Genes regulating transporters: serotonin (*SLC6A4* and *HTR2A)* norepinephrine (*SL6A2)*
  - Genes mediating stress response: *BDNF, CRHBP, IL-6*
  - Genes mediating neurotransmitter synthesis: *TPH2*
  - Genes mediating metabolism of drugs: Cytochrome P450 enzyme system

Baskys 2019, Bousman and Mueller 2018, Hess et al 2016, Fabbri et al 2018, Lohoff 2011

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PHARMACOGENETICS AND DEPRESSION

- Rationale for PGx testing in depression treatment
  - More than 40 antidepressant drugs
  - Among most frequently prescribed in US
  - “Trial and error” approach with 4-12 week wait periods
  - Of those treated, 25-50% do not respond sufficiently to treatment
  - ~40% of patients discontinue their medications within the first 90 days of therapy because of a lack of response, side effects, or both.

Baskys 2019, Bousman and Mueller 2018, Hess et al 2016, Fabbri et al 2018

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DRUG METABOLISM EFFECTS

TABLE 1

ANTIDEPRESSANT METABOLISM BY CYP ENZYME[8]

CYP Enzyme	*Primarily Metabolized*	*Substantially Metabolized*	*Minimally Metabolized*
2D6	desipramine doxepin fluoxetine nortriptyline paroxetine venlafaxine	amitriptyline bupropion duloxetine imipramine mirtazapine trazodone	citalopram escitalopram fluvoxamine sertraline
2C19	amitriptyline citalopram clomipramine escitalopram	doxepin imipramine moclobemide notriptyline sertraline	venlafaxine
1A2	fluvoxamine	clomipramine duloxetine imipramine	amitriptyline mirtazapine
2C9	None	amitriptyline fluoxetine	sertraline

Mrazek D. *Psychiatric Pharmacogenomics*. New York, NY: Oxford University Press; 2010. Reprinted with permission from Oxford University Press. Copyright 2010.

CYP=cytochrome P450.

Wall CA, Oldenkamp C, Swintak C. *Primary Psychiatry*. Vol 17, No 5. 2010.

TABLE 2

ANTIPSYCHOTIC METABOLISM BY CYP ENZYME[8]

CYP Enzyme	*Primarily Metabolized*	*Substantially Metabolized*	*Minimally Metabolized*
2D6	chlorpromazine haloperidol perphenazine risperidone thioridazine	aripiprazole olanzapine	clozapine quetiapine ziprasidone
2C19	None	clozapine	thioridazine
1A2	clozapine olanzapine	chlorpromazine	haloperidol thioridazine

Mrazek D. *Psychiatric Pharmacogenomics*. New York, NY: Oxford University Press; 2010. Reprinted with permission from Oxford University Press. Copyright 2010.

CYP=cytochrome P450.

Wall CA, Oldenkamp C, Swintak C. *Primary Psychiatry*. Vol 17, No 5. 2010.

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GENE DRUG INTERACTIONS

TABLE 1. Antidepressant Drug-by-Gene Associations With Moderate to High Levels of Evidence or Included in One of the Combinatorial Pharmacogenetic Tests Evaluated Here[a]

	Pharmacodynamic										Pharmacokinetic				
Agent	ADRA2A	BDNF	COMT	CRHR1	FKBP5	GRIK4	HTR1A	HTR2A	SLC6A2	SLC6A4	ABCB1	CYP1A2	CYP2B6	CYP2C19	CYP2D6
Amitriptyline[b]											3				1A
Bupropion															
Citalopram[b]		3			2B			2B		2A	3			1A	3
Desipramine[b]		3													1A
Doxepin[b]															1A
Duloxetine[b]					3			3		2A		1A			1A
Escitalopram[b]		3		3	2B		3			3		3			3
Fluoxetine[b]		3	3				3	3			3			1A	3
Fluvoxamine[b]											3				1A
Imipramine[b]														2A	1A
Maprotiline															3
Mirtazapine					2B					3			3		
Nefazodone[b]					3						3				
Nortriptyline[b]		3									3				1A
Paroxetine[b]		3	3		2B		3			3	3	3			1A
Sertraline							3			3	3			1A	
Trimipramine[b]															1A
Venlafaxine[b]			3		2B				3		3				2A
Antidepressants, unspecified		3		3	2B	2B	3	2B			3				1A
SSRIs, unspecified	3		2B		2B		3	2B			3				
Number of variants per gene	1	6	2	2	4	2	3	5	1	3	15	9	5	8	14
Interaction type[c]	E	E,T	E	E	E,T	E	E	E,T	E	E,T	E,T	E,T	E,O	E,M,T	E,D,M,T

[a] This is not a comprehensive representation of antidepressant drug-by-gene associations; it is limited to the PharmGKB search terms "depressive disorder, major; depressive disorder; depression; [antidepressant name]"; it excludes drug-gene interactions related to "bipolar disorder; anxiety disorder"; it excludes antipsychotic and some antidepressant drugs; and it excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB. The PharmGKB knowledge base, which was used to generate this table, is not the sole source of relevant pharmacogenetic information. BDNF=brain-derived neurotrophic factor; COMT=catechol *O*-methyltransferase; SSRI=selective serotonin reuptake inhibitor.

[b] These agents have U.S. Food and Drug Administration labeling with CYP450 pharmacogenetic information.

[c] Pharmacogenetic information relevant to drug efficacy (E), dosage (D), metabolism/pharmacokinetics (M), toxicity/adverse drug reactions (T), and other (O). Values correspond to a high (1A, 1B), moderate (2A, 2B), or low (3) level of evidence according to the PharmGKB rating scale.

- APA Task Force for Novel Biomarkers and Treatments Report in 2018
- Scale: 1A (strong evidence) to 4 (preliminary evidence)

Zeier et al 2018

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PHARMACOGENETIC TESTS

- 40+ tests currently available
- Most include information about metabolizers, some include candidate gene information
  - No two panels are precisely the same
- Example test: GeneSight Psychotropic test

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EXAMPLE TEST

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurehealth.com

PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES (PK)

CYP1A2 — **Extensive (Normal) Metabolizer**
*1/*1

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 — **Ultrarapid Metabolizer**
*17/*17

CYP2C19*17 allele enzyme activity: Increased
CYP2C19*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal 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 — **Poor Metabolizer**
*4/*4 (Duplication)

CYP2D6*4 allele enzyme activity: None
CYP2D6*4 allele enzyme activity: None

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.

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

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 — **Intermediate Metabolizer**
*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*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.

Patient, Sample
DOB: 7/22/1984
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PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

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.

HLA-B*1502 — **Higher Risk**
Present

This patient carries either the HLA-B*1502 allele or a closely related *15 allele. Presence of HLA-B*1502 or some of the closely related *15 alleles suggests higher risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

HLA-A*3101 — **Higher Risk**
A/T

This patient is heterozygous for the A allele and the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher 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.

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GENE-DRUG INTERACTIONS

USE AS DIRECTED

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
desvenlafaxine (Pristiq®)			●		○			
levomilnacipran (Fetzima®)			●		○	●		
vilazodone (Viibryd®)			●		○	●		
ANXIOLYTICS AND HYPNOTICS								
alprazolam (Xanax®)					○			
buspirone (BuSpar®)					○	●		
clonazepam (Klonopin®)					○			
eszopiclone (Lunesta®)				●	○			
temazepam (Restoril®)		●		●	○			●
zolpidem (Ambien®)	○		●	●	○	●		
ANTIPSYCHOTICS								
asenapine (Saphris®)	○				○	●	○	
lurasidone (Latuda®)					○			
paliperidone (Invega®)					○	●		
thiothixene (Navane®)	○							
ziprasidone (Geodon®)	○				○			
MOOD STABILIZERS								
lamotrigine (Lamictal®)							○	

MODERATE GENE-DRUG INTERACTION

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
citalopram (Celexa®)			●		○	●		
escitalopram (Lexapro®)			●		○	●		
fluoxetine (Prozac®)			●	●	○	●		
selegiline (Emsam®)	○	●	●		○			
sertraline (Zoloft®)		●	●	●	○	●		
trazodone (Desyrel®)	○				○	●		
venlafaxine (Effexor®)			●	●	○	●		
ANXIOLYTICS AND HYPNOTICS								
chlordiazepoxide (Librium®)	○				○			●
clorazepate (Tranxene®)	○				○			●
diazepam (Valium®)	○	●	●	●	○			●
lorazepam (Ativan®)								●
oxazepam (Serax®)								●

● - Variation was found in patient genotype that may impact medication response. ○ - This gene is associated with medication response, but patient genotype is normal.

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GENE-DRUG INTERACTIONS

MODERATE GENE-DRUG INTERACTION

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIPSYCHOTICS								
clozapine (Clozaril®)	○				○	●	○	
fluphenazine (Prolixin®)	○		●	●	○	●		
haloperidol (Haldol®)	○				○	●	○	
olanzapine (Zyprexa®)	○				○	●	○	
quetiapine (Seroquel®)					○	●		
MOOD STABILIZERS								
valproic acid/divalproex (Depakote®)		●		●			○	

SIGNIFICANT GENE-DRUG INTERACTION

	CYP1A2	CYP2B6	CYP2C19	CYP2C9	CYP3A4	CYP2D6	UGT1A4	UGT2B15
ANTIDEPRESSANTS								
amitriptyline (Elavil®)	○		●	●	○	●	○	
bupropion (Wellbutrin®)		●			○	●		
clomipramine (Anafranil®)	○		●		○	●		
desipramine (Norpramin®)						●		
doxepin (Sinequan®)	○		●	●	○	●	○	
duloxetine (Cymbalta®)	○					●		
fluvoxamine (Luvox®)	○					●		
imipramine (Tofranil®)	○		●		○	●		
mirtazapine (Remeron®)	○			●	○	●		
nortriptyline (Pamelor®)						●		
paroxetine (Paxil®)					○	●		
vortioxetine (Trintellix®)		●	●	●	○	●		
ANXIOLYTICS AND HYPNOTICS								
propranolol (Inderal®)	○					●		
ANTIPSYCHOTICS								
aripiprazole (Abilify®)					○	●		
brexpiprazole (Rexulti®)					○	●		
chlorpromazine (Thorazine®)	○				○	●		
iloperidone (Fanapt®)					○	●		
perphenazine (Trilafon®)	○		●		○	●		
risperidone (Risperdal®)					○	●		
thioridazine (Mellaril®)	○		●		○	●		
MOOD STABILIZERS								
carbamazepine (Tegretol®)		●			○			
oxcarbazepine (Trileptal®)								

● - Variation was found in patient genotype that may impact medication response. ○ - This gene is associated with medication response, but patient genotype is normal.

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
desvenlafaxine (Pristiq®)	**trazodone** (Desyrel®)	1	**bupropion** (Wellbutrin®)	1,6
levomilnacipran (Fetzima®)	**venlafaxine** (Effexor®)	1	**mirtazapine** (Remeron®)	1,6
vilazodone (Viibryd®)	**selegiline** (Emsam®)	2	**amitriptyline** (Elavil®)	3,8
	fluoxetine (Prozac®)	1,4	**clomipramine** (Anafranil®)	1,6,8
	citalopram (Celexa®)	3,4	**desipramine** (Norpramin®)	1,6,8
	escitalopram (Lexapro®)	3,4	**doxepin** (Sinequan®)	1,6,8
	sertraline (Zoloft®)	3,4	**duloxetine** (Cymbalta®)	1,6,8
			imipramine (Tofranil®)	1,6,8
			nortriptyline (Pamelor®)	1,6,8
			vortioxetine (Trintellix®)	1,6,8
			fluvoxamine (Luvox®)	1,4,6,8
			paroxetine (Paxil®)	1,4,6,8

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.
8: FDA label identifies a potential gene-drug interaction for this medication.

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ANTIPSYCHOTICS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
asenapine (Saphris®)	**fluphenazine** (Prolixin®)	1	**chlorpromazine** (Thorazine®)	1,6
lurasidone (Latuda®)	**olanzapine** (Zyprexa®)	1	**aripiprazole** (Abilify®)	1,6,8
paliperidone (Invega®)	**quetiapine** (Seroquel®)	1	**brexpiprazole** (Rexulti®)	1,6,8
thiothixene (Navane®)	**clozapine** (Clozaril®)	1,8	**iloperidone** (Fanapt®)	1,6,8
ziprasidone (Geodon®)	**haloperidol** (Haldol®)	1,8	**perphenazine** (Trilafon®)	1,6,8
			risperidone (Risperdal®)	1,6,8
			thioridazine (Mellaril®)	1,6,9

CLINICAL CONSIDERATIONS

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

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Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CB[P]

Questions? Call 855.891.9415 or email medrfx@assurexhealth.com

ANXIOLYTICS AND HYPNOTICS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
alprazolam (Xanax®)	**chlordiazepoxide** (Librium®)	1	**propranolol** (Inderal®)	1,6,8
buspirone (BuSpar®)	**clorazepate** (Tranxene®)	1		
clonazepam (Klonopin®)	**diazepam** (Valium®)	1		
eszopiclone (Lunesta®)	**lorazepam** (Ativan®)	1		
temazepam (Restoril®)	**oxazepam** (Serax®)	1		
zolpidem (Ambien®)				

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
6: Use of this drug may increase risk of side effects.
8: FDA label identifies a potential gene-drug interaction for this medication.

Patient, Sample
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Reference: 1456CB[P]

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MOOD STABILIZERS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
lamotrigine (Lamictal®)	**valproic acid/divalproex** (Depakote®)	1	**oxcarbazepine** (Trileptal®)	6,8
			carbamazepine (Tegretol®)	6,8,9

NO PROVEN GENETIC MARKERS			
gabapentin (Neurontin®)	10	**topiramate** (Topamax®)	10
lithium (Eskalith®)	10		

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
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: This medication does not have clinically proven genetic markers that allow it to be categorized.

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LITERATURE REVIEW: *PGX AND ANTIDEPRESSANTS*

- Major topics in literature currently
  - Testing patient outcomes using PGx: safety, tolerability and efficacy
  - Testing effects on prescribing practices
  - Economic and cost effectiveness analyses
  - Patient sub-population and generalizability of results
- RCTs: GeneSight, CNSDose, Genelex, Neuropharmagen, NeuroIDgenetix
- Case-control studies: GeneSight, Genecept, GeneLex
- Observational studies with no comparator group: AmpliChip, CNSDose, GeneSight, Genecept, Genelex, Neuropharmagen, HILOmet, Pillcheck
- Most studies commercially funded (except one case-control study, one RCT)

Fabbri et al 2018

META-ANALYSIS: MDD AND PGX

- Two meta-analyses from Rosenblatt group
- 2018:
  - Aim: the effect of PGx testing-guided MDD treatment on response and remission rates vs unguided treatment using HAMD-17
  - Results:
    - 4 RCTs: all at least partially funded by the companies manufacturing the pharmacogenomic tests
      - Blinding not possible
    - 2 open label prospective cohort studies

Rosenblatt et al 2018

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META-ANALYSIS: MDD AND PGX

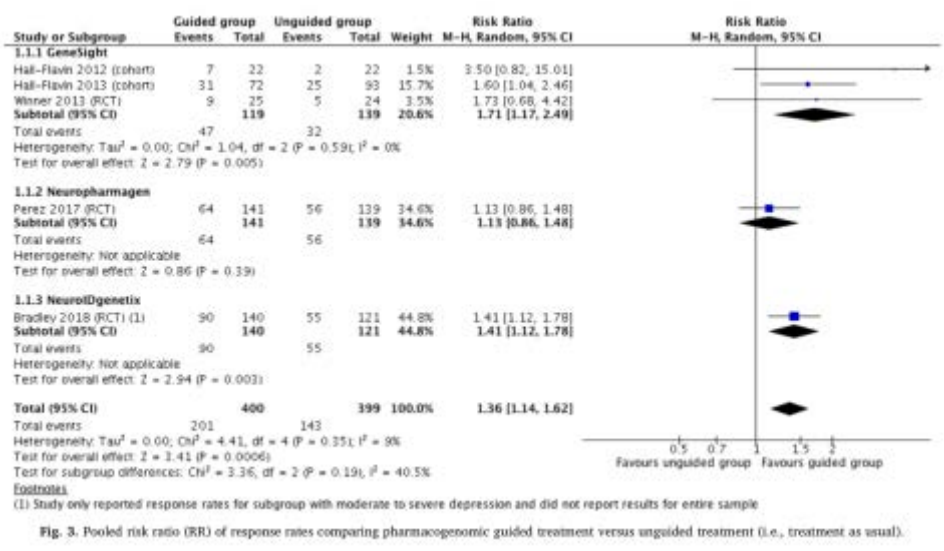

Fig. 3. Pooled risk ratio (RR) of response rates comparing pharmacogenomic guided treatment versus unguided treatment (i.e., treatment as usual).

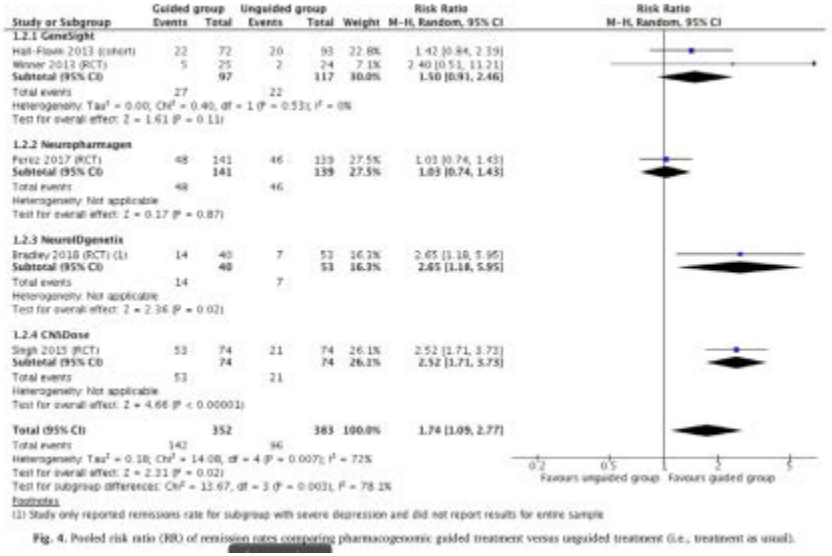

Fig. 4. Pooled risk ratio (RR) of remission rates comparing pharmacogenomic guided treatment versus unguided treatment (i.e., treatment as usual).

- RR for treatment response: 1.36 (95% CI = 1.14 to 1.62; p = 0.0006; n = 799)
- RR for remission: 1.74 (95%CI = 1.09 to 2.77; p = 0.02, n = 735)
- Conclusions:
  - Treatment outcomes might be improved by PGx guidance
  - Blinding issues: are improved enhanced placebo effect?
  - “No PGx test had replicated findings to support improved therapeutic efficacy.”

Rosenblatt et al 2018

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META-ANALYSIS: MDD AND PGX

- Bousman et al 2018
  - Aim: Include prospective RCTs that examined pharmacogenetic tests and depressive sx remission in MDD
  - 1737 eligible subjects from five RCTs
    - Studies included same four RCTs from Rosenblatt PLUS results from large GeneSight funded GUIDED trial

Bousman et al 2018

META-ANALYSIS: MDD AND PGX

- **Results**: Pts with pharmacogenetic testing (n = 887) were 1.71 (95% CI: 1.17–2.48; p = 0.005) times more likely to achieve symptom remission compared to patients in TAU group (n = 850).
- **Conclusion**: Pharmacogenetic testing might improve symptom remission among those with MDD.

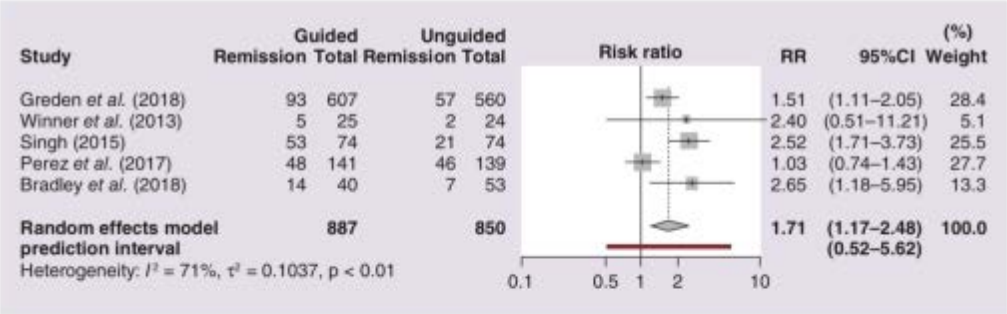

Figure 2. Forest plot of random-effects meta-analyses of five prospective, randomized controlled trials that examined the effect of pharmacogenetic-guided therapy on remission in major depressive disorder.
RR: Relative risk.

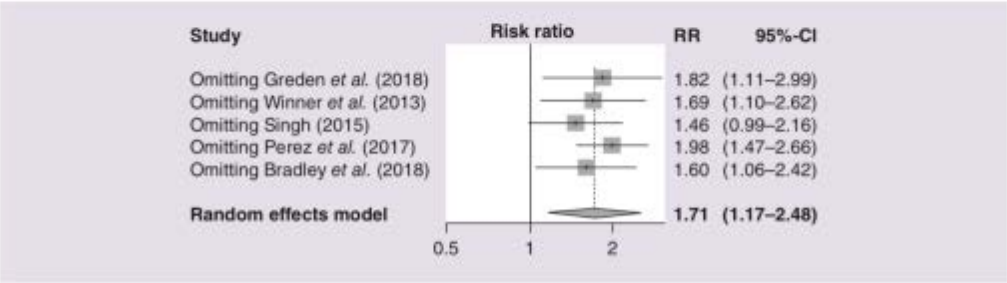

Figure 3. Forest plot of random-effects meta-analyses after omission of each of the five prospective, randomized controlled trials.
RR: Relative risk.

Bousman et al 2018

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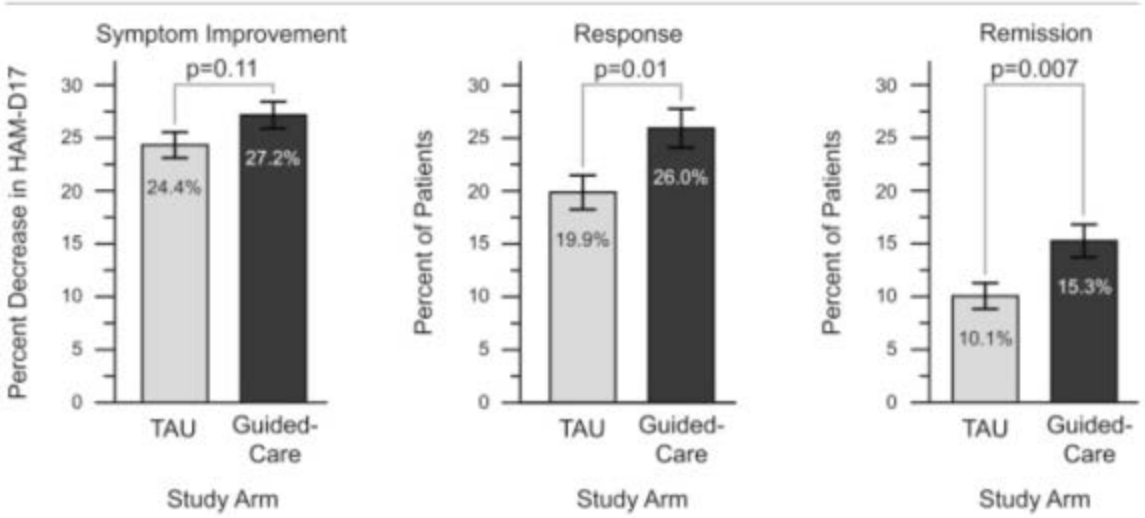
GUIDED TRIAL (2019)

- Large (N=1,200) blinded RCT evaluating GeneSight guided tx vs TAU
- In guided arm, MDs have PGx test and can use or not use results to help prescribe
- Primary outcome: sx improvement at week 8



Greden et al 2019

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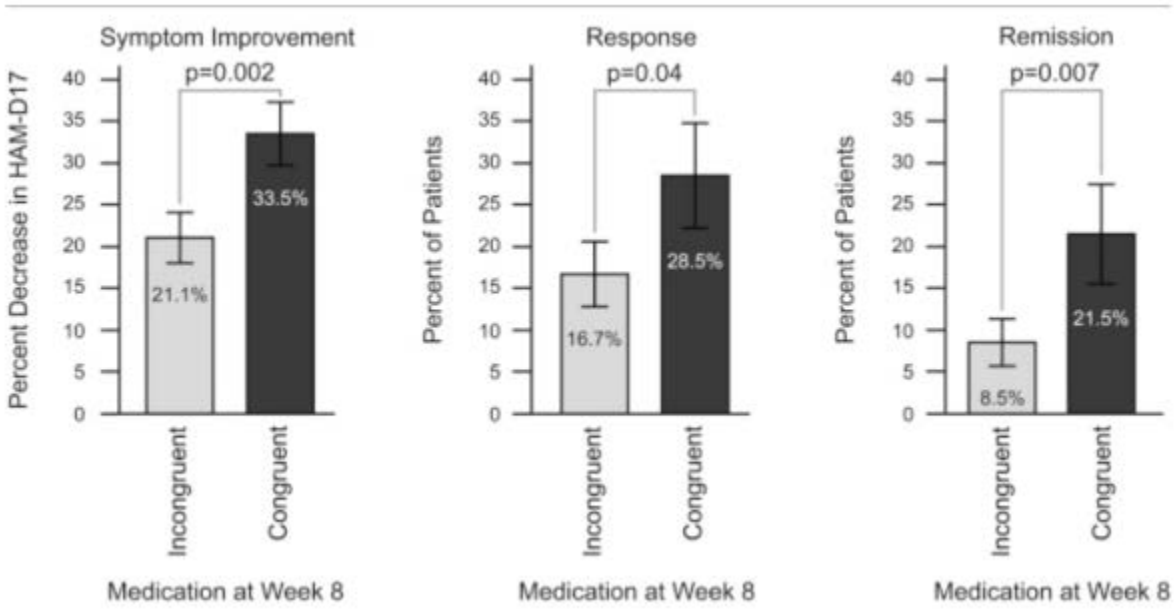
GUIDED TRIAL (2019)

- Patients were evaluated according to whether they were prescribed congruent (n = 77) or incongruent (n = 136)
- Significant differences in sx improvement, response, remission



Greden et al 2019

APA TASK FORCE FOR NOVEL BIOMARKERS AND TREATMENTS REPORT (2018)

- Reviewed RCTs, observational and cost effectiveness studies for 4 companies
- **Conclusions**:
- "We conclude that there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools at this point in time."

IDgenetix							
NCT02878928	Completed	Major depression, anxiety	Interventional	12-week prospective multicenter DB RCT	IDgenetix versus TAU	579	Dec. 2016
NCT02411123	Completed	Depression, anxiety	Interventional	4-month prospective randomized clinical study	IDgenetix versus TAU	220	Dec. 2015
NCT02599870	Ongoing	Acute pain surgery	Interventional	Prospective randomized clinical study	IDgenetix versus TAU	56	July 2016
NCT02605343	Completed	Acute pain surgery	Observational	Prospective observational clinical study	IDgenetix versus TAU	110	April 2016
CNSDose							
ACTRN12613001135707	Completed	Major depression	Interventional	12-week prospective DB RCT	CNSDose versus TAU	174	July 2013
GeneCept							
NCT01507155	Completed	Treatment-resistant depression, generalized anxiety disorder	Observational	3-month prospective open-label nonrandomized	Single group assignment	685	May 2014
ClinicalTrials.gov Identifier	**Status**	**Condition**	**Study Type**	**Study Design**	**Comparators**	**Enrollment**	**Estimated Completion Date**
GeneCept							
NCT02634177[b]	Recruiting	Major depression	Interventional	8-week prospective DB RCT	GeneCept versus TAU	335 (estimated)	May 2017
NCT01438242	Withdrawn						
NCT01426516	Terminated						
NCT02883660	Recruiting	Depression adverse effects	Observational	Retrospective case-control study		100	Aug. 2018
NCT01555021	Terminated						
NCT02566057	Recruiting	Psychosis	Interventional	12-month prospective SB RCT	GeneCept versus TAU	100	June 2017

Zeier et al 2018

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JAMA PSYCHIATRY VIEWPOINT 2018

- "The available evidence suggests that Pgen tests will not contribute much to care."
- No single gene/gene set determines more than 2-3% of disease course
  - Extremely rapid or slow metabolism is rare
- Concerns about unproven procedures distracting from hx taking
  - Focus on thoughtful dose choice, SE monitoring
- Blinding of studies, appropriate controls are research issues
- Conflicts of interest are an issue

- Bousman response: "Pharmacogenetics in Psychiatry: A Companion, Rather Than Competitor, to Protocol-Based Care"

Zubenko et al 2018

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FDA STATEMENTS (2019)

- FDA supports tests for drug metabolism but rejects claim that some genetic tests results can be used to choose antidepressant medication (better efficacy).
- Providers have made changes to patients' medication based on these results.
- April 2019: Warning letter to Inova Genomics Lab

"The relationship between DNA variations and the effectiveness of antidepressant medications has never been established."

FDA Press Announcement Nov 2018, update April 2019

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REVIEW: WASHINGTON HCA 2016

PRESCRIBING PRACTICES

- Does pharmacogenetic testing change the drug or dose selected by physicians compared with usual care? → ***YES***

COST EFFECTIVENESS

- *Effectiveness*: 2 studies, both found to be not cost effective

"Pharmacogenomic Testing for Selected Conditions Final Evidence Report"
https://www.hca.wa.gov/assets/program/pharmacogenomics-final-rpt-20161209.pdf

GUIDELINES: WASHINGTON HCA

- Evidence for PGx testing effect on pt outcomes is too limited, compromised and poor in quality
- ***"Evidence is insufficient for conclusions regarding clinical use."***

Quantity of Individual GLs	Individual GL Quality	Pharmacogenomics Recommendations
Depressive Disorders		
5 (beyondblue; EPA; ICSI; VA/DoD; WFSBP)	2 Good 2 Fair 1 Poor	Four of 5 GLs present no formal recommendations for the use of PGx testing. WFSBP recommends: In possibly nonadherent patients (e.g., low drug plasma levels despite high doses of the antidepressant), a combination of TDM and genotyping may be informative. Such analyses can aid in identifying those individuals who are slow or rapid metabolizers of certain antidepressants.
Schizophrenia Spectrum and Other Psychotic Disorders		
No GLs addressing PGx testing specific to schizophrenia spectrum disorders were identified.		
Bipolar Disorder and Related Disorders		
No GLs addressing PGx testing specific to bipolar disorder and related disorders were identified.		
Anxiety Disorders		
1 (APA)	1 Fair	No formal recommendations for use of PGx testing.
Attention Deficit/Hyperactivity Disorder		
No GLs addressing PGx testing specific to attention deficit/hyperactivity disorder were identified.		
Substance Use Disorders		
2 (APA; BAP)	1 Fair 1 Poor	No formal recommendations for use of PGx testing.

https://www.hca.wa.gov/assets/program/pharmacogenomics-final-rpt-20161209.pdf

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GUIDELINES: VA (2016)

- VA Evidence-based Synthesis Program
- PGx guided treatment has not shown 1) an improvement in remission, response, and tolerability, and 2) these improvement being due to prescribing changes 2/2 PGx testing.
- Concerns re: generalizability
  - Study population demographics: females
  - Diagnostic criteria: no comorbidities, PTSD excluded
- In 2014, VA awarded federal supply contract to GeneSight

Petersen et al 2016

CURRENT IMPLEMENTATIONS

- As of July 2018, at least 8 institutions have implemented PGx testing for med guidance
  - Mt Sinai, Cincinatti Children's, Indiana University, Vanderbilt
  - Research is ongoing
- Reactive vs preemptive strategies
  - Reactive: order testing only when someone fails multiple medications or does not tolerate medications
  - Preemptive: order testing on most patients before first med trial

Cavallari et al 2019

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HOW DO I ORDER PHARMACOGENETIC TESTING?

- Choosing a test
- Obtaining a test
- Insurance coverage
- Coding information

Hess et al 2016

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CHOOSING A TEST

Table 1

Description of commercialized pharmacogenetic tests. RCT = Randomized controlled trail. In RCT(s) and non-RCTs columns only studies that included the investigation of antidepressant outcomes and were publishe international peer-reviewed journals were considered. The number of studies and type of non-RCT (case-control study or observational study) is reported in parenthesis. The most part of reported pharmacogenetic include also medications different from antidepressants, thus only genes included in the antidepressant panel were reported when this information was retrieved, otherwise the reported genes may be relevant also to psychotropic medications' response or side effects (*). References reported in this table are referred to companies' webpages or publications, for references to published studies and quality evaluation of each stud main text and Supplementary Tables 1, 2 and 3.

Name	Producing company	Included genes	RCT(s)	Non-RCT(s)
AmpliChip (Jain, 2005, p. 450)	Roche	CYP2D6 and CYP2C19	No	Yes (2 observational)
Genefolio (Arcera, 2018)	ABG's pharmacogenomics	17 genes (not otherwise specified)*	No	No
Healthspek PGT (Healthspek, 2018)	Healthspek	ABCB1,CYP2C19, F2, MTHFR, ABCG2, CYP2C9, F5, NR1H3, ADRA2A, CYP2D6, GNB3, OPRM1, ADRB1, CYP3A4, GRIK4, RYR1, AGT, CYP3A5, HTR1A, SLC6A2, CACNA1C, DPYD, HTR2A, SLCO1B1, CES1, DRD1, HTR2C, TPMT, CFTR, DRD2, IFNL3, VKORC1, COMT, DRD3, KCNIP1, CYP1A2, EDN1, LDLR*	No	No
Millennium PGT (Millennium Health, 2018)	Millennium Health	CYP2C19, CYP2D6, MTHFR	No	No
DNA4LIFE (DNA4LIFE, 2018)	DNA4LIFE	CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, VKORC1, OPRM1, SLC6A4, SLCO1B1*	No	No
MyDNA (MyDNA, 2018)	MyDNA	CYP2C19, CYP2C9, CYP2D6, CYP1A2, CYP3A4/A5, VKORC1, SLCO1B1*	No	No
GeneSight (Assurex, 2018)	Assurex	CYP2D6, CYP2C19, CYP1A2, CYP2B6, CYP2C9, CYP3A4, SLC6A4, HTR2A	Yes (1)	Yes (3 case-control; 1 observational)
Genecept (Genomind, 2018)	Genomind	SLC6A4, CACNA1C, ANK3, 5HTR2C, MC4R, DRD2, MTHFR, BDNF, YP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4/5	No	Yes (1 case-control; 1 observational)
CNSDose (CNSDose, 2018)	CNSDose	ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1	Yes (1)	Yes (1 observational)
Youscript psychotropic (Geneles, 2018)	Geneles	CYP2D6, CYP2C9, CYP2C19, CYP3A4/A5, CYP1A2, SLC6A4, HTR2A	Yes (1)	Yes (1 observational; 1 case-control)
Neuropharmagen (AB-Biotics SA, 2018)	AB-Biotics SA	ABCB1, AKT1, BDNF, CACNG2, CES1, COMT, CHRH1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HTR1A, HTR2A/2C, LPHN3, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT2B15	Yes (1)	Yes (1 observational)
Mental Health DNA Insight (Pathway genomics, 2018)	Pathway genomics	CYP1A2, CYP2C19, CYP2D6, DRD2, HLA-B, HTR2A/2C, SLC6A4, UGT1A4*	No	No
RightMed (OneOme, 2018)	OneOme	CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4/A5, GRIK4, HTR2A	No	No
BiogenIQ (BIOGENIQ, 2018)	BIOGENIQ	CYP2C19, CYP2C9, CYP2D6, CYP2B6, POR	No	No
Antidepressant panel (Quest Diagnostics, 2018)	Quest Diagnostics	CYP2D6	No	No
INFINITI CYP2C19 Assay (AutoGenomics, 2018)	AutoGenomics	CYP2C19	No	No
Drug-gene testing (Mayo Clinic, 2018)	Mayo Clinic	CYP2D6, CYP2C19	No	No
STA2R (StureGene and PGxI, 2018)	StureGene and PGxI	SULT4A1, CYP2D6, CYP2C9, CYP2C19, CYP1A2, CYP3A4, CYP3A5, SLC6A4, MTHFR*	No	No
Pharmacogenetic testing (LabCorp, 2018)	LabCorp	CYP2D6, CYP2C9, CYP2C19, CYP1A2, SLC6A4, HTR2A/C*	No	No
TreatGx (GenXys, 2018)	GenXys	> 60 genetic markers in genes including CYP2C19, CYP2C9, CYP2D6, VKORC1, G6PD, HLA-A, HLA-B, SLCO1B1*	No	No
HELOmet (Genomas, 2018)	Genomas	CYP2D6, CYP2C9, CYP2C19	No	Yes (1 observational, only inclu CYP2D6)
Knight (MD labs, 2018)	MD labs	ANKK1, ADRA2A, COMT, CYP2B6, CYP2C19, CYP2C8, CYP2C9, CYP2D6, CYP3A4/A5, DPYD, GRIK4, HTR2C, MTHFR, OPRM1, SLCO1B1, TPMT, UGT2B15, VKORC1	No	No
GeneAlign (GeneAlign, 2018)	GeneAlign	19 genes associated with the metabolism, response and interactions (not otherwise specified)*	No	No
RenaissanceRX (RenaissanceRX, 2018)	RenaissanceRX	CYP3A4/3A5, CYP2C19, CYP2D6	No	No
Antidepressants and antipsychotics pharmacogenetics (CGC Genetics, 2018)	CGC Genetics	CYP2D6, CYP2C19	No	No
PGxOne (Admera Health, 2018)	Admera Health	GRIK4, HTR2A/1A, SLC6A4, ABCB1, ADRA2A, CYP2D6, CYP2C19, CYP3A4, CYP1A2	No	No
PGxcheck (Genoyouin, 2018)	Genoyouin	CYP2D6, CYP2C19, CYP2C9, CYP3A4/A5, CYP1A2, OPRM1, SLCO1B1, VKORC1*	No	Yes (1 observational)
GeneTrait Psychotropic Panel (GeneTrait Laboratories, 2018)	GeneTrait Laboratories	9 genes (not otherwise specified)*	No	No
Pharmacogenetic panel (Bio.logis, 2018)	Bio.logis	COMT, CYP1A2, CYP2C19, CYP2D6, OPRM1, SLC19A1	No	No
Pharmacogenetic Screen (Sonic Genetics, 2018)	Sonic Genetics	CYP2D6, CYP2C19	No	No
Pharmacogenomic tests (Lab Tests Online, 2018)	Lab Tests Online	CYP2D6, CYP2C9, CYP2C19, CYP1A2, SLC6A4, HTR2A/C*	No	No
Pharmacogenetic Psychiatry report (Alpha Genomix, 2018)	Alpha Genomix	CYP2D6, CYP2C9, CYP2C19, CYP3A, CYP1A2	No	No
Pharmacogenetic testing (Ancillary Medical Solutions, 2018)	Ancillary Medical Solutions	CYP450 genes	No	No
Drug metabolism (Vantari Genetics, 2018)	Vantari Genetics	CYP2D6, CYP2C19	No	No

(continued on next

- Over 40 available, some in labs
- Order from company directly or call lab
- Complete patient sample in office (blood or cheek swab) and send per package instructions
- Turn around advertised as 36 hours to a few weeks

"Pharmacogenetic tests to guide drug treatment in depression"
Fabbri et al 2018

FDA TABLE OF BIOMARKERS

- FDA drug labeling for 28 psychiatric medications includes CYP450 pharmacogenetic information
  - Antidepressants with dosing guidelines: citalopram, nortriptyline, venlafaxine, vortioxetine
  - Others: Aripripazole, brexpripazole, clozapine, atomoxetine, iloperidone

Table of Pharmacogenomic Biomarkers in Drug Labeling

Amitriptyline	Psychiatry	CYP2D6	Precautions
Amoxapine	Psychiatry	CYP2D6	Precautions
Amphetamine	Psychiatry	CYP2D6	Clinical Pharmacology
Aripiprazole	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Aripiprazole Lauroxil	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Atomoxetine	Psychiatry	CYP2D6	Dosage and Administration, Warnings and Precautions, Adverse Reactions, Drug Interactions, Use in Specific Populations, Clinical Pharmacology
Brexpiprazole	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Cariprazine	Psychiatry	CYP2D6	Clinical Pharmacology
Citalopram (1)	Psychiatry	CYP2C19	Dosage and Administration, Warnings, Clinical Pharmacology
Citalopram (2)	Psychiatry	CYP2D6	Clinical Pharmacology
Clomipramine	Psychiatry	CYP2D6	Precautions
Clozapine	Psychiatry	CYP2D6	Dosage and Administration, Use in Specific Populations, Clinical Pharmacology
Desipramine	Psychiatry	CYP2D6	Precautions
Desvenlafaxine	Psychiatry	CYP2D6	Clinical Pharmacology
Doxepin (1)	Psychiatry	CYP2D6	Clinical Pharmacology
Doxepin (2)	Psychiatry	CYP2C19	Clinical Pharmacology
Duloxetine	Psychiatry	CYP2D6	Drug Interactions

https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

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FDA TABLE OF BIOMARKERS

- Example of guidelines based on biomarker: citalopram
  - Take away points for citalopram: change maximum dose based on metabolizing status (CYP2C19 poor metabolizers), but no change based on other metabolizer types (CYP2D6)

020822, 01/04/2017	Citalopram (1)	Psychiatry	CYP2C19	Dosage and Administration, Warnings, Clinical Pharmacology	**DOSAGE AND ADMINISTRATION** *Special Populations* 20 mg/day is the maximum recommended dose for patients who are greater than 60 years of age, patients with hepatic impairment, and for CYP2C19 poor metabolizers or those patients taking cimetidine or another CYP2C19 inhibitor. (see WARNINGS) **WARNINGS** *QT-Prolongation and Torsade de Pointes* The citalopram dose should be limited in certain populations. The maximum dose should be limited to 20 mg/day in patients who are CYP2C19 poor metabolizers or those patients who may be taking concomitant cimetidine or another CYP2C19 inhibitor, since higher citalopram exposures would be expected. **CLINICAL PHARMACOLOGY** **Pharmacokinetics** *Population Subgroups* (…) CYP2C19 poor metabolizers – In CYP2C19 poor metabolizers, citalopram steady state Cmax and AUC was increased by 68% and 107%, respectively. Celexa 20 mg/day is the maximum recommended dose in CYP2C19 poor metabolizers due to the risk of QT prolongation (see WARNINGS and DOSAGE AND ADMINISTRATION). CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
020822, 01/04/2017	Citalopram (2)	Psychiatry	CYP2D6	Clinical Pharmacology	**CLINICAL PHARMACOLOGY** **Pharmacokinetics** *Population Subgroups* CYP2D6 poor metabolizers - Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6. *Drug-Drug Interactions* Coadministration of a drug that inhibits CYP2D6 with Celexa is unlikely to have clinically significant effects on citalopram metabolism, based on the study results in CYP2D6 poor metabolizers.

https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

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INSURANCE COVERAGE

MEDICARE AND MEDICAID

- Traditional Medicare and Medicaid cover some tests as of recently

COMMERCIAL PAYORS

- Coverage varies
- Not covered to prior authorization required (Regence, Aetna, UHC)
- Recommend calling insurer

UnitedHealthcare®

UnitedHealthcare® Commercial
Medical Policy

PHARMACOGENETIC TESTING

COVERAGE RATIONALE

The use of pharmacogenetic multigene testing panels for genetic polymorphisms is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.
Examples of these panels include, but are not limited to the following:

- AIBioTech® CardioloGene Genetic Panel
- AIBioTech® Pain Management Panel
- AIBioTech® PsychiaGene Genetic Panel
- AIBioTech® Urologene Panel
- AIBioTech® PersonaGene Panel
- Genecept™ Assay
- GeneSight® Analgesic
- GeneSight® Psychotropic
- GeneSight® ADHD
- Millennium PGT℠
- Proove® Drug Metabolism test panel
- Proove® Narcotic Risk test panel
- SureGene Test for Antipsyc[Screenshot]pressant Response (STA²R)

https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/pharmacogenetic-testing.pdf

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CODING INFORMATION

- Some pharmacogenetic tests may require more than one CPT code
- Can consider contacting PGx company to ask about other CPT codes

Examples of Pharmacogenomic Tests with Associated CPT Codes for Identification and Documentation

CPT Code	Test	Description of Test
81225	CYP2C19 genotyping	Detects genetic variants of CYP2C19 associated with variable drug metabolism
81226	CYP2D6 genotyping	Detects genetic variants of CYP2D6 associated with variable drug metabolism
81227	CYP2C9 genotyping	Detects genetic variants of CYP2C9 associated with variable drug metabolism

CPT Code	Description
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
0078U	Pain management (opioid-use disorder) genotyping panel, 16 common variants (ie, ABCB1, COMT, DAT1, DBH, DOR, DRD1, DRD2, DRD4, GABA, GAL, HTR2A, HTTLPR, MTHFR, MUOR, OPRK1, OPRM1), buccal swab or other germline tissue sample, algorithm reported as positive or negative risk of opioid-use disorder

Hefti and Blanco 2016

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DIRECT TO CONSUMER TESTING

FDA News Release

FDA authorizes first direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism

- FDA permits marketing of the 23andMe Personal Genome Service Pharmacogenetic Reports test as a direct-to-consumer test
  - Self collected saliva samples
  - 33 possible genetic variants, 4 members of CYP 450 family
- FDA authorizes information about metabolizer status, but not predicted response to specific medications
- >12 million Americans have used companies like 23andMe and AncestryDNA.

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ETHICAL CONSIDERATIONS

- Genetic Information Nondiscrimination Act (GINA, 2008)
  - Regulates how genetic information is used
  - Protects against discrimination in health insurance and employment.
  - Significant limitations - life insurance, long-term care insurance and to employers with less than 15 employees.

The NEW ENGLAND JOURNAL of MEDICINE

"Our current regulatory approach to privacy in direct-to-consumer genealogic testing has permitted the creation of a Wild West environment."

May, *NEJM* 2018; Forbes 2018

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TAKE HOME POINTS

- Evidence is limited for PGx testing
  - Guidelines do not recommend routine screening
  - No clear recommendations on when or who to test
- Insurance and cost limitations persist
  - If patients are interested or ask, can inquire with insurance companies first
- Strategies for Pgx testing
  - Focus on metabolizer status
  - If patient has failed multiple medication trials, especially at high doses
  - If patient has repeatedly intolerable SE to multiple medications

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PHARMACOGENETICS RESOURCES

- Clinical Pharmacogenetics Implementation Consortium: https://cpicpgx.org/guidelines/
- FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
  - https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm
- Pharmacogenomics Knowledgebase (PharmGKB):
  - Recommended by APA: www.pharmgkb.org
- IGNITE Network (NIH funded): https://www.genome.gov/27554264/implementing-genomics-in-practice-ignite/
- Dutch Pharmacogenetic Working Group: https://upgx.eu/guidelines/
- APA Task Force Report: "Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing"
- Washington Health Care Authority Report: https://www.hca.wa.gov/assets/program/pharmacogenomics-final-rpt-20161209.pdf
- Fabbri, Chiara, Joseph Zohar, and Alessandro Serretti. "Pharmacogenetic Tests to Guide Drug Treatment in Depression." *Progress in Neuro-psychopharmacology & Biological Psychiatry.* 86 (2018): 36-44.

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GUIDELINES: CPIC

- Clinical Pharmacogenetics Implementation Consortium (CPIC®) : international consortium of volunteers interested in facilitating of PGx tests for patient care.
  - For CYP2D6 or CY2C19 poor metabolizers with greatly reduced metabolism of tricyclic antidepressants or SSRIs, consider a 25% to 50% reduction of the recommended starting dose.
  - Dose tricyclic antidepressants or SSRIs based on CYP2D6 or CYP2D6 gene phenotypes (ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, or poor metabolizer).
    - Use alternative drug not predominantly metabolized by the either the CYP2D6 or CY2C19 for ultra-rapid metabolizers

Fabbri et al 2018

COMBINATORIAL PHARMACOGENOMIC TEST

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

PATIENT GENOTYPES AND PHENOTYPES

PHARMACOKINETIC GENES (PK)

CYP1A2 — **Extensive (Normal) Metabolizer**
*1/*1

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 — **Ultrarapid Metabolizer**
*17/*17

CYP2C19*17 allele enzyme activity: Increased
CYP2C19*17 allele enzyme activity: Increased

This genotype is most consistent with the ultrarapid metabolizer phenotype. This patient may have increased enzyme activity as compared to individuals with the normal 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 — **Poor Metabolizer**
*4/*4 (Duplication)

CYP2D6*4 allele enzyme activity: None
CYP2D6*4 allele enzyme activity: None

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.

A duplication of the gene CYP2D6 has been detected in this patient. While current genotyping techniques allow for the detection of this duplication, in the case of heterozygosity, such techniques do not allow for the identification of the allele that has been duplicated. This duplication, depending on the allele duplicated, can result in increased expression of CYP2D6.

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 — **Intermediate Metabolizer**
*2/*2

UGT2B15*2 allele enzyme activity: Reduced
UGT2B15*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.

COMBINATORIAL PHARMACOGENOMIC TEST

Patient, Sample
DOB: 7/22/1984
Order Number: 9904
Report Date: 6/22/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

PATIENT GENOTYPES AND PHENOTYPES

PHARMACODYNAMIC GENES (PD)

SLC6A4 — **Reduced Response**
S/S

This patient is homozygous for the short promoter polymorphism of the serotonin transporter gene. The short promoter allele is reported to decrease expression of the serotonin transporter compared to the homozygous long promoter allele. The patient may have a decreased likelihood of response to selective serotonin reuptake inhibitors due to the presence of the short form of the gene and may benefit from medications with an alternative mechanism of action.

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.

HLA-B*1502 — **Higher Risk**
Present

This patient carries either the HLA-B*1502 allele or a closely related *15 allele. Presence of HLA-B*1502 or some of the closely related *15 alleles suggests higher risk of serious dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) when taking certain mood stabilizers.

HLA-A*3101 — **Higher Risk**
A/T

This patient is heterozygous for the A allele and the T allele of the rs1061235 A>T polymorphism indicating presence of the HLA-A*3101 allele or certain HLA-A*33 alleles. This genotype suggests a higher 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.

According to APA Task Force and FDA, pharmacokinetic testing has some evidence base, but pharmacodynamic does not

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REVIEW: WASHINGTON HCA 2016

Washington State Health Care Authority

"Pharmacogenomic Testing for Selected Conditions Final Evidence Report"

Number, Size, and Quality of Studies	Quality of Evidence	Direction of Findings	Key Study Results
KQ #1a. Impact of pharmacogenomic testing on clinical decision-making			
4 studies Exp n=183 Ctl n=183 ***Depressive disorders*** Singh 2015 (RCT, fair) Winner 2013 (RCT, fair) Hall-Flavin 2012 (controlled trial, fair) Breitenstein 2014 (comparative, poor)	**OVERALL: LOW** **Study quality:** Poor-Fair **Quantity and precision:** Few studies, small sample sizes, some patient populations limited by race/ethnicity; precision unknown **Consistency:** Outcomes generally consistent; not measured similarly **Applicability to PICO:** ✓ **Reference standard:** ✓ **Publication bias:** Unknown	Limited results suggest that PGx test results, whether single-gene or interpretive panels, may change prescribing patterns in favor of PGx recommendations compared with treatment as usual.	***Singh 2015 (Exp n=74)*** • Treatment prescribers indicated that in 65% of cases, a PGx panel interpretive report led to medication dosing different from their usual practice. ***Winner 2013 (Exp n=26 vs Ctl n=25; all genotyped, see Key)*** • 100% of baseline medications that a PGx panel interpretive report indicated should be used with caution and frequent monitoring were changed in the Exp group; 50% of similarly classified medications were changed/dose adjusted in Ctls. ***Hall-Flavin 2012 (Exp n=25 vs Ctl n=26; all genotyped, see Key)*** • At 8 wks, 5.9% of Exp cases were prescribed a medication designated "use with caution" on PGx panel interpretive report vs 21.4% of controls (*P*=0.02). ***Breitenstein 2014 (Exp n=58)*** • By 5 wks, prescribers increased dose of appropriate antidepressants 1.63-fold for genotyped pts (Exp) with an unfavorable *ABCB1* genotype (*P*=0.012) and changed antidepressant prescribed more often (*P*=0.011) compared with other genotypes.

https://www.hca.wa.gov/assets/program/pharmacogenomics-final-rpt-20161209.pdf

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