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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

PHARMACOGENETICS TESTING IN PSYCHIATRY

FOCUS ON ANTIDEPRESSANTS AND MOOD STABILIZERS

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SPEAKER DISCLOSURES

✓ I have no disclosures

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OBJECTIVES

- Review background of pharmacogenetics
- Evidence base for use in selecting antidepressant and mood stabilizer
- Current guidelines and recommendations
- Concerns: cost, ethical, privacy
- Review logistics of tests available

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PHARMACOGENETIC TESTING IN PSYCHIATRY ON THE RISE

Health & Science

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

March 31, 2019
Washington Post

PSYCHIATRIC NEWS — AMERICAN PSYCHIATRIC ASSOCIATION

Pharmacogenomic Tests in Psychiatry: Not Ready for Prime Time

CHARLES NEMEROFF, M.D., Ph.D.

Published Online: 14 May 2019 | https://doi.org/10.1176/appi.pn.2019.5b12

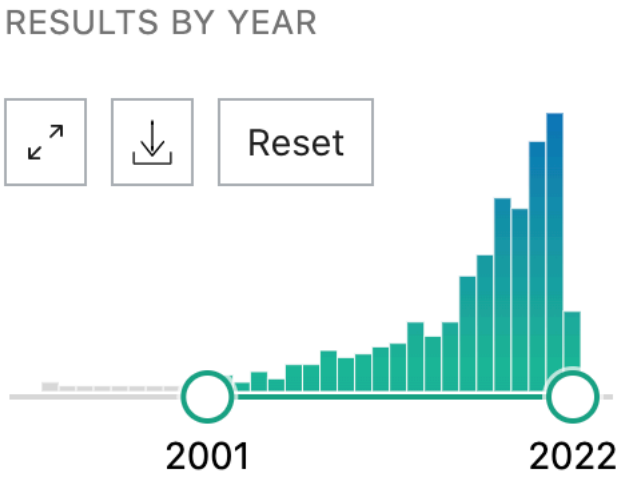
Pharmacogenetic testing for psychotropic medications of limited value in children

July 1, 2020

Samantha A. Schrier Vergano, M.D., FACMG, FAAP

AAP News™

PubMed Search Results



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PHARMACOGENETIC TESTING ON THE RISE IN PSYCHIATRY

- Why is pharmacogenetic testing on the rise?
- Why are there concerns about its use in practice?
- Why is it on the market if it's "not ready for primetime"?
- What are the evidence-based ways we can utilize it, and for what?

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PHARMACOGENETICS

- Pharmacogenetics (PGx): study of DNA/gene variations and their effect on drug metabolism, efficacy and tolerability, to predict patient response to medication.
- History:
  - 1900, three blood groups → 1956, G6PD deficiency → 1977, cytochrome P450 enzymes
- Currently utilized for a wide range of medications
  - >140 FDA-approved drugs with pharmacogenetic information
- Support from policy level:
  - In Jan 2015, the Precision Medicine Initiative was introduced
- Language: 'personalized' or 'precision' medicine, PGx or PGen

Baskys 2019, Hess et al 2016, Zeier et al 2018, Butler 2018;
https://obamawhitehouse.archives.gov/precision-medicine

WHY PHARMACOGENETICS IN PSYCHIATRY?

- 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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PHARMACOGENETICS MECHANISMS

- Pharmacokinetics
- Pharmacodynamics

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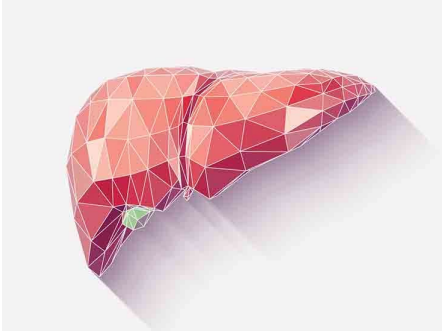
PHARMACOKINETICS: MEDICATION METABOLISM

- 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



Baskys 2018, Ruano et al 2013, Butler 2018

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MEDICATION METABOLISM

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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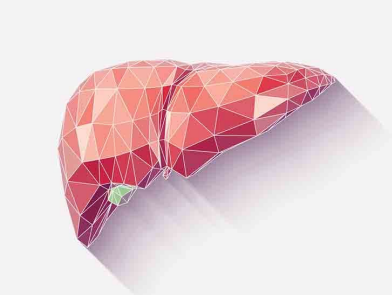
GENETIC VARIANTS AND MED METABOLISM



- Changes in CYP 450 enzymes' genes can impact medication efficacy, SE
  - Deletions = no or poor enzyme activity
  - Duplications/multiplications = increased or rapid activity

Baskys 2018, Ruano et al 2013, Butler 2018

METABOLIZER GENOTYPE AND PHENOTYPE

Likely Phenotype	Genotype (An individual carrying…)
Ultrarapid metabolizer (5-30% of patients)	-two increased function alleles or -one normal function allele and one increased function allele
Extensive (normal) metabolizer (~35–50% of patients)	-two normal function alleles
Intermediate metabolizer (~18–45% of patients)	-one normal function allele or -one increased function allele and one no function allele
Poor metabolizer (~2–15% of patients)	-two no function alleles

Slide by Jennifer Jepsen, Clinical Psychiatric Pharmacist, Harborview

Hick J, et al. Clinical Pharmacology and Therapeutics. 2015 Feb;98(2):127-134.

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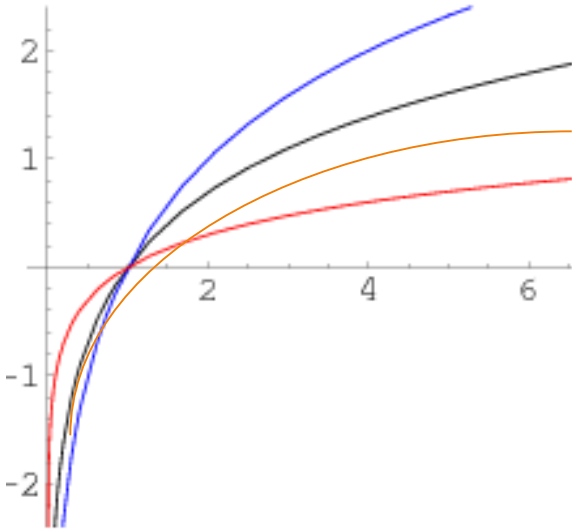
MEDICATION LEVEL BY PHENOTYPE



- PM=Poor Metabolizer
  - increased toxicity or increased efficacy
- IM=Intermediate Metabolizer
  - possible increase in adverse effects and efficacy
- EM=Extensive Metabolizer
  - normal adverse effects and efficacy
- UM=Ultrarapid Metabolizer
  - decreased efficacy but little adverse effects

Slide by Jennifer Jepsen, Clinical Psychiatric Pharmacist, Harborview

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PHARMACODYNAMICS

- 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*

Baskys 2019, Bousman and Mueller 2018, Hess et al 2016, Fabbri et al 2018, Lohoff 2011; Bousman C et al 2021

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PHARMACODYNAMICS

- Immunology and adverse medication reaction
- Human Leukocyte Antigens (HLA) part of immune response
- Specific genetic variants of HLA are associated with antiepileptic induced adverse effects (Steven's Johnson Syndrome, for example)

Yang 2007
Jaurthompsophon 2017

Slide by Jennifer Jepsen, Clinical Psychiatric Pharmacist, Harborview

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PHARMACOGENETIC TEST EXAMPLES

- 40+ tests currently available
- Can include information about metabolizer status, candidate gene information and HLA variants
  - No two panels are precisely the same
  - “combinatorial” – includes multiple types of tests

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@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.

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

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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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Patient, Sample
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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.

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

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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.

Just because information/results are on the test doesn't mean there is good evidence for their use!

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OVERVIEW OF CURRENT RESEARCH

- 16+ systematic reviews of PGx in psychiatry
- 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 and provider satisfaction
- RCTs: GeneSight, CNSDose, Genelex, Neuropharmagen, NeuroIDgenetix
- Most studies commercially funded, though now more with other funding sources

Fabbri et al 2018; Lara DV et al 2021

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

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.

"(STAR * D) study, the Genome-based Therapeutic Drugs for Depression (GENDEP) Project, and the Munich Antidepressant Response Signature (MARS), as well as the International SSRI Pharmacogenomics Consortium GWAS analysis have not consistently supported any single pharmacodynamic gene variant as a significant predictor of antidepressant treatment response."
- Bousman C et al 2021

Scale: 1A (strong evidence) to 4 (preliminary evidence)
Reviewed RCTs, observational and cost effectiveness studies

Zeier et al 2018; Bousman C et al 2021

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

- Pharmacokinetic testing for metabolizer status has some evidence base, but pharmacodynamic has less
- "insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects"

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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META-ANALYSIS: ANTIDEPRESSANTS AND PGX

- Bousman et al 2018
  - RCTs that examined pharmacogenetic tests and depressive sx remission in MDD
  - 1737 eligible subjects from five RCTs

Bousman et al 2018

META-ANALYSIS: ANTIDEPRESSANTS AND PGX

- **Results**: Pts with pharmacogenetic testing were 1.71 times more likely to achieve symptom remission compared to patients in usual care.

- **Conclusion**: Pharmacogenetic testing might improve symptom remission among those with MDD.

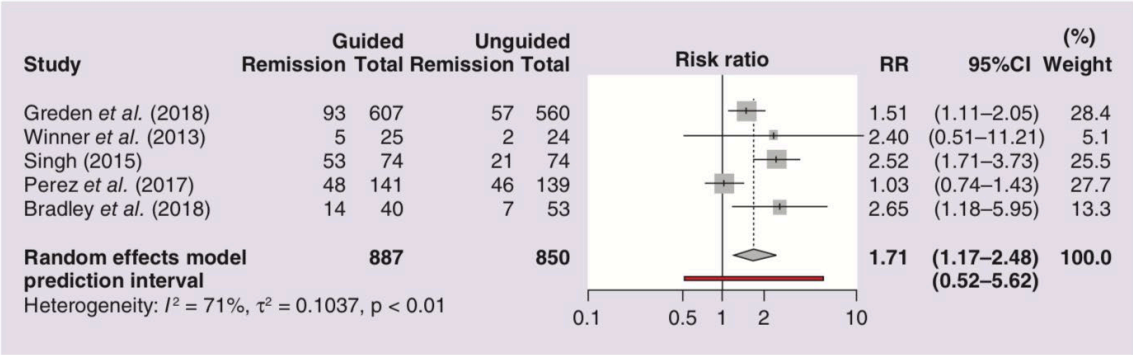

Figure 2. Forest plot of random-effects meta-analyses of five prospective, randomized controlled trials that examined the effect of pharmacogenetic-guided therapy on remission in major depressive disorder.
RR: Relative risk.

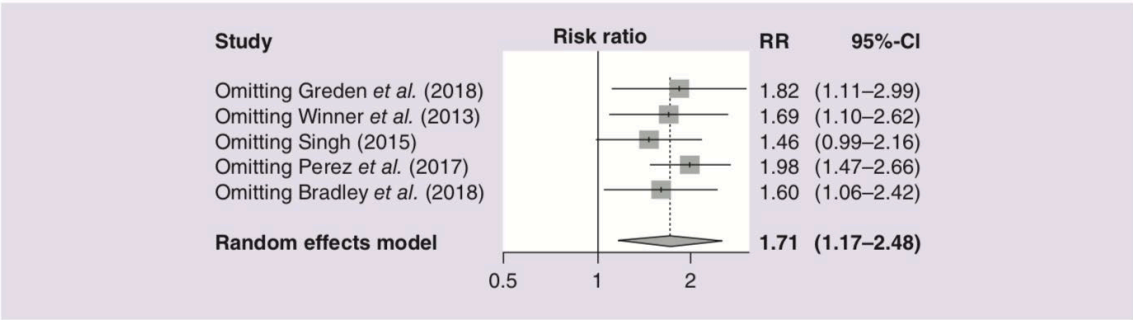

Figure 3. Forest plot of random-effects meta-analyses after omission of each of the five prospective, randomized controlled trials.
RR: Relative risk.

Bousman et al 2018

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RCTS IN CHILD/ADOLESCENTS

- Not as much literature for PGx in child and adolescents
- One RCT (VandeVort 2022) for the pharmacologic treatment of adolescents (N = 176; 13-18yo) with moderate to severe MDD
- One pragmatic randomized trial (Claudio-Campos K 2021) (N = 49; 8-20 yo) with depression, anxiety, OCD
- Both PGx vs usual care
- No differences between groups for clinical endpoints (12 weeks, 6 mos)
- Pragmatic study:
  - 8-14 days to receive results
  - All physicians felt it facilitated med choice
  - Parents/pts openness improved
  - $100-$200 cost per test

Vande Vort et al 2022; Claudio-Campos K et al 2021

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MOOD STABILIZERS AND ADVERSE REACTIONS

- Clinical Pharmacogenetics Implementation Consortium (CPIC) evidence summary:
  - HLA-B*15:02 is strongly associated with greater risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine.
  - HLA-A*31:01 is associated with greater risk of maculopapular exanthema, drug reaction with eosinophilia and systemic symptoms, and SJS/TEN in patients treated with carbamazepine.

https://files.cpicpgx.org/data/guideline/publication/carbamazepine/2017/CPIC_HLA_CBZ_OXC.pdf

LAMOTRIGINE AND ADVERSE REACTIONS

- 2018 meta-analysis “Association between HLA alleles and lamotrigine-induced cutaneous adverse drug reactions in Asian populations”
- 11 studies
- Based on Chinese, Korean, and Thai populations
- Observed that HLA-B*1502 is a risk allele for LTG-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in Chinese populations (pooled OR 2.4, 95% CI: 1.20–4.78, P = 0.01)

Deng y et al 2018

FDA STATEMENT (2020)

- *"FDA has evaluated and believes there is sufficient scientific evidence to suggest that subgroups of patients with certain genetic variants … are likely to have altered drug metabolism, and in certain cases, differential therapeutic effects, including differences in risks of adverse events."*

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

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FDA TABLE OF PHARMACOGENETIC ASSOCIATIONS

- Tables of pharmacogenetic associations with:
  - 1) Therapeutic Management Recommendations
  - 2) Potential Impact on Safety or Response
  - 3) Potential Impact on Pharmacokinetic Properties Only

Section 1: Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations

Drug	Gene	Affected Subgroups+	Description of Gene-Drug Interaction
Abacavir	HLA-B	*57:01 allele positive	Results in higher adverse reaction risk (hypersensitivity reactions). Do not use abacavir in patients positive for HLA-B*57:01.
Amifampridine	NAT2	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Use lowest recommended starting dosage and monitor for adverse reactions. Refer to FDA labeling for specific dosing recommendations.
Amifampridine Phosphate	NAT2	poor metabolizers	Results in higher systemic concentrations. Use lowest recommended starting dosage (15 mg/day) and monitor for adverse reactions.
Amphetamine	CYP2D6	poor metabolizers	May affect systemic concentrations and adverse reaction risk. Consider lower starting dosage or use alternative agent.
Aripiprazole	CYP2D6	poor metabolizers	Results in higher systemic concentrations and higher adverse reaction risk. Dosage adjustment is recommended. Refer to FDA labeling for specific dosing recommendations.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

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FDA TABLE OF BIOMARKERS

- FDA drug labeling for 40 psychiatric medications includes pharmacogenetic information
- 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.

https://www.fda.gov/media/124784/download
https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm

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ISPG REVIEW/CONSENSUS (2021)

- International Society of Psychiatric Genetics supports PGx testing for:
  - antidepressants (CYP2C19 and CYP2D6)
  - antipsychotics (CYP2D6)
  - ADHD medication atomoxetine (CYP2D6)
  - anticonvulsants (CYP2C9, HLA-A, and HLA-B)
- The current evidence does not support the use of genetic variants in pharmacodynamic genes (e. g., SLC6A4, COMT, MTHFR) to inform prescribing.

Bousman C et al 2021, **Review and Consensus on Pharmacogenomic Testing in Psychiatry**
https://ispg.net/genetic-testing-statement/

ISPG REVIEW/CONSENSUS (2021)

▶ **Table 1** Actionable pharmacogenetic guidelines and product labels by antidepressants.

	Actionable Guideline Available[1]		Product Label[2]			
Antidepressant	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Amitriptyline	CYP2C19, CYP2D6	CYP2D6	CYP2D6	–	–	–
Amoxapine	–	–	CYP2D6	–	–	–
Citalopram	CYP2C19	CYP2C19	CYP2C19	–	–	CYP2C19
Clomipramine	CYP2C19, CYP2D6	CYP2D6	CYP2D6	–	–	–
Desipramine	CYP2D6	–	CYP2D6	–	–	–
Doxepin	CYP2C19, CYP2D6	CYP2D6	CYP2C19, CYP2D6	–	–	–
Duloxetine	–	–	CYP2D6	CYP2D6	–	–
Escitalopram	CYP2C19	CYP2C19	–	–	CYP2C19	–
Fluvoxamine	CYP2D6	–	CYP2D6	–	–	–
Imipramine	CYP2C19, CYP2D6	CYP2C19, CYP2D6	CYP2D6	–	–	–
Nortriptyline	CYP2D6	CYP2D6	CYP2D6	–	–	CYP2D6
Paroxetine	CYP2D6	CYP2D6	–	–	–	–
Protriptyline	–	–	CYP2D6	–	–	–
Sertraline	CYP2C19	CYP2C19	–	–	–	–
Trimipramine	CYP2C19, CYP2D6	–	CYP2D6	–	–	–
Venlafaxine	–	CYP2D6	CYP2D6	–	–	–
Vortioxetine	–	–	CYP2D6	CYP2D6	–	CYP2D6

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: agomelatine, buproprion, desvenlafaxine, fluoxetine, levomilnacipran, mianserin, mirtazapine, milnacipran, nefazodone, phenelzine, reboxetine, selegiline, tranylcypromine, trazodone, and vilazodone.

Screenshot

Bousman C et al 2021, **Review and Consensus on Pharmacogenomic Testing in Psychiatry**

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ISPG REVIEW/CONSENSUS (2021)

▶ **Table 2** Actionable pharmacogenetic guidelines and product labels by antipsychotics.

	Actionable Guideline Available[1]		Product Label[2]			
Antipsychotic	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Aripiprazole	–	CYP2D6	CYP2D6	CYP2D6	–	CYP2D6
Brexpiprazole	–	CYP2D6	CYP2D6	CYP2D6	–	–
Clozapine	–	–	CYP2D6	–	–	–
Haloperidol	–	CYP2D6	–	–	–	–
Iloperidone	–	–	CYP2D6	–	–	–
Perphenazine	–	–	CYP2D6	–	CYP2D6	–
Pimozide	–	CYP2D6	CYP2D6	–	–	–
Risperidone	–	CYP2D6	–	–	–	–
Thioridazine	–	–	CYP2D6	–	–	–
Zuclopenthixol	–	CYP2D6	–	–	–	–

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: asenapine, cariprazine, chlorpromazine, fluphenazine, loxapine, lurasidone, olanzapine, paliperidone, promethazine, quetiapine, thiothixene, trifluoperazine, and ziprasidone.

Bousman C et al 2021, **Review and Consensus on Pharmacogenomic Testing in Psychiatry**

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ISPG REVIEW/CONSENSUS (2021)

▶ **Table 3** Actionable pharmacogenetic guidelines and product labels by mood stabilizers/anticonvulsants.

	Actionable Guideline Available[1]		Product Label[2]			
Mood stabilizers/ anticonvulsants	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Carbamazepine	HLA-A, HLA-B	–	HLA-A, HLA-B	–	HLA-A, HLA-B	HLA-A, HLA-B
Oxcarbazepine	HLA-B	–	HLA-B	–	–	HLA-B
Phenytoin	CYP2C9, HLA-B	CYP2C9	HLA-B	–	–	HLA-B
Valproic acid	–	–	OTC, POLG	–	CPS1, OTC	OTC, POLG

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: eslicarbazepine, gabapentin, lamotrigine, levetiracetam, lithium, phenobarbital, pregabalin, topiramate, vigabatrin, and zonisamide.

Bousman C et al 2021, **Review and Consensus on Pharmacogenomic Testing in Psychiatry**

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GUIDELINES: CLINICAL PHARMACOGENETICS IMPLEMENTATION CONSORTIUM

- *CYP2D6 and Atomoxetine*
- *CYP2D6, CYP2C19 and Selective Serotonin Reuptake Inhibitors*
- *CYP2D6, CYP2C19 and Tricyclic Antidepressants*
- *CYP2D6, OPRM1, COMT, and Opioids*
  - Not sufficient evidence for OPRM1 and COMT
- *HLA-A, HLA-B and Carbamazepine and Oxcarbazepine*

Fabbri et al 2018; https://cpicpgx.org/guidelines/

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GUIDELINES: CPIC AND ANTIDEPRESSANTS

- Dose antidepressants based on metabolizer status
  - For poor metabolizers, consider a 25% to 50% reduction of the recommended starting dose of antidepressants.
  - Use alternative drug not predominantly metabolized by the either the CYP2D6 or CY2C19 for ultra-rapid metabolizers

Fabbri et al 2018; https://cpicpgx.org/guidelines/

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GUIDELINES: CPIC AND MOOD STABILIZERS

Genotype	Implication	Recommendation	Strength of Recommendation	Regarding other aromatics
HLA-B *15:02 Negative	Normal risk of SJS/TEN	Use carbamazepine or oxcarbazepine per standard dosing.	Strong	N/A
HLA-B *15:02 Positive	Greater risk of drug induced SJS/TEN	If pt is carb/oxcarb naïve, do not use.	Strong	Use caution with other aromatics*

Of note: lamotrigine not included, but meta-analyses suggest potential for increased risk of SJS/adverse reaction witih HLA-B15:02 positive or carrier

https://files.cpicpgx.org/data/guideline/publication/carbamazepine/2017/CPIC_HLA_CBZ_OXC.pdf

Slide by Jennifer Jepsen, Clinical Psychiatric Pharmacist, Harborview

AACAP (2020)

- **The American Academy of Child and Adolescent Psychiatry recommends:**
  - **Clinicians avoid using pharmacogenetic testing to select psychotropic medications in children and adolescents.**
  - **Future high-quality prospective studies to assess the clinical significance of pharmacodynamic and combinatorial pharmacogenomic testing in children and adolescents.**

https://www.aacap.org/aacap/Policy_Statements/2020/Clinical-Use-Pharmacogenetic-Tests-Prescribing-Psychotropic-Medications-for-Children-Adolescents.aspx

ANTIDEPRESSANTS: WHO TO TEST?

- Antidepressants/antipsychotics
  - ISPG: decision support tool, NOT routine screening
- Strategies in practice:
  - Suspicion of metabolizer status variant:
    - If patient has failed multiple medication trials, especially at high doses
    - If patient has repeatedly intolerable SE to multiple medications, especially at lower doses

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MOOD STABILIZERS AND WHO TO TEST

*FDA: for ox/carbamazepine states, "patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating tx."*

Continent	Population	Allele Frequency (%)	n
Asia	Korean	0.5	200
	Han Chinese	10.2	572
	Singapore	11.6	86
	Malay	8.4	101
	Thai	6.1	99
	Filipino	5.3	94
	India Mumbai Marathas	1	72
	India North Hindi	2	91
	India Khandesh Pawra	6	50

Ferrell 2008

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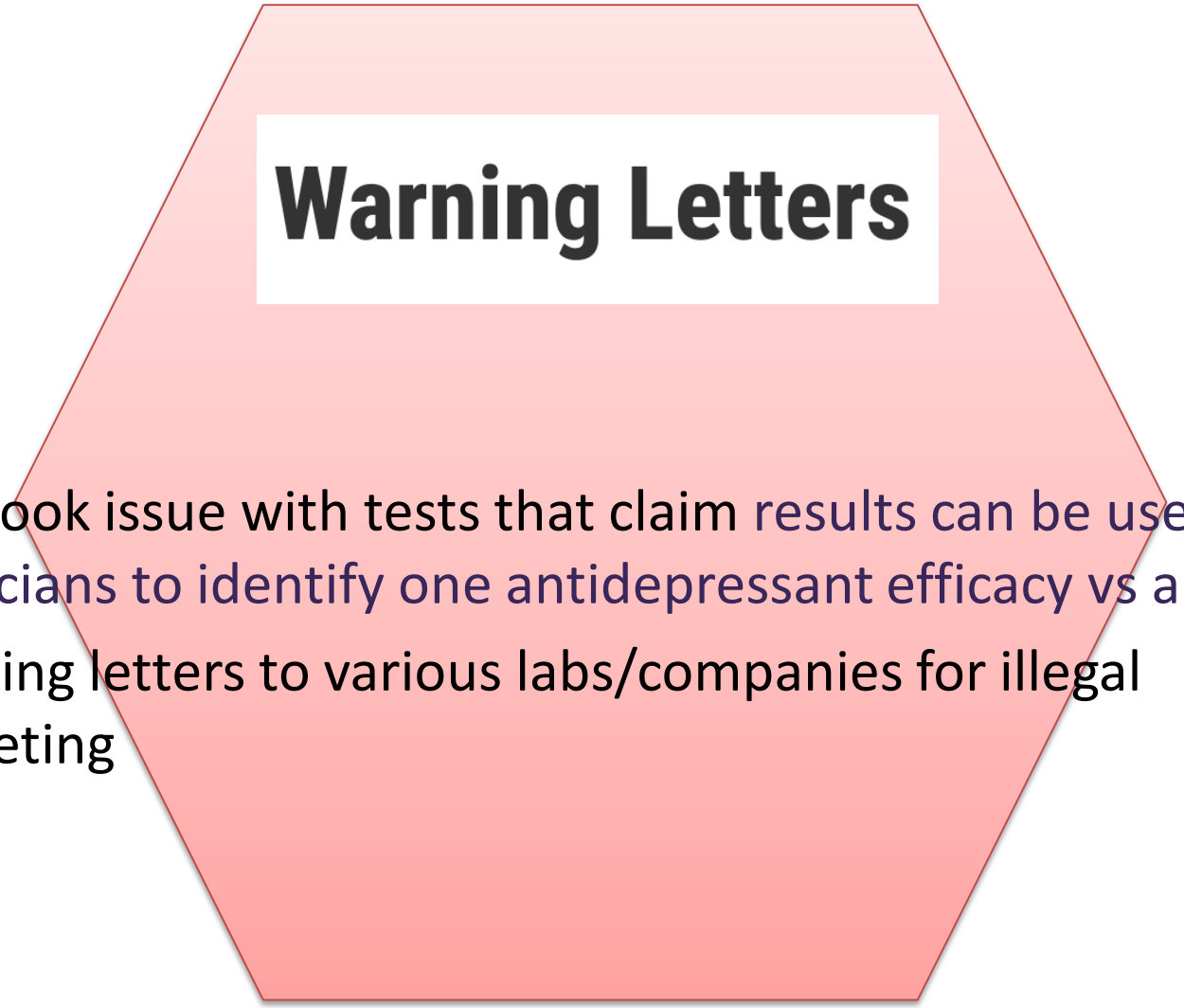
FDA CONCERNS



- FDA took issue with tests that claim results can be used by physicians to identify one antidepressant efficacy vs another.
- Warning letters to various labs/companies for illegal marketing

FDA Press Announcement Nov 2018, update April 2019

FDA CONCERNS

FDA STATEMENT

FDA Announces Collaborative Review of Scientific Evidence to Support Associations Between Genetic Information and Specific Medications

- "The FDA remains concerned with the safe use of these medications based on pharmacogenetic test reports that are not supported by sound science."
- FDA working with Congress to develop new oversight framework for laboratory developed tests (not enough premarket review)

FDA Press Announcement Feb 2020;
https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic

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 authorizes information about metabolizer status, but not predicted response to specific medications

- ***ISIG: Direct to consumer tests come with risks (lack of informed consent, misinterpretation of results) and they do not recommend DTC genetic testing for medical purposes for psychiatry***

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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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RESEARCH AND CLINICAL PRACTICE

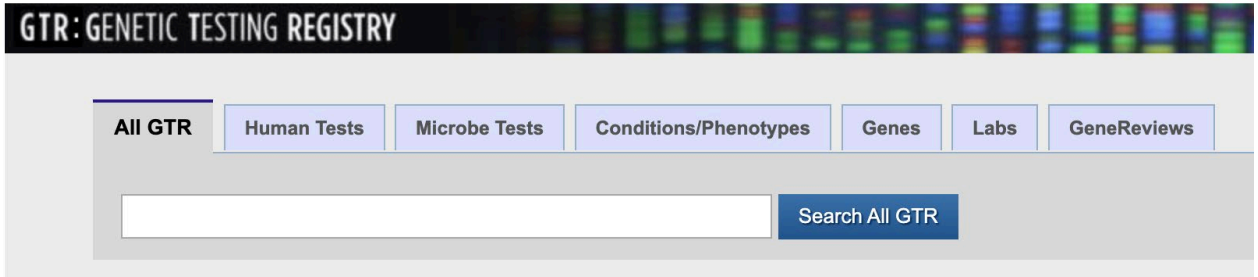
- Research
  - Lack of blinding
  - Conflicts of interest
  - Small sample sizes
  - Short duration of follow-up
  - Lack of appropriate control groups

- Clinical:
  - Concerns about unproven procedures distracting from hx taking
    - JAMA 2018 Viewpoint: Focus on thoughtful dose choice, SE monitoring
    - Bousman response: “Pharmacogenetics in Psychiatry: A Companion, Rather Than Competitor, to Protocol-Based Care”
  - Furthering gaps in health inequities due to expense, barriers to access

Zubenko et al 2018

CHOOSING A TEST

- Both commercial (DTC, branded) and non-commercial (hospital/organization/in-house labs).
- 75+ laboratories/tests in the US
- Options include:
  - 1) Search NIH Genetic Testing Registry (https://www.ncbi.nlm.nih.gov/gtr/)
  - 2) Order from company directly
  - 3) Call local lab or pharmacist



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

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INSURANCE COVERAGE

- **Medicaid and Medicare**
  - Traditional Medicare and Medicaid cover some tests as of recently
- **Commercial payors**
  - Coverage varies
  - Not covered to PA required to coverage for certain tests
  - Recommend pt calling their insurer

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

Park SK 2020

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INSURANCE COVERAGE

2019

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[redacted]pressant R[redacted]

Screenshot

2022

Coverage Rationale

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressant and antipsychotic medications when all the following criteria are met:

- The individual has a diagnosis of major depressive disorder or generalized anxiety disorder; and
- The individual has failed at least one prior medication to treat their condition; and
- The Multi-Gene Panel has no more than 15 relevant genes

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, 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:

- GeneSight® Analgesic
- GeneSight® ADHD
- SureGene Test
- Pain Medication DNA Insights®
- PharmacoDx

The use of the PrismRA® molecular signature test is unproven and not medically necessary for evaluating likelihood of inadequate response to anti-TNF therapies for rheumatoid arthritis due to insufficient evidence of efficacy.

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 insurance or PGx company to ask about other CPT codes

CPT Codes*	Required Clinical Information
Pharmacogenetic Testing	
0173U 0175U 81479	Medical notes documenting the following, when applicable: • Diagnosis • History of illness, including treatments tried and failed • Genes included in the Panel • Name of lab performing test and name of test, if available • Physician treatment plan based on results of genetic testing

**For code descriptions, see the Applicable Codes section.*

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

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TAKE HOME POINTS

- Evidence only for specific aspects of PGx testing
  - Metabolizer status, HLA alleles (anticonvulsants-assoc SJS)
  - Guidelines do not recommend routine screening
  - Mixed consensus on recommendations on when or who to test
- Insurance and cost limitations persist
  - If patients are interested or ask, can inquire with insurance companies
- Strategies for Pgx testing
  - Antidepressants and antipsychotics:
    - If patient has failed multiple medication trials, especially at high doses
    - If patient has repeatedly intolerable SE to multiple medications
  - Mood stabilizers
    - If considering anticonvulsant mood stabilizer in patient with Asian ancestry

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PHARMACOGENETICS RESOURCES

- Clinical Pharmacogenetics Implementation Consortium: https://cpicpgx.org/guidelines/
- International Society of Psychiatry Genetics
  - https://ispg.net/genetic-testing-statement/
- FDA Table of Pharmacogenomic Associations
  - https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
- 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 2018: "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

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