WASHINGTON STATE UNIVERSITY

Pharmacogenomics of Depression

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Conflict of Interest Disclosure

- Nothing to disclose

Learning Objectives

- Determine the impact of genetic variation on drug pharmacokinetics, pharmacodynamics, and drug response
- Interpret pharmacogenomic test results by identifying clinically actionable drug-gene pairs using high-quality, evidence-based pharmacogenomic databases and guidelines to formulate therapeutic recommendations
- Summarize main findings from the literature supporting the use of pharmacogenomics-guided treatment for depression
- Recommend pharmacogenomic testing when appropriate and integrate test results with other clinical variables to optimize medication therapy
- Discuss case examples utilizing various pharmacogenomic testing results to inform appropriate selection of antidepressants for treatment of depression

Status of Mental Health in the United States

- As of 2018, **16 million Americans** suffer from moderate or severe depression
  - Lifetime prevalence of depression is 17%
  - **$210 billion** in annual healthcare costs

- **Antidepressants are the 3rd most prescribed medication** (20% by psychiatrists and 80% by primary care provider)
  - This number is anticipated to be higher from COVID-19 pandemic
  - More than 20 million antidepressants were prescribed between October 2020 and December 2020 – a *6% increase* from those same months in 2019

- Anxiety disorders are the **most common** mental health disorder in the US (**40 million Americans** ≥ 18yrs with a lifetime prevalence of **29%**)
  - **$42 billion** in annual healthcare costs

- **Anxiety and depression diagnoses** frequently coexist and have been INCREASING rapidly in US over the past several decades

Ettman CK, et al. *JAMA Netw Open*. 2020; 3(9):e2019686.
Robinson J. *The Pharmaceutical Journal.* 2021; 306: 7947.

The Top 200 Drugs of 2021

Rank	Drug Name	Total Prescriptions (2018)	Annual Change
1	Atorvastatin	112,474,023	↑ 1
2	Levothyroxine	105,773,990	↑ 1
3	Lisinopril	97,608,879	↓ 2
4	Metformin Hydrochloride	83,762,981	0
5	Amlodipine	75,811,947	0
6	Metoprolol	71,581,961	0
7	Albuterol	60,526,457	↑ 3
8	Omeprazole	58,364,556	↓ 1
9	Losartan Potassium	50,479,750	0
10	Simvastatin	48,007,043	↓ 2
11	Gabapentin	45,586,654	0
12	Acetaminophen; Hydrocodone Bitartrate	42,073,176	↑ 1
13	Hydrochlorothiazide	40,575,075	↓ 1
14	Sertraline Hydrochloride	38,383,042	0
15	Montelukast	35,222,630	↑ 1
16	Fluticasone	34,253,764	↓ 1
17	Amoxicillin	31,371,675	↑ 1
18	Furosemide	29,857,945	↓ 1
19	Pantoprazole Sodium	28,958,134	0
20	Acetaminophen	27,907,360	↑ 5
21	Prednisone	27,057,494	↑ 1
22	Escitalopram Oxalate	25,978,773	↓ 2
23	Fluoxetine Hydrochloride	25,619,277	↑ 8
24	Dextroamphetamine; Dextroamphetamine Saccharate; Amphetamine; Amphetamine Aspartate	25,331,775	↑ 3
25	Tramadol Hydrochloride	24,952,328	↑ 7
26	Insulin Glargine	24,911,721	↑ 7
27	Bupropion	24,488,843	↓ 4
28	Ibuprofen	24,453,501	0
29	Rosuvastatin	24,138,061	↑ 10
30	Pravastatin Sodium	24,022,031	↓ 6
31	Trazodone Hydrochloride	23,889,624	↓ 1
32	Tamsulosin Hydrochloride	23,254,004	↑ 3
33	Carvedilol	22,737,638	↓ 4
34	Meloxicam	22,610,690	↑ 4
35	Citalopram	22,224,263	↓ 9
36	Duloxetine	21,217,653	↑ 10
37	Alprazolam	20,843,479	↓ 16
38	Potassium	20,414,037	↓ 1
39	Clopidogrel Bisulfate	20,016,095	↑ 1

Note the **antidepressants in the Top 200 drugs of 2021** such as #14 sertraline, #22 escitalopram, #23 fluoxetine, #27 bupropion, #35 citalopram, and #36 duloxetine

https://clincalc.com/DrugStats/Top300Drugs.aspx. Accessed February 17th, 2022.

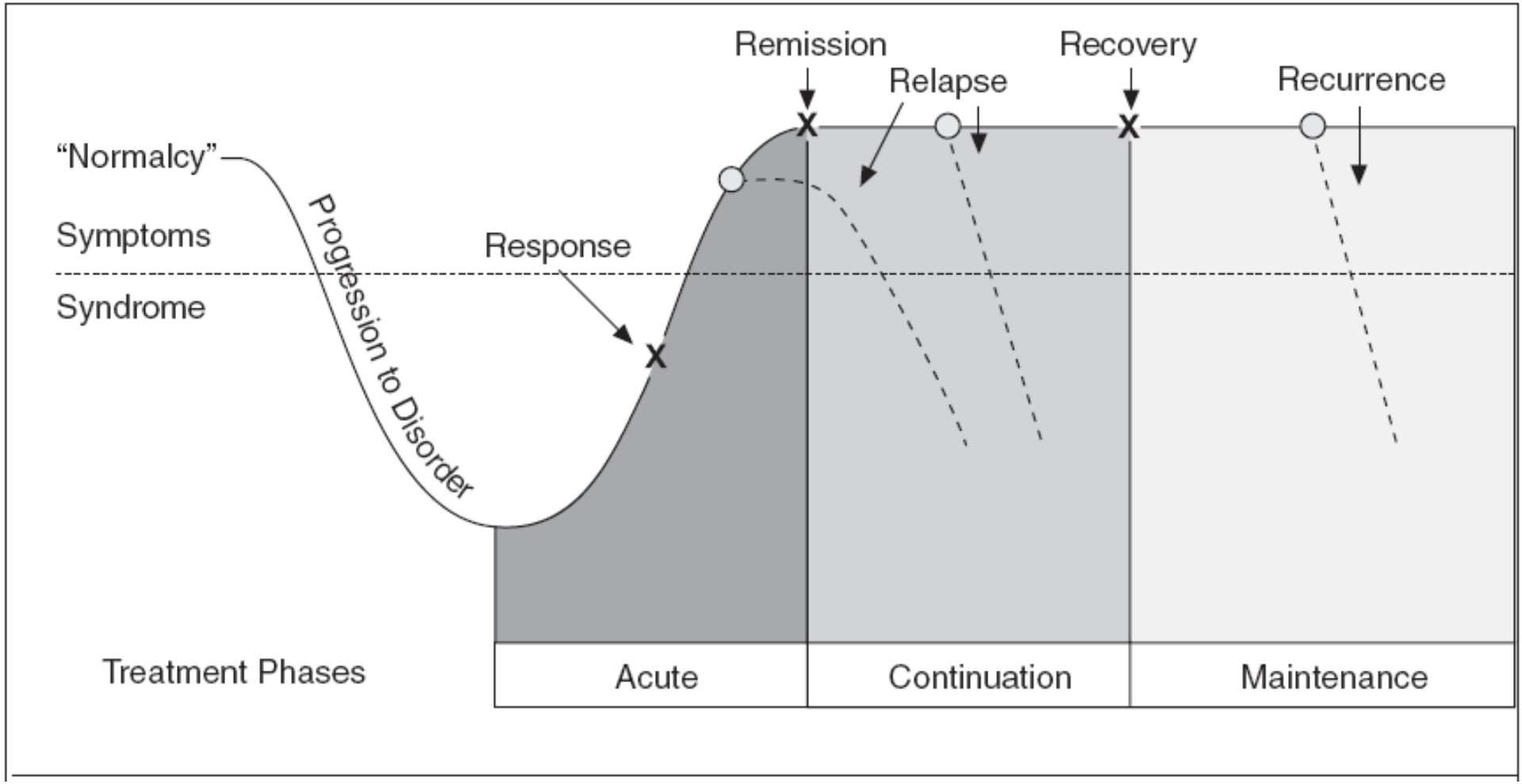
Diagnostic Criteria of Major Depressive Episode

Table 3: Diagnostic Criteria for Major Depressive Episode based on DSM-5 [2]

Criterion A	Five or more of the following symptoms present during the same two-week period; at least one of the symptoms is either (1) depressed mood or (2) loss of interest/ pleasure: a. Depressed mood most of the day, nearly every day b. Markedly diminished interest or pleasure in almost all activities most of the day, nearly every day c. Significant weight loss when not dieting or weight gain d. Insomnia or hypersomnia nearly every day e. Psychomotor agitation or retardation nearly every day f. Fatigue or loss of energy every day g. Feelings of worthlessness or excessive inappropriate guilt h. Diminished ability to think, concentrate, or indecisiveness, nearly every day i. Recurrent thought of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
Criterion B	The symptoms cause significant distress or functional impairment.
Criterion C	The episode is not attributable to the physiological effects of a substance or another medical condition

United States Department of Veteran Affairs. (2016). Management of Major Depressive Disorder (MDD). https://www.healthquality.va.gov/guidelines/MH/mdd/

Course of Depression



Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991;52(suppl 5):28-34.
APA. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd edition, 2010.

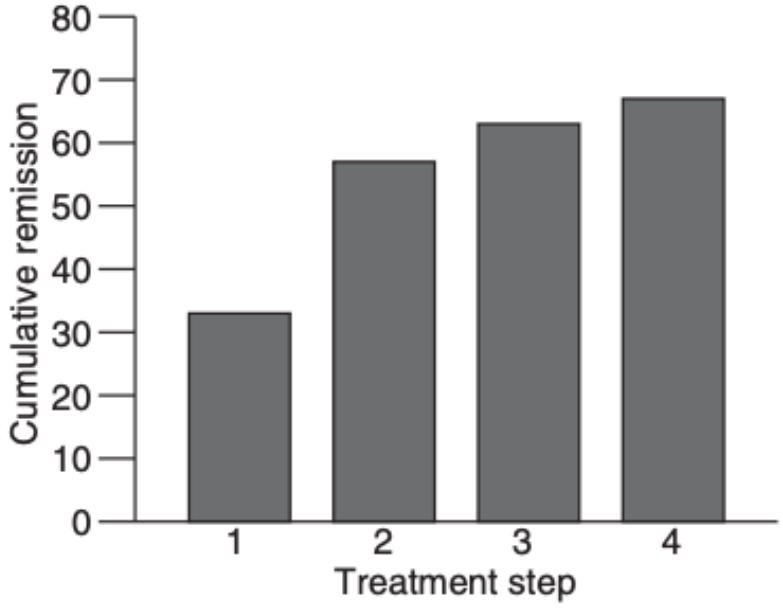
Goals of Therapy for Depression

- **Acute Phase**
  - Lasts *6-12 weeks*
  - Goal: remission (absence of symptoms)
- **Continuation Phase**
  - Lasts *4-9 months* after remission achieved
  - Goal: eliminate residual symptoms or prevent relapse
- **Maintenance Phase**
  - Lasts at least *12-36 months*
  - Goal: prevent recurrence (separate episode of depression)

Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991;52(suppl 5):28-34.
APA. Practice Guideline for the Treatment of Patients with Major Depressive Disorder. 3rd edition, 2010.

Figure 2

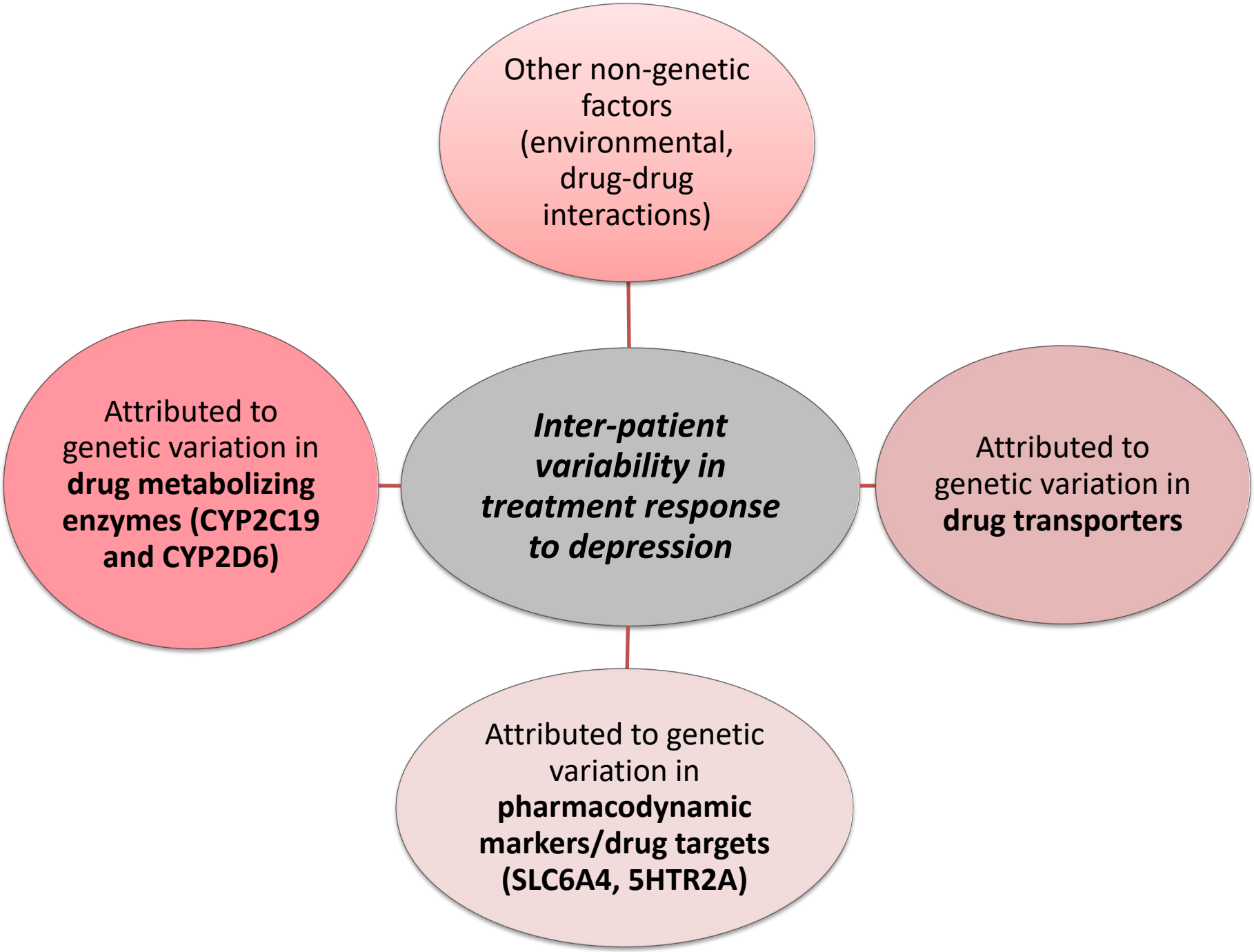
Cumulative remission rate by STAR*D treatment level

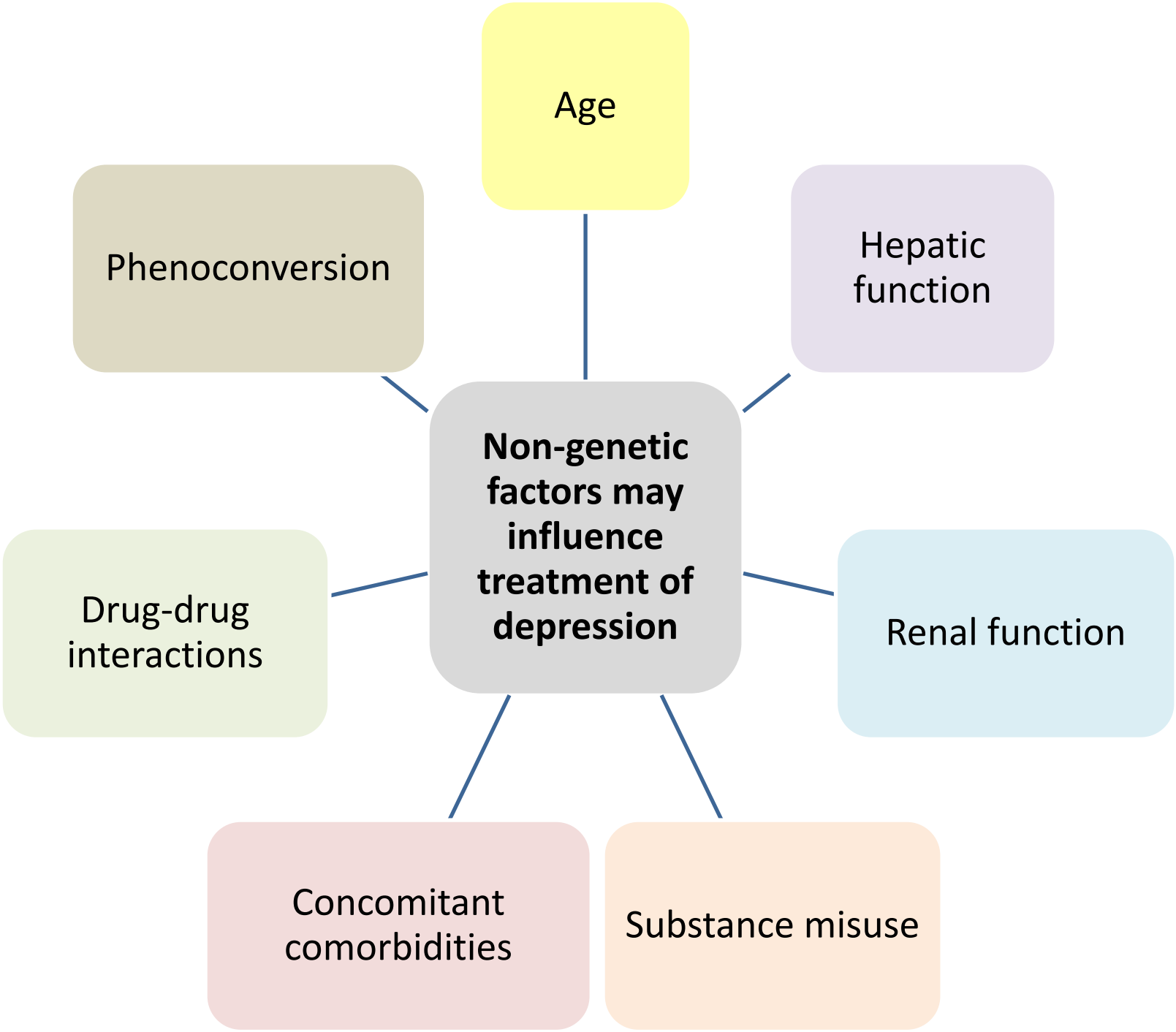


Theoretical cumulative remission rate over 4 periods = 67%

Remission was more likely to occur during the first two treatment levels (20%–30%) than during levels 3 and 4 (10%–20%)

Gaynes BN, et al. *Psychiatr Serv.* 2009; 60:1439-1445


Other non-genetic factors (environmental, drug-drug interactions)
Attributed to genetic variation in **drug metabolizing enzymes (CYP2C19 and CYP2D6)**
Inter-patient variability in treatment response to depression
Attributed to genetic variation in **drug transporters**
Attributed to genetic variation in **pharmacodynamic markers/drug targets (SLC6A4, 5HTR2A)**


Age
Phenoconversion
Hepatic function
Non-genetic factors may influence treatment of depression
Drug-drug interactions
Renal function
Concomitant comorbidities
Substance misuse

Patient Case Example

CC: AJ is a 55-year-old Hispanic male who reports to the clinic with increased apathy in daily activities. Denies suicidal ideations/plan. He has been taking venlafaxine XR 150mg daily for depression for the past 4 weeks and admits to good compliance with taking his medication. AJ has failed prior antidepressants trials including citalopram and sertraline. He admits to experiencing numerous adverse effects with these two latter antidepressants even with adjustments in using lower doses of these medications.

PMH: Percutaneous coronary intervention with coronary artery stent placement 5 years ago. He has a history of hyperlipidemia and hypertension.

SH: denies alcohol, recreational drug use and smoking.

Current Medications: venlafaxine XR 150mg daily, simvastatin 20mg qhs, lisinopril 20mg daily

Current Vitals: BP 125/85, HR 75, RR 12

Labs: SCr 0.9 mg/dL, ALT 25 IU/L and AST 20 IU/L, fasting lipid panel (TC 150, HDL 45, LDL 85 and TG 90), and A1c 5.5%

His psychiatrist ordered pharmacogenomic testing to guide next steps in managing AJ's treatment-resistant depression. The PGx test comes back 4 days later (refer to next slide) and consults you regarding input on treatment recommendations.

Manchester University

FOR ACADEMIC PURPOSES ONLY - NOT FOR CLINICAL USE

PATIENT INFORMATION		SPECIMEN DETAILS		ORDERED BY
NAME:	Patient 27522	**SPECIMEN TYPE:**		
ACC #:	27522	**COLLECTION DATE:**	1/1/1900	
DOB:	1/1/1900	**RECEIVED DATE:**	1/1/1900	
SEX:		**REPORT DATE:**	2/1/2018	

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*2/*2	Poor Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *4, *5, *6, *11
CYP3A5	*1D/*3	Intermediate Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17, *22
VKORC1	-1639G>A A/A	High Warfarin Sensitivity	-1639G>A
Apolipoprotein E	Indeterminate	Unknown Phenotype	ε2, ε4, (ε3 is reference)
CYP2D6	*1/*2xN	Ultra-Rapid Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
SLCO1B1	521T>C T/T	Normal Function	521T>C, 388A>G
COMT	Val158Met A/A	Low COMT Activity	Val158Met
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
CYP1A2	*1F/*1L	Normal Metabolizer- Possible Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
MTHFR	1298A>C AA 677C>T TT	Increased Risk of Hyperhomocysteinemia	1298A>C, 677C>T
MTHFR	677C>T TT	Reduced MTHFR Activity	1298A>C, 677C>T
Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis	20210G>A, 1691G>A

Additional Test Results (added to this original report)

HLA-B*15:02	negative/negative	Negative	HLA-A*31:01	negative/negative	Negative
HLA-B*57:01	negative/positive	Positive			
HLA-B*58:01	negative/negative	Negative			

Patient Case Example

Which of the following treatment choices would you recommend as the next best step for managing AJ's depression? Select all that apply.

a. Venlafaxine
b. Desvenlafaxine
c. Amitriptyline
d. Paroxetine
e. Escitalopram
f. Fluoxetine
g. Bupropion
h. Vortioxetine

Antidepressant Classes

- **Selective serotonin reuptake inhibitors (SSRIs)**
- Serotonin partial agonist/reuptake inhibitors (SPARIs)
- **Serotonin-norepinephrine reuptake inhibitors (SNRIs)**
- Norepinephrine-dopamine reuptake inhibitors (NDRIs)
- Selective norepinephrine reuptake inhibitors (NRIs)
- Serotonin antagonist/reuptake inhibitors (SARIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)

Stephen M. Stahl. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications – 4th Ed. New York. Cambridge University Press. 2013.

First Line Options for Initial Treatment of Depression

Table 3. Summary Recommendations for Antidepressants.

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level I Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[a] (Tolvon)	α_2-Adrenergic antagonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic antagonist; 5-HT_2 antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} agonist; 5-HT_{1B} partial agonist; 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 antagonist	10-20 mg

Kennedy SH et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *The Canadian Journal of Psychiatry*; 2016, Vol. 61(9): 540-560

Second and Third Line Options for Treatment of Depression

Second line (Level I Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[e]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[a] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; 5-HT_2 antagonist	150-300 mg
Vilazodone (Viibryd)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} partial agonist	20-40 mg (titrate from 10 mg)
Third line (Level I Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

Kennedy SH et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *The Canadian Journal of Psychiatry*; 2016, Vol. 61(9): 540-560

Options for Treatment Resistant Depression

Switching to another SSRI, SNRI, TCA, or MAOI

Augmenting an antidepressant with lithium, antipsychotic or mirtazapine

Combination therapy with antidepressants

Electroconvulsive therapy (ECT)

Transcranial magnetic stimulation (TMS)

National Collaborating Centre for Mental Health (UK). 2020. Depression: The Treatment and Management of Depression in Adults (Updated Edition). https://www.nice.org.uk/guidance/cg90

Prevalence of Adverse Events Among Antidepressants

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain
Citalopram	21		8	19				3	3	2		5	11		8	4		
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2
Fluoxetine	21			10			13	14	12		16		8	9	10	11		
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15		
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1	
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1	
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2			
Duloxetine	20	11	8	15		8	7		3		11	8	6		3			
Levomilnacipran	17	9		10	17	8			2		6		9					
Milnacipran	12	7		9	10				4		7	3	4		3			
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11		
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8		
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C					
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3			
Bupropion XL	13	9		26	34	6			5	2	16				3			
Mirtazapine		13		25		7	54							8	7		17	12
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5			
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2
Vortioxetine[f]	23	4	5	6		5	3				3	3	2					

Kennedy SH et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. *The Canadian Journal of Psychiatry*; 2016, Vol. 61(9): 540-560

Genetic Variability in Pharmacokinetic (PK) Factors and Depression

Primary metabolizing enzyme of interest/ PK factor	Variant allele	Allele Function	Examples of medications using metabolizing enzyme	CPIC Level	PharmGKb Level of Evidence
CYP2C19	*2, *3 *17	No function Increased	SSRIs (citalopram/ escitalopram/ sertraline) and TCAs (amitriptyline)	A	1A
CYP2D6	*1 x N, *2 x N *3, *4, *5, *6 *10, *17, *41	Increased No function Reduced	Paroxetine, Amitriptyline, Nortriptyline Venlafaxine	A A/B	1A 2A

M. Whirl-Carrillo, E.M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein. "Pharmacogenomics Knowledge for Personalized Medicine" Clinical Pharmacology & Therapeutics (2012) 92(4): 414-417.

Allelic Variability among Different Populations

Table 1. Selection of P450 allelic variation across populations, highlighting variability within and among populations.

Allelic variant	Function	Africa	African American	Caucasian	East Asia	Americas	Middle East	South Central Asia	Oceania
CYP2C9									
**2*	Decreased	0–9%	1–4%	8–16%	0–1%	0.3–14%	5–27%	2–26%	0–3%
**3*	None	0–3%	0.5–2%	4–11%	1–5%	0–6%	2–19%	6–13%	1–4%
**5*	Decreased	0–3%	0.7–2.5%	0%	0%	0–2%	0–0.1%	0%	n/a
**6*	None	0–2%	0–1.3%	0%	0%	0–1%	0%	0%	n/a
**8*	Decreased	2–8%	3–12%	0–1%	0%	0–2%	0–1%	0–1%	n/a
**11*	Decreased	1–5%	1–2%	0–1%	0–0.2%	0–1%	0%	0–1%	n/a
CYP2C19									
**2*	None	4–22%	12–25%	8–27%	6–49%	2–31%	6–24%	9–51%	20–78%
**3*	None	0–7%	0–1%	0–6.8%	0–21%	0–4%	0–20%	0–6%	2–33%
**4*	None	0%	0%	0–1%	0–0.5%	0–0.2%	n/a	0%	0%
**17*	Increased	10–18%	18–22%	11–33%	0–6.2%	1–25%	22–26%	12–18%	3–6%
CYP2D6									
**4*	None	1–7%	4–8%	8–33%	0–4%	0.2–43%	4–13%	3–18%	0–8%
**5*	Gene deletion	1–17%	3–9%	0–9%	0–10%	0–5%	1–4%	0–16%	1–8%
**10*	Decreased	3–19%	3–8%	0.4–15%	9–64%	0–12%	1–9%	4–55%	0–6%
**17*	Decreased	9–34%	14–26%	0–2.2%	0–0.2%	0–18%	0–3%	0–1%	0–0.2%
**29*	Decreased	4–20%	5–8%	0–0.3%	0%	0–11%	0–2%	0–0.2%	0%

Allele frequencies for *CYP2C9*, *CYP2C19* and *CYP2D6* are from tables compiled for the Clinical Pharmacology Implementation Consortium (CPIC) and available through PharmGKB. Frequencies are rounded and might slightly deviate from those posted as new literature is added.
n/a, no frequencies are available.

Rashmi RR, et al. *Ther Adv Drug Saf*. 2018; 9(1) 45–62

Therapeutic Recommendations for SSRIs based on CYP2C19 Phenotypes

Table 3 Dosing recommendations for CYP2C19 and SSRIs

Table 3a Dosing recommendations for citalopram and escitalopram based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers. Lower plasma concentrations will increase probability of pharmacotherapy failure.	Consider an alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[c,d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Moderate

Table 3b Dosing recommendations for sertraline based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 Ultrarapid metabolizer	Increased metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose. If patient does not respond to recommended maintenance dosing, consider alternative drug not predominantly metabolized by CYP2C19.[b]	Optional
CYP2C19 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers.	Initiate therapy with recommended starting dose.	Strong
CYP2C19 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Consider a 50% reduction[d] of recommended starting dose and titrate to response or select alternative drug not predominantly metabolized by CYP2C19.[b]	Optional

Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clinical Pharmacology and Therapeutics.* 2015; 98(2):127-134.

Therapeutic Recommendations for SSRIs based on CYP2D6 Phenotypes

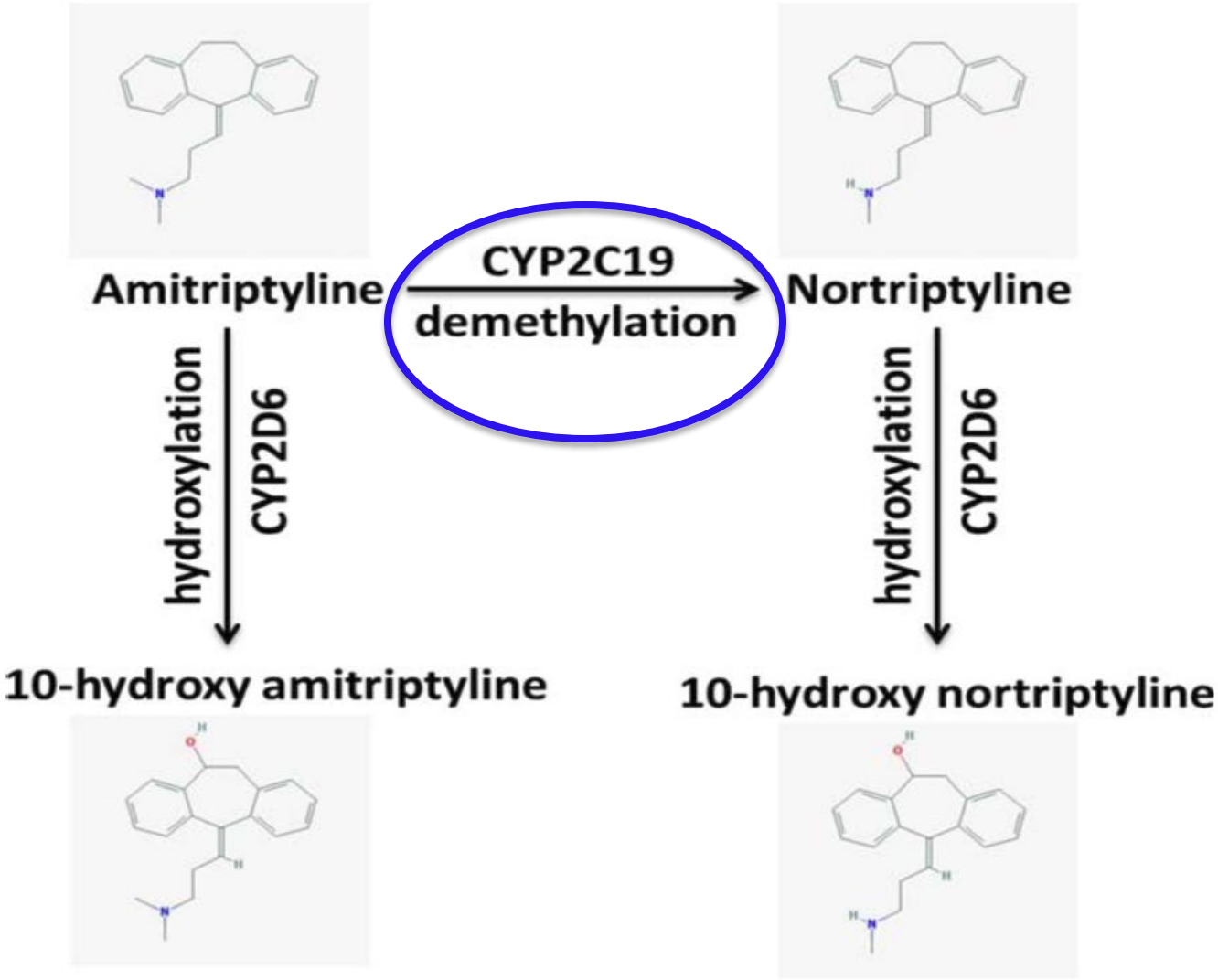
Table 2 Dosing recommendations for CYP2D6 and SSRIs

Table 2a Dosing recommendation for paroxetine based on CYP2D6 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2D6 Ultrarapid metabolizer	Increased metabolism to less active compounds when compared to extensive metabolizers. Lower/undetectable plasma concentrations may increase probability of pharmacotherapy failure.	Select alternative drug not predominantly metabolized by CYP2D6.[b]	Strong
CYP2D6 Extensive metabolizer	Normal metabolism	Initiate therapy with recommended starting dose.	Strong
CYP2D6 Intermediate metabolizer	Reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Initiate therapy with recommended starting dose.	Moderate
CYP2D6 Poor metabolizer	Greatly reduced metabolism when compared to extensive metabolizers. Higher plasma concentrations may increase the probability of side effects.	Select alternative drug not predominantly metabolized by CYP2D6[b] or if paroxetine use warranted, consider a 50% reduction of recommended starting dose and titrate to response.	Optional

Hicks JK et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors. *Clinical Pharmacology and Therapeutics.* 2015; 98(2):127-134.

Beyond SSRIs: PGx of Tricyclic Antidepressants



Hicks JK, et al. *Clin Pharmacol Ther.* 2017;102(1):37-44

Therapeutic Recommendations for Amitriptyline based on CYP2C19 Phenotypes

Table 3 Dosing recommendations of amitriptyline based on CYP2C19 phenotype

Phenotype	Implication	Therapeutic recommendation	Classification of recommendation[a]
CYP2C19 ultrarapid metabolizer	Increased metabolism of amitriptyline as compared with extensive metabolizers	Consider alternative drug not metabolized by CYP2C19 If a tricyclic is warranted, use therapeutic drug monitoring to guide dose adjustments	Optional
CYP2C19 extensive metabolizer	Normal metabolism of amitriptyline	Initiate therapy with recommended starting dose[b]	Strong
CYP2C19 intermediate metabolizer	Reduced metabolism of amitriptyline as compared with extensive metabolizers	Initiate therapy with recommended starting dose[b]	Strong
CYP2C19 poor metabolizer	Greatly reduced metabolism of amitriptyline as compared with extensive metabolizers Higher plasma concentrations of amitriptyline will increase the probability of side effects	Consider a 50% reduction of recommended starting dose.[b] Use therapeutic drug monitoring to guide dose adjustments	Moderate

Hicks JK, et al. *Clin Pharmacol Ther.* 2017; 102(1):37-44

Therapeutic Recommendations for Tricyclic Antidepressants based on CYP2D6 Phenotypes

Table 2 Dosing recommendations for tricyclic antidepressants based on cyp2d6 phenotype

Phenotype	Implication	Therapeutic recommendation[a,b]	Classification of recommendation for amitriptyline and nortripyline[c]	Classification of recommendation for other TCAs[c,d]
CYP2D6 ultrarapid metabolizer	Increased metabolism of TCAs to less active compounds compared to normal metabolizers Lower plasma concentrations of active drug will increase probability of pharmacotherapy failure	Avoid tricyclic use due to potential lack of efficacy. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider titrating to a higher target dose (compared to normal metabolizers).[e] Utilize therapeutic drug monitoring to guide dose adjustments.	Strong	Optional
CYP2D6 normal metabolizer	Normal metabolism of TCAs	Initiate therapy with recommended starting dose.[f]	Strong	Strong
CYP2D6 intermediate metabolizer	Reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Consider a 25% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Moderate	Optional
CYP2D6 poor metabolizer	Greatly reduced metabolism of TCAs to less active compounds compared to normal metabolizers Higher plasma concentrations of active drug will increase the probability of side effects	Avoid tricyclic use due to potential for side effects. Consider alternative drug not metabolized by CYP2D6. If a TCA is warranted, consider a 50% reduction of recommended starting dose.[f] Utilize therapeutic drug monitoring to guide dose adjustments.[e]	Strong	Optional

Hicks JK, et al. *Clin Pharmacol Ther.* 2017; 102(1):37-44

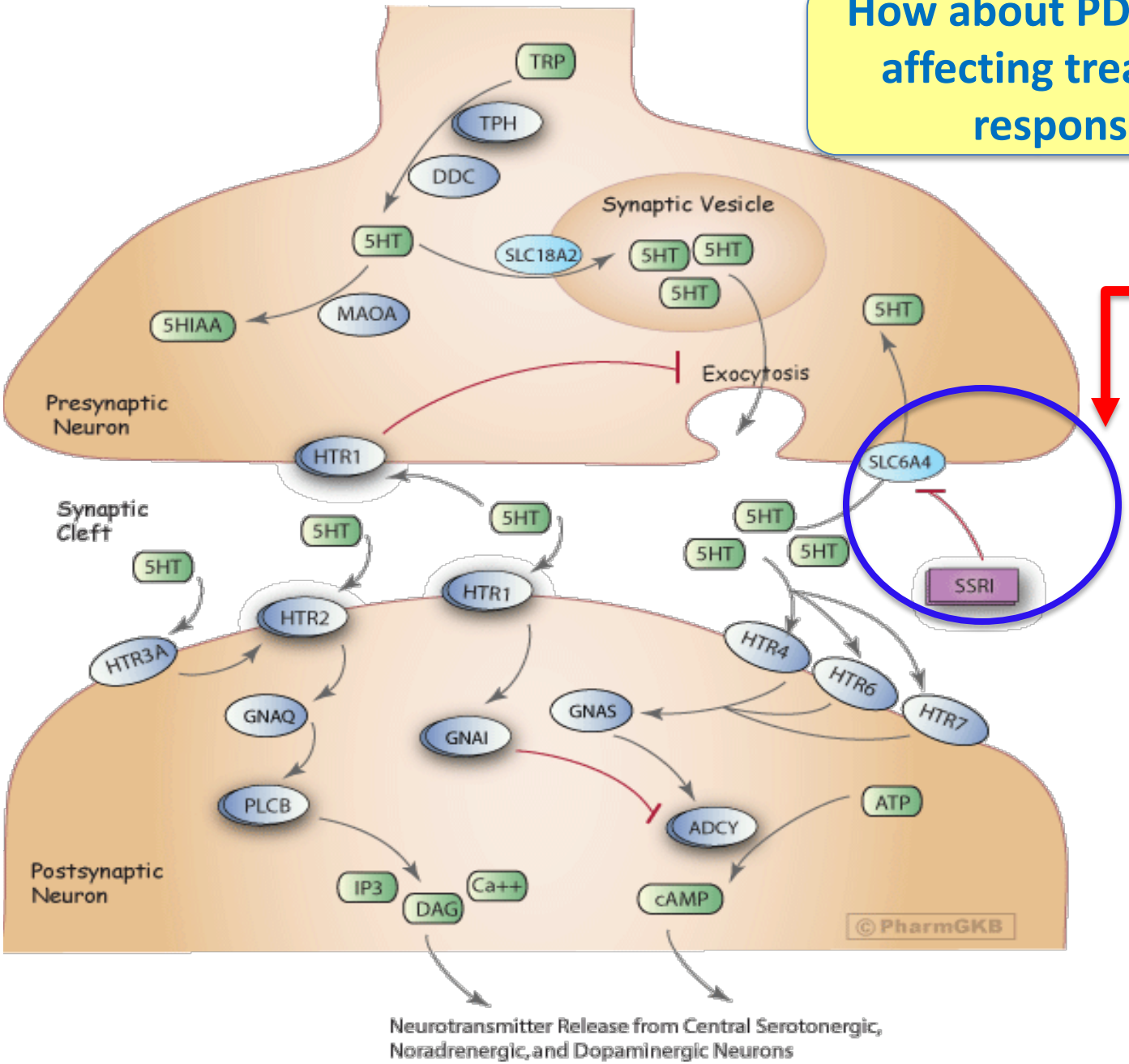
Therapeutic Recommendations for Amitriptyline based on both CYP2C19 and CYP2D6 Phenotypes

Table 4 Dosing recommendations for amitriptyline based on both CYP2D6 and CYP2C19 phenotypes[a,b]

Phenotype	CYP2D6 ultrarapid metabolizer	CYP2D6 normal metabolizer	CYP2D6 intermediate metabolizer	CYP2D6 poor metabolizer
CYP2C19 ultrarapid or rapid metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional	Consider alternative drug not metabolized by CYP2C19[c,e] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional
CYP2C19 normal metabolizer	Avoid amitriptyline use. If amitriptyline is warranted, consider titrating to a higher target dose (compared to normal metabolizers)[f,g] Classification of recommendation[d]: Strong	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Strong
CYP2C19 intermediate metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Initiate therapy with recommended starting dose[h] Classification of recommendation[d]: Strong	Consider a 25% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Optional
CYP2C19 poor metabolizer	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use. If amitriptyline is warranted, consider a 50% reduction of recommended starting dose[f,h] Classification of recommendation[d]: Moderate	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional	Avoid amitriptyline use[c] Classification of recommendation[d]: Optional

Hicks JK, et al. *Clin Pharmacol Ther.* 2017; 102(1):37-44

How about PD variants affecting treatment response?



M. Whirl-Carrillo, E.M. McDonagh, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein. "Pharmacogenomics Knowledge for Personalized Medicine" Clinical Pharmacology & Therapeutics (2012) 92(4): 414-417.

Journal of *Personalized Medicine*

MDPI

Review

Serotonin Transporter Genetic Variation and Antidepressant Response and Tolerability: A Systematic Review and Meta-Analysis

Kiera Stein [1], Abdullah Al Maruf [2,3,4], Daniel J. Müller [5,6,7], Jeffrey R. Bishop [8] and Chad A. Bousman [1,3,4,9,*]

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Citation: Stein, K.; Maruf, A.A.; Müller, D.J.; Bishop, J.R.; Bousman, C.A. Serotonin Transporter Genetic Variation and Antidepressant Response and Tolerability: A Systematic Review and Meta-Analysis. *J. Pers. Med.* **2021**, *11*, 1334. https://doi.org/10.3390/jpm11121334

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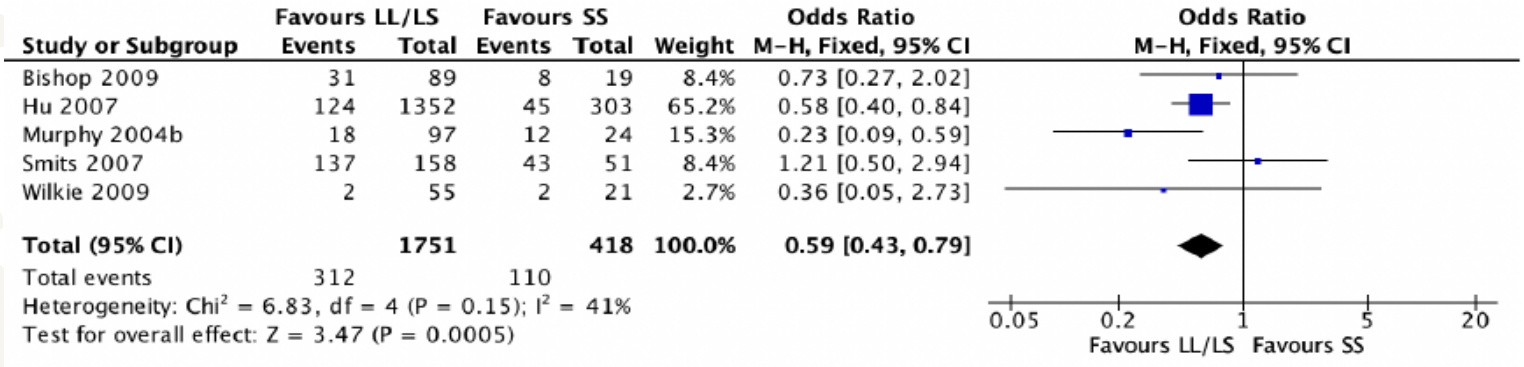
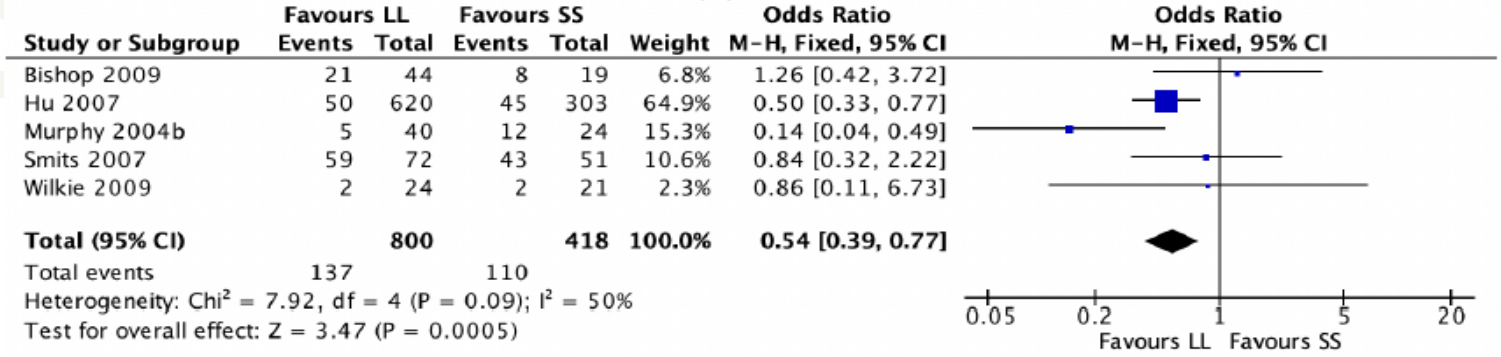
Accepted: 7 December 2021
Published: 9 December 2021

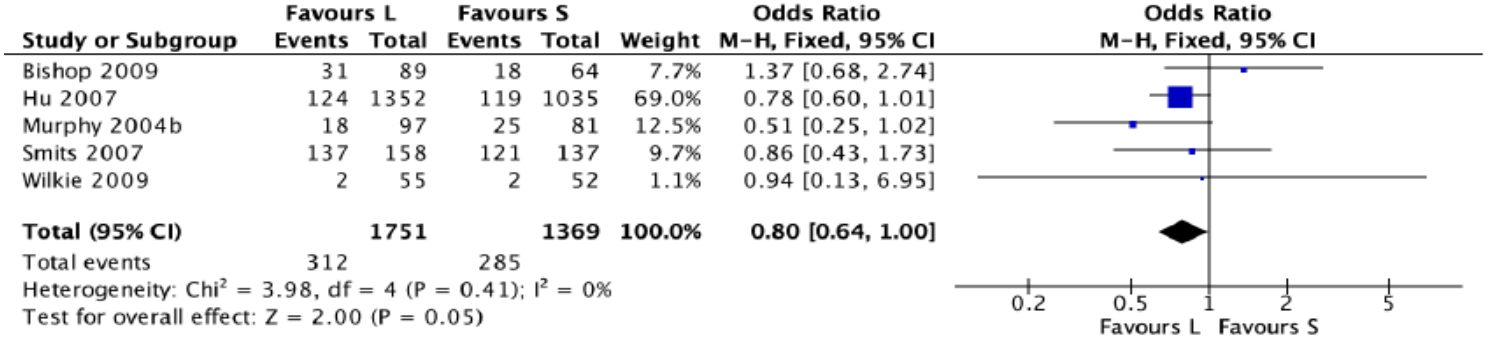
Abstract: Antidepressants are used to treat several psychiatric disorders; however, a large proportion of patients do not respond to their first antidepressant therapy and often experience adverse drug reactions (ADR). A common insertion–deletion polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter (*SLC6A4*) gene has been frequently investigated for its association with antidepressant outcomes. Here, we performed a systematic review and meta-analysis to assess 5-HTTLPR associations with antidepressants: (1) response in psychiatric disorders other than major depressive disorder (MDD) and (2) tolerability across all psychiatric disorders. Literature searches were performed up to January 2021, yielding 82 studies that met inclusion criteria, and 16 of these studies were included in the meta-analyses. Carriers of the 5-HTTLPR LL or LS genotypes were more likely to respond to antidepressant therapy, compared to the SS carriers in the total and European ancestry-only study populations. Long (L) allele carriers taking selective serotonin reuptake inhibitors (SSRIs) reported fewer ADRs relative to short/short (SS) carriers. European L carriers taking SSRIs had lower ADR rates than S carriers. These results suggest the 5-HTTLPR polymorphism may serve as a marker for antidepressant outcomes in psychiatric disorders and may be particularly relevant to SSRI treatment among individuals of European descent.



(A)



(B)



(C)

Figure 4. Forest plots of 5-HTTLPR polymorphisms and adverse drug reactions in studies with participants of European background taking SSRIs by genotype comparisons. (**A**) LL/LS vs. SS; (**B**) LL vs. SS; (**C**) L vs. S.

Stein K, et al. *J. Pers. Med.* 2021; 11: 1334. https://doi.org/10.3390/jpm11121334

Summarize main findings from the literature supporting the use of pharmacogenomics-guided treatment for depression

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: A randomized clinical trial demonstrating clinical utility

Paul Bradley [a, h], Michael Shiekh [b], Vishaal Mehra [c], Keith Vrbicky [d, e, f], Stacey Layle [c], Marilyn C. Olson [g], Alejandra Maciel [g, *], Ali Cullors [g], Jorge A. Garces [g], Andrew A. Lukowiak [g]

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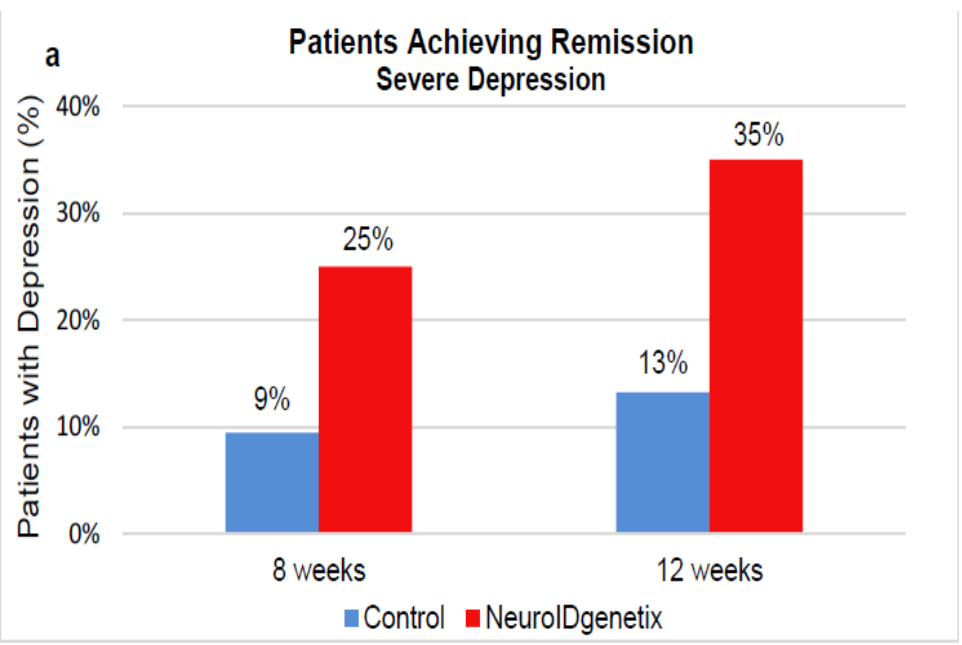
[h] *Meridian Clinical Research, Savannah, GA, United States*

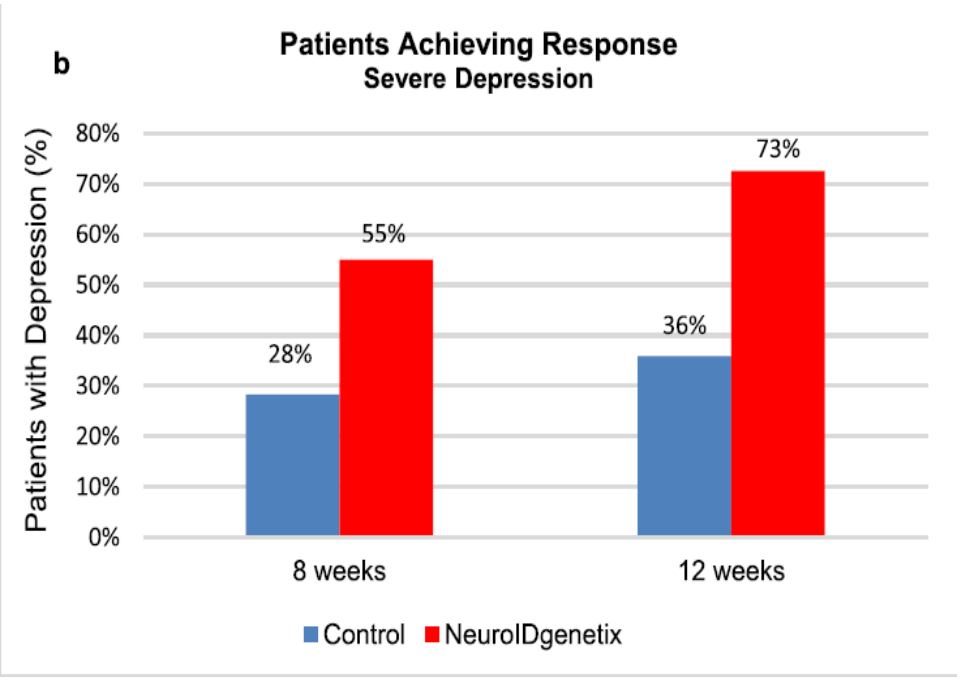
20 independent clinical sites within the US

Randomized in a 1:1 ratio to the experimental group (guided by the NeuroIDgenetix® test) or control group (standard of care)

HAM-A and HAM-D17 interviews were used to monitor and assess patients for depression and anxiety symptoms

Bradley P, et al. *Journal of Psychiatric Research.* 2018; 96:100-107





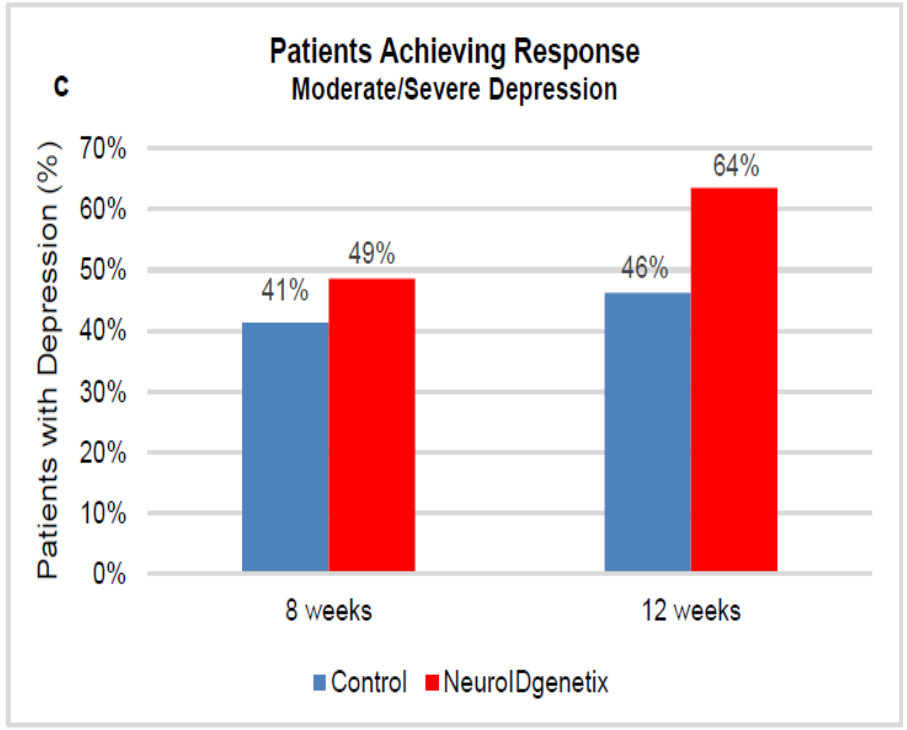


Fig. 2. Remission and Response Rates for Patients with Depression. **(a)** Remission rates (HAM-D17 scores ≤7) and **(b)** response rates (50% reduction in HAM-D17 scores) for the experimental group (red bars, n = 40) compared to the control group (blue bars, n = 53) for patients with severe depression. Percentage of patients achieving remission and response at 12 weeks was higher in the experimental group ($p = 0.02$, $p = 0.001$ respectively). **(c)** Response rates for patients with moderate and severe depression (HAM-D17 scores ≥20) were higher ($p = 0.01$) in the experimental group (red bars, n = 140) versus control (blue bars, n = 121). P values were calculated using two-sided Fisher's exact test.

Bradley P, et al. *Journal of Psychiatric Research.* 2018; 96:100-107

Clinical Implications of Study

Significantly increased number of medication changes made by physicians at 2 weeks in the PGx-guided group vs. standard of care (81% vs. 64%, $p < 0.0001$)

PGx test results were informative and helpful in guiding and supporting physicians with medication changes

Using PGx information as one of the tools for making prescribing decisions may improve overall antidepressant use **increasing the probability for patients to achieve remission**

Demonstrates the clinical validity and utility of PGx-guided treatment for depression and anxiety in diverse clinical settings

Bradley P, et al. *Journal of Psychiatric Research.* 2018; 96:100-107

Journal of Psychiatric Research 111 (2019) 59–67

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study

John F. Greden[a,*], Sagar V. Parikh[a], Anthony J. Rothschild[b], Michael E. Thase[c], Boadie W. Dunlop[d], Charles DeBattista[e], Charles R. Conway[f], Brent P. Forester[g], Francis M. Mondimore[h], Richard C. Shelton[i], Matthew Macaluso[j], James Li[k], Krystal Brown[l], Alexa Gilbert[k], Lindsey Burns[k], Michael R. Jablonski[k], Bryan Dechairo[k,l]

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[j] University of Kansas School of Medicine-Wichita, Department of Psychiatry and Behavioral Sciences, 1010 N Kansas St, Wichita, KS, 67214, USA
[k] Assurex Health, Inc., 6960 Cintas Blvd, Mason, OH, 45040, USA
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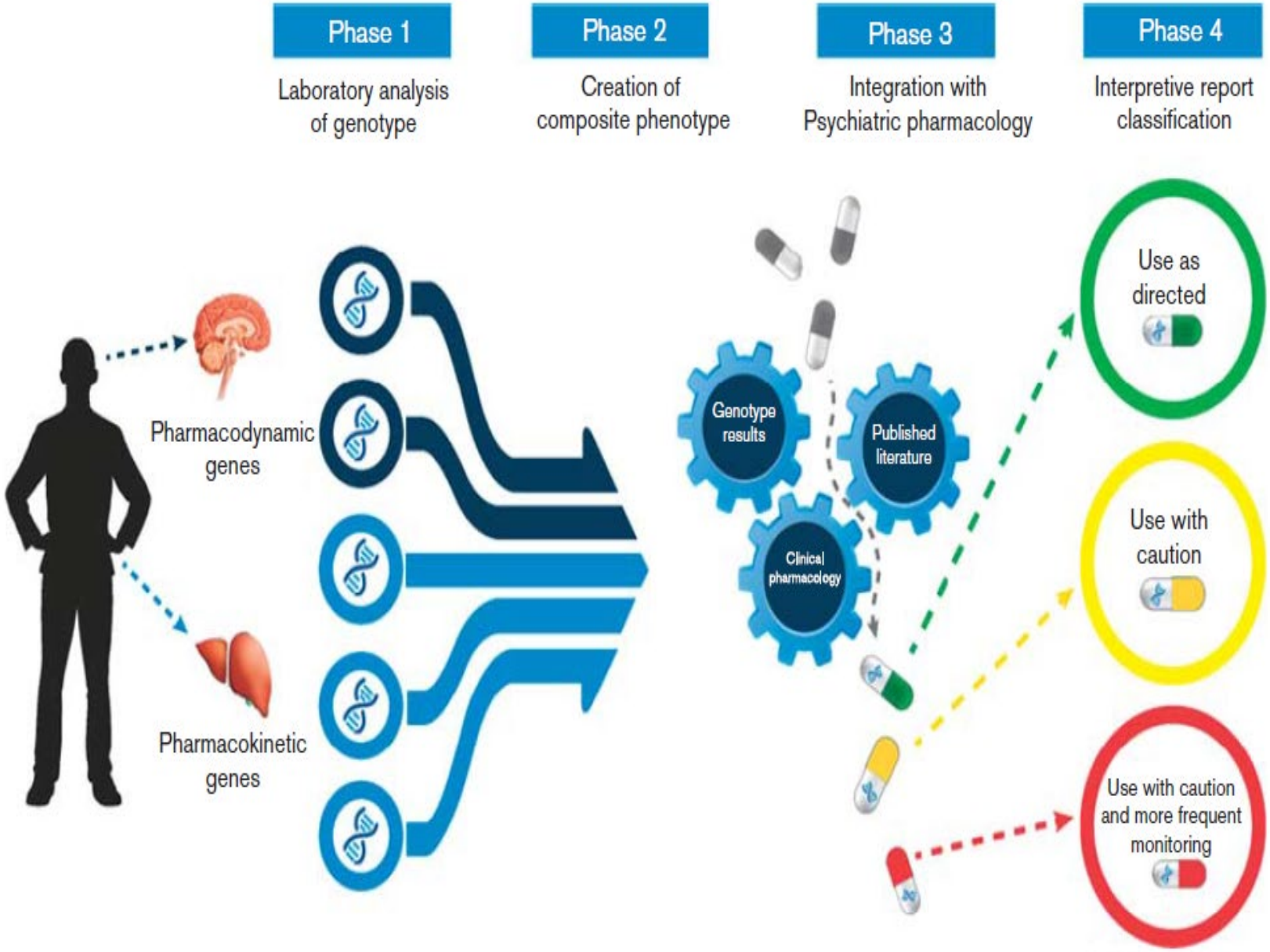


Medication binning methodology of the GeneSight interpretive report.

Hall-Flavin DK, et al. *Pharmacogenet Genomics.* 2013; 23(10): 535-48

Table 1

Baseline demographics for patients in the per-protocol cohort who completed the baseline visit.

Characteristic	Treatment Arm				Total (N = 1398)	
	TAU (N = 717)		Guided–Care (N = 681)			
	N	%	N	%	N	%
Age Group						
18–34 years	158	22.0	162	23.8	320	22.9
35–49 years	192	26.8	200	29.4	392	28.0
50–64 years	266	37.1	235	34.5	501	35.8
65 years and over	101	14.1	84	12.3	185	13.2
Sex						
Female	498	69.5	489	71.8	987	70.6
Male	219	30.5	192	28.2	411	29.4
Ethnicity						
Hispanic or Latino	54	7.5	57	8.4	111	7.9
Not Hispanic or Latino	663	92.5	624	91.6	1287	92.1
Race						
White	589	82.1	538	79.0	1127	80.6
Black	94	13.1	114	16.7	208	14.9
Asian	17	2.4	12	1.8	29	2.1
American Indian or Alaska Native	3	0.4	5	0.7	8	0.6
Native Hawaiian or Other Pacific Islander	0	0	1	0.1	1	0.1
Other or Multiple	14	2.0	11	1.6	25	1.8
Depression Category						
Moderate (HAM-D17 14-18)	187	26.1	205	30.1	392	28.0
Severe (HAM-D17 19-22)	264	36.8	229	33.6	493	35.3
Very Severe (HAM-D17 ≥ 23)	266	37.1	247	36.3	513	36.7
Psychiatric Comorbidities						
General anxiety disorder	96	13.4	116	17.0	212	15.2
Panic disorders/social phobia	108	15.1	104	15.3	212	15.2
Post-traumatic stress disorder	32	4.5	36	5.3	68	4.9
Pharmacogenomic Report Category[a]						
Use as Directed	181	25.2	176	25.8	357	25.5
Use with Caution	295	41.1	280	41.1	575	41.1
Use with Increased Caution and with More Frequent Monitoring	138	19.2	118	17.3	256	18.3
Not Applicable[b]	103	14.4	107	15.7	210	15.0
	Mean (SD)	**Min, Max**	**Mean (SD)**	**Min, Max**	**Mean (SD)**	**Min, Max**
Age (years)	48.0 (14.5)	18, 85	46.9 (14.5)	18, 90	47.5 (14.5)	18, 90
HAM-D17 Score	21.4 (4.22)	14, 35	21.1 (4.20)	14, 37	21.3 (4.21)	14, 37
Failed Medication Trials	3.53 (3.01)	1, 34	3.48 (3.09)	1, 25	3.51 (3.05)	0, 34

Greden JF, et al. *Journal of Psychiatric Research* 2019; 111: 59-67

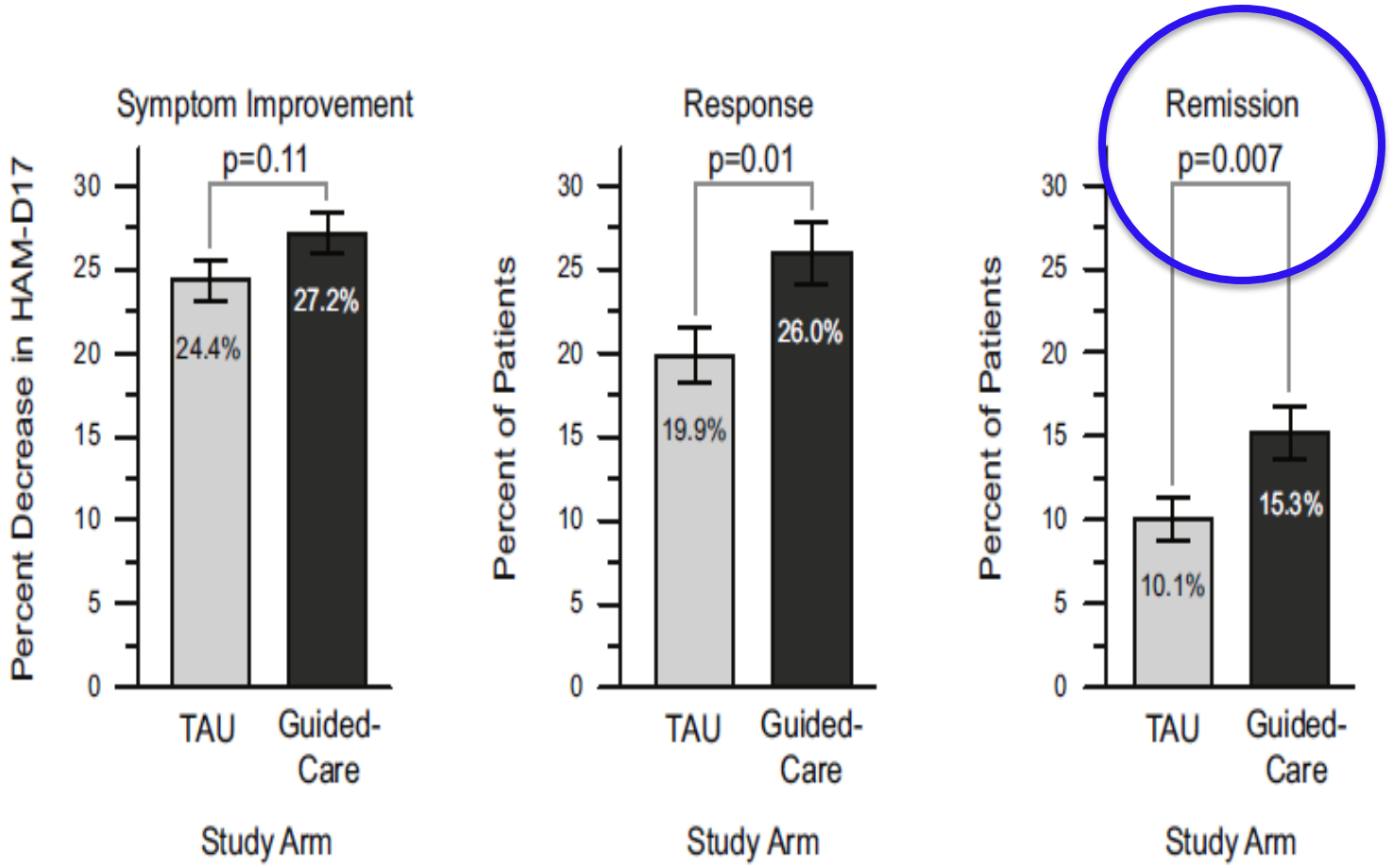


Fig. 1. Patient outcomes at week 8 in the pharmacogenomics guided-care arm (n = 560) compared to treatment as usual (n = 607). Outcomes were evaluated using the HAM-D17 depression rating scales.

Greden JF, et al. *Journal of Psychiatric Research* 2019; 111: 59-67

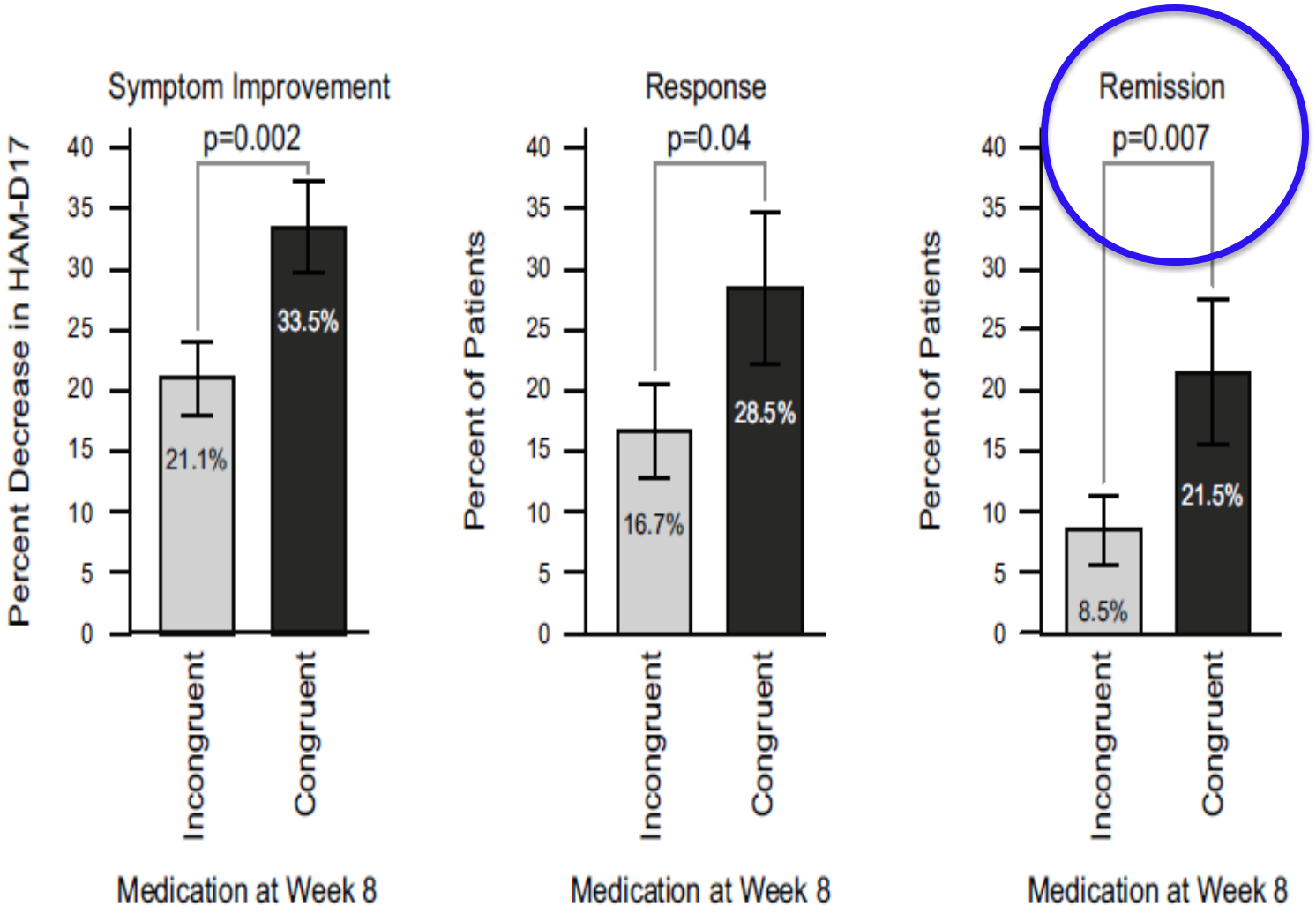


Fig. 4. Patient outcomes among those who were taking incongruent medications at baseline in both study arms (n = 213). Patients were evaluated according to whether they were prescribed congruent (n = 77) or incongruent (n = 136) medications at week 8. Outcomes were evaluated using the HAM-D17 depression rating scale.

Greden JF, et al. *Journal of Psychiatric Research* 2019; 111: 59-67

Improved Treatment Outcomes for Patients in PGx-Guided Care Arm over 24 Weeks

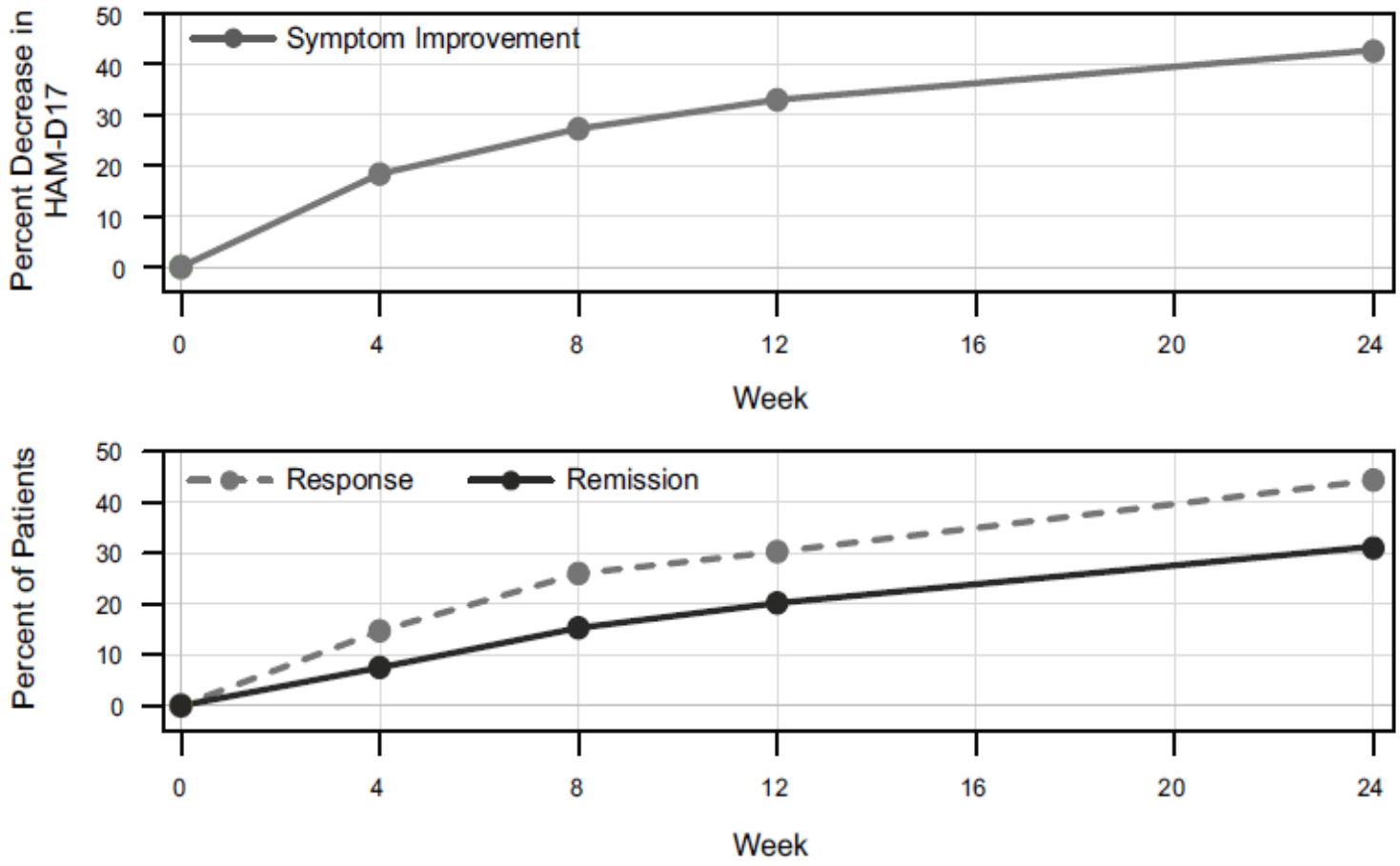


Fig. 3. Durability of improvements in patient outcome throughout the 24-week study in the pharmacogenomics guided-care arm. Outcomes were evaluated using the HAM-D17 depression rating scale.

Greden JF, et al. *Journal of Psychiatric Research* 2019; 111: 59-67

Clinical Implications of GUIDED Study

Treatment outcomes significantly improved at week 8 among patients who switched to genetically *congruent* medications versus those who remained on genetically incongruent medications

Patients in the PGx guided-care arm experienced improved and sustainable treatment outcomes over 24 weeks

PGx testing improves treatment outcomes for patients who have treatment-resistant depression and underlying gene-drug interactions

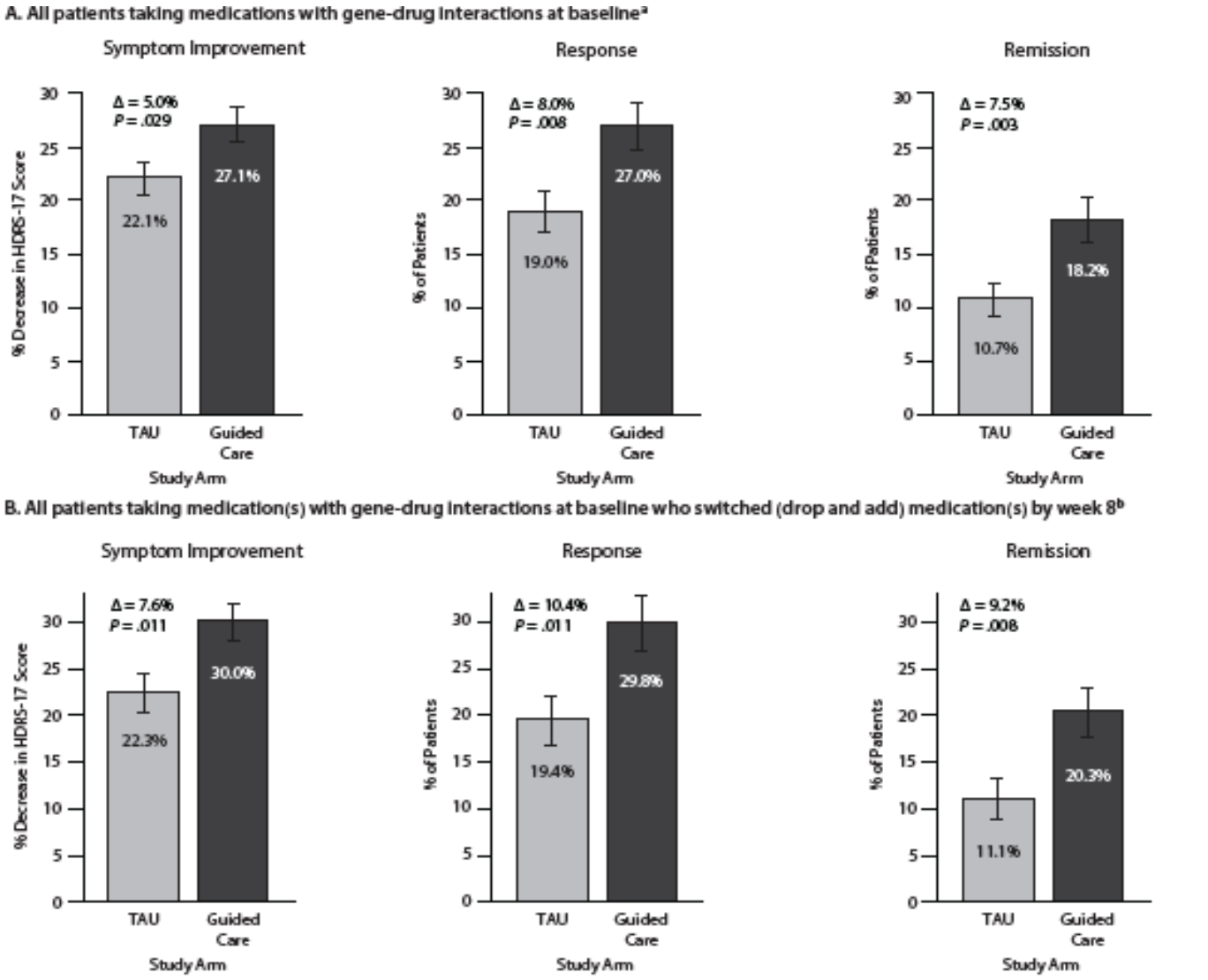
Evaluation of study findings in diverse populations and treatment-naïve depressed individuals is critically needed

Greden JF, et al. *Journal of Psychiatric Research* 2019; 111: 59-67

GUIDED Trial Post hoc Analysis

Objective:

"To assess outcomes for subset of patients expected for benefit from combinatorial pharmacogenomic testing because they were taking medications with predicted gene-drug interactions"



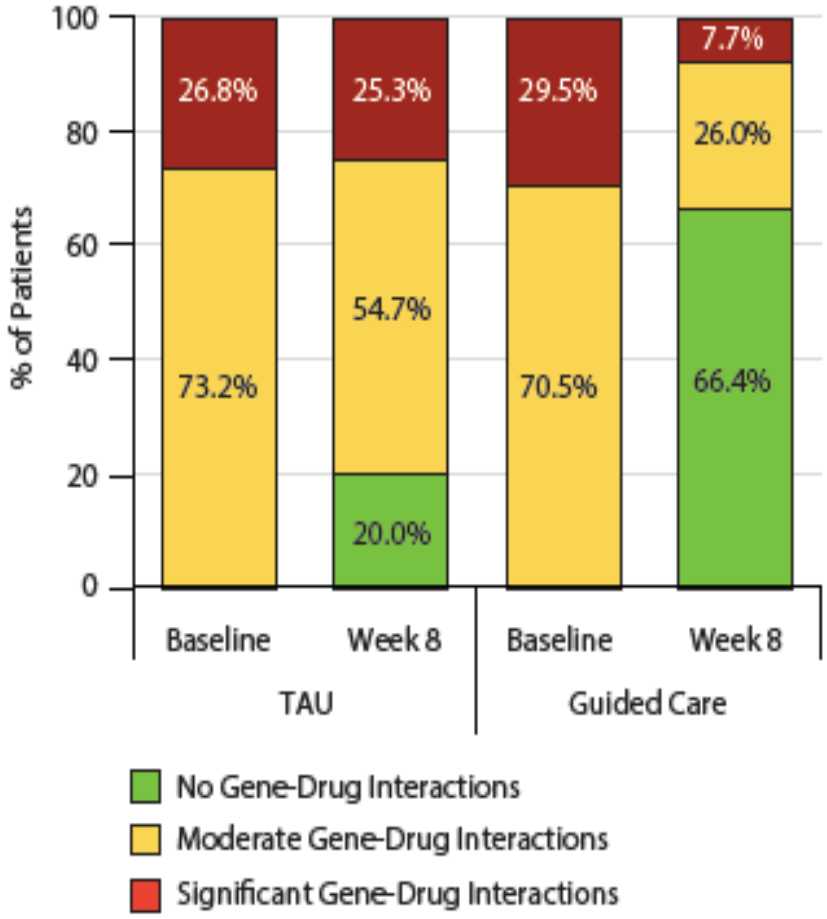
[a]Guided care: n = 357; TAU: n = 430.
[b]Guided care: n = 235; TAU: n = 225.
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, TAU = treatment as usual.
Symbol: Δ = difference between study arms.

Thase ME, et al. *J Clin Psychiatry*. 2019; 31;80(6):19m12910

GUIDED Trial Post hoc Analysis

Increased proportion of patients with *no drug-gene interactions* at week 8 in guided care arm versus treatment as usual (TAU)

Treatment outcomes including remission improved significantly at week 8 for those in guided care arm compared to TAU



[a]For patients taking more than 1 medication, the most severe level of gene-drug interactions is shown.
Abbreviation: TAU = treatment as usual.

Thase ME, et al. *J Clin Psychiatry*. 2019; 31;80(6):19m12910

Clinical Implications of GUIDED Post hoc Analysis

Pharmacogenomic testing can help to identify genetic factors responsible for treatment failure

PGx testing information can help to inform selection of new medications that avoid additional gene-drug interactions

Study findings support clinical utility of PGx testing in patients who fail current medications due to genetic reasons

Thase ME, et al. *J Clin Psychiatry*. 2019; 31;80(6):19m12910

Patient Care | Mental Health Disorders | Topics | Molecular Dx | News & Features | Pharmacogenomic Testing | Precision Medicine

UnitedHealthcare To Cover Genetic Testing for Precision Medicine in Depression, Anxiety

August 2, 2019

*The **nation's largest private health insurer, UnitedHealthcare**, announced August 1 that it will cover testing that will allow physicians to match their patients to anti-depressants most likely to work for them based on their genetic profiles. **The new coverage policy, which also includes multi-gene panel testing for antipsychotic medications, goes into effect on October 1, 2019**.*

UnitedHealthcare cited, among others, the GUIDED study as support for its new coverage decision regarding antidepressants. The study was published in the 4 January 2019 issue of the *Journal of Psychiatric Research*. It included more than 1,100 patients with depression and is the largest of its kind to date. The study

https://www.insideprecisionmedicine.com/topics/molecular-dx-topic/unitedhealthcare-to-cover-genetic-testing-for-precision-medicine-in-depression-anxiety/. Accessed March 15, 2022.

Cost Effectiveness of PGx Testing in Patients with Depression

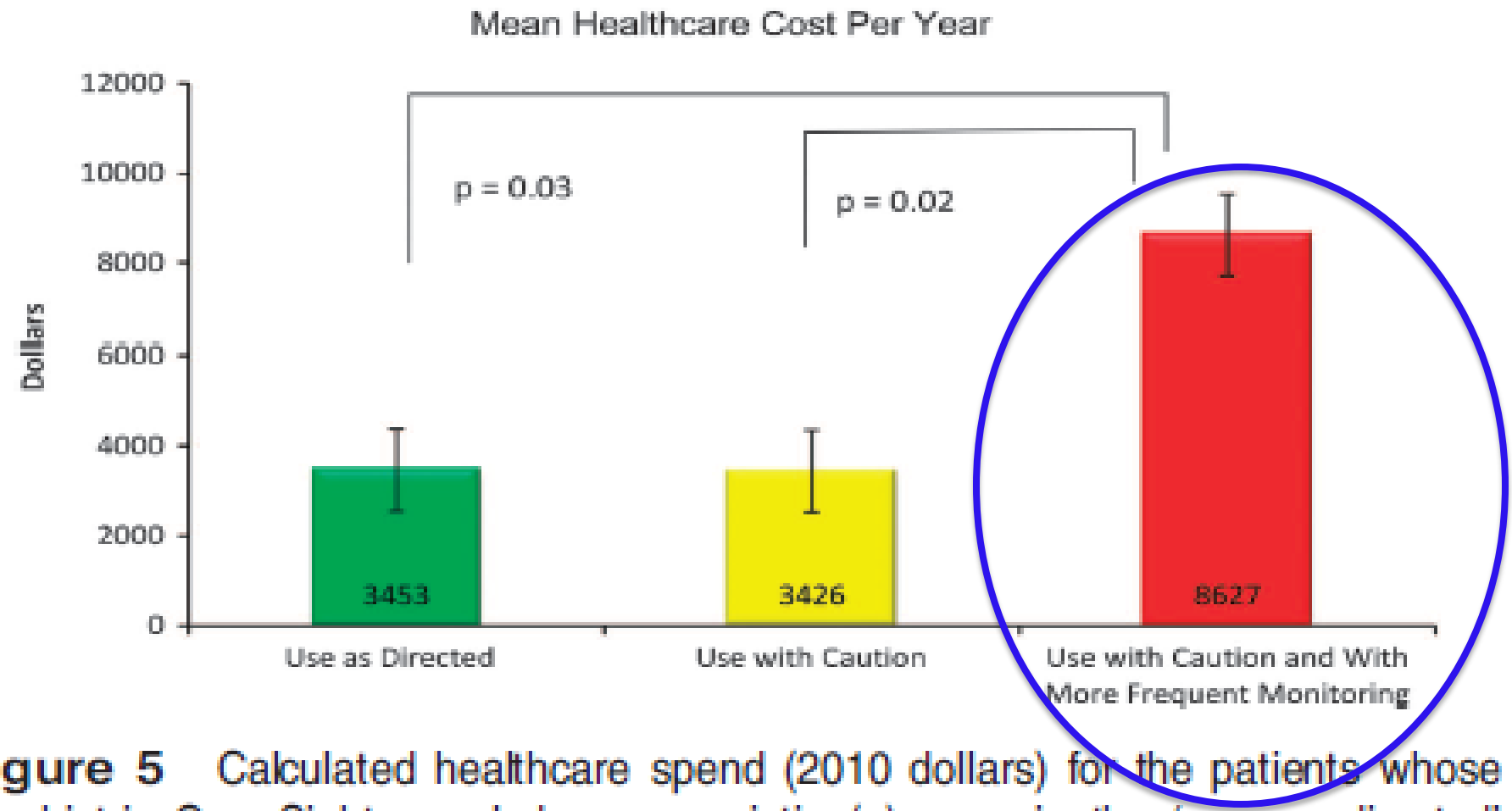


Figure 5 Calculated healthcare spend (2010 dollars) for the patients whose psychiatric GeneSight panel drug prescription(s) were in the 'use as directed' ($n = 40$) category, or had one or more 'use with caution' ($n = 48$) or 'use with caution and more frequent monitoring' ($n = 9$) drug ranked as the most severe category among the panel drug(s) they were prescribed. Significantly greater healthcare spends were calculated for the nine red-bin status patients than those in the green or yellow categories (*t*-test).

Winner J, et al. *Translational Psychiatry.* 2013; 3: e242; doi:10.1038/tp.2013.2

PGx Testing Improved QALYs and Cost Savings in Moderate to Severe Depressed Patients

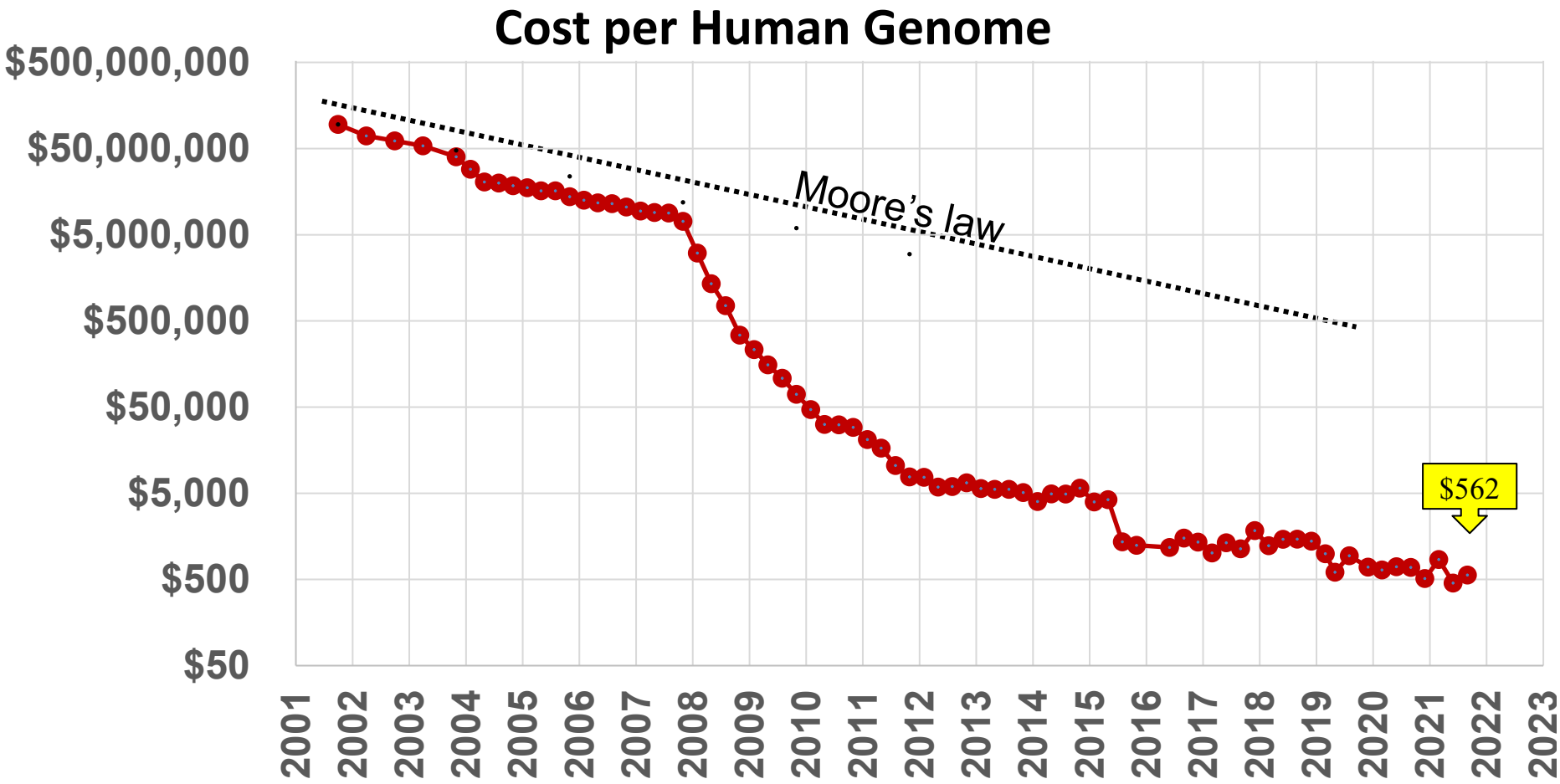
TABLE 2 Moderate to Severe MDD Compared with Severe-Only MDD over a 3-Year Time Horizon

	Moderately to Severely Depressed			Severely Depressed		
	SOC	IDGx	Difference	SOC	IDGx	Difference
Outcome						
Probability of death from suicide, %	0.351	0.328	−0.023	0.356	0.311	−0.045
QALYs	1.97	2.07	0.10	1.98	2.15	0.17
Costs, $						
Test	0	2,000	2,000	0	2,000	2,000
Direct medical costs	32,908	29,990	−2,918	33,345	27,258	−6,087
Indirect medical costs	14,387	12,707	−1,680	13,680	11,957	−1,723
Total costs (including test)	47,295	44,697	−2,598	47,025	41,215	−5,810

IDGx = IDgenetix; MDD = major depressive disorder; QALYs = quality-adjusted life-years; SOC = standard of care.

Groessl E, et al. *Journal of Managed Care and Specialty Pharmacy*. 2018; 14: 225–230.

Rapid Fall in Costs per Human Genome



NHGRI, 1/19/22

How About Preemptive PGx Testing in Depression?

Preemptive PGx Testing for Depression: PrePGx Trial

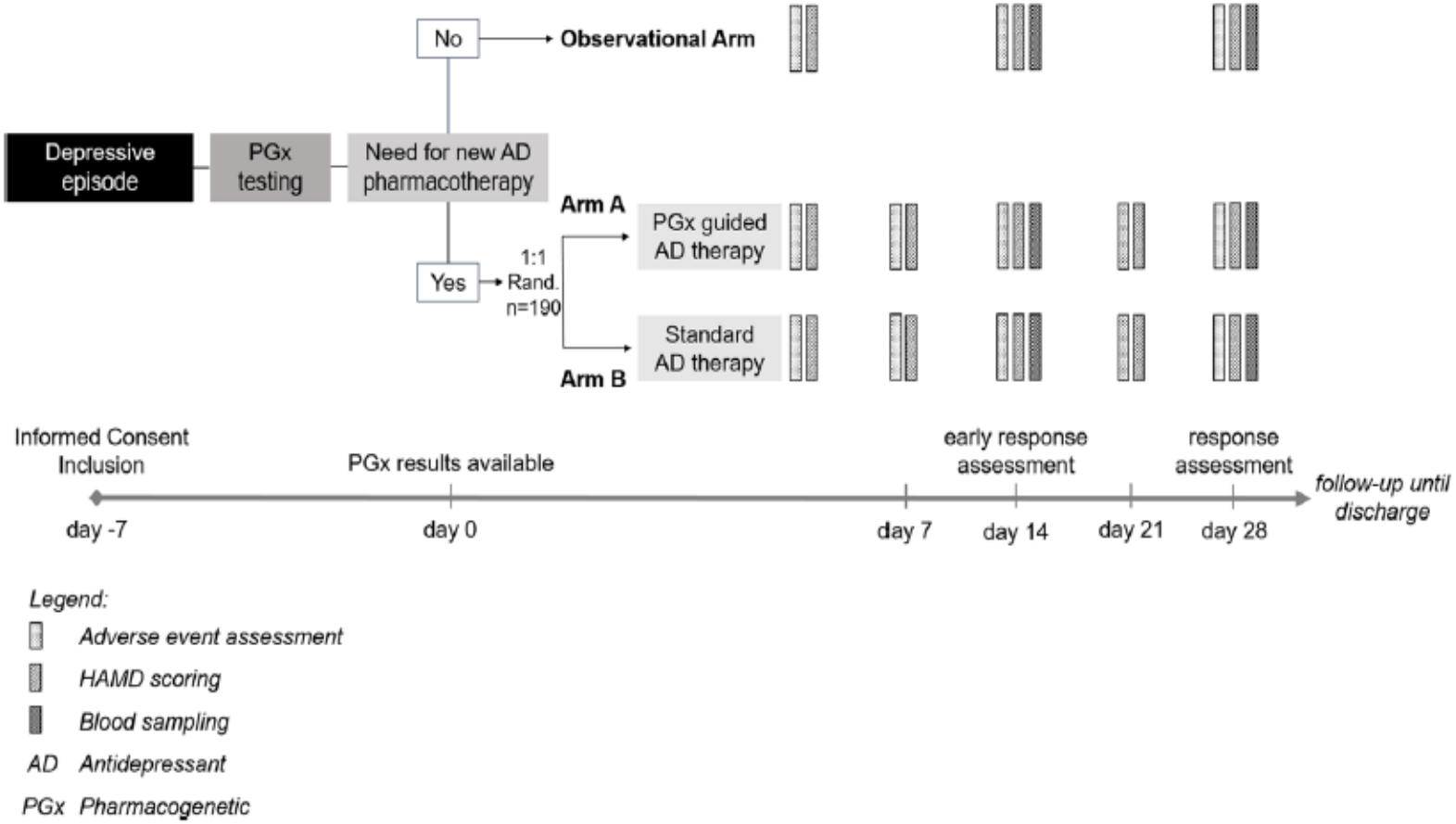


Fig. 1 Study procedures

Stäuble et al. Trials (2021) 22:919 https://doi.org/10.1186/s13063-021-05724-5

Preemptive PGx Testing for Depression: PRIME Trial

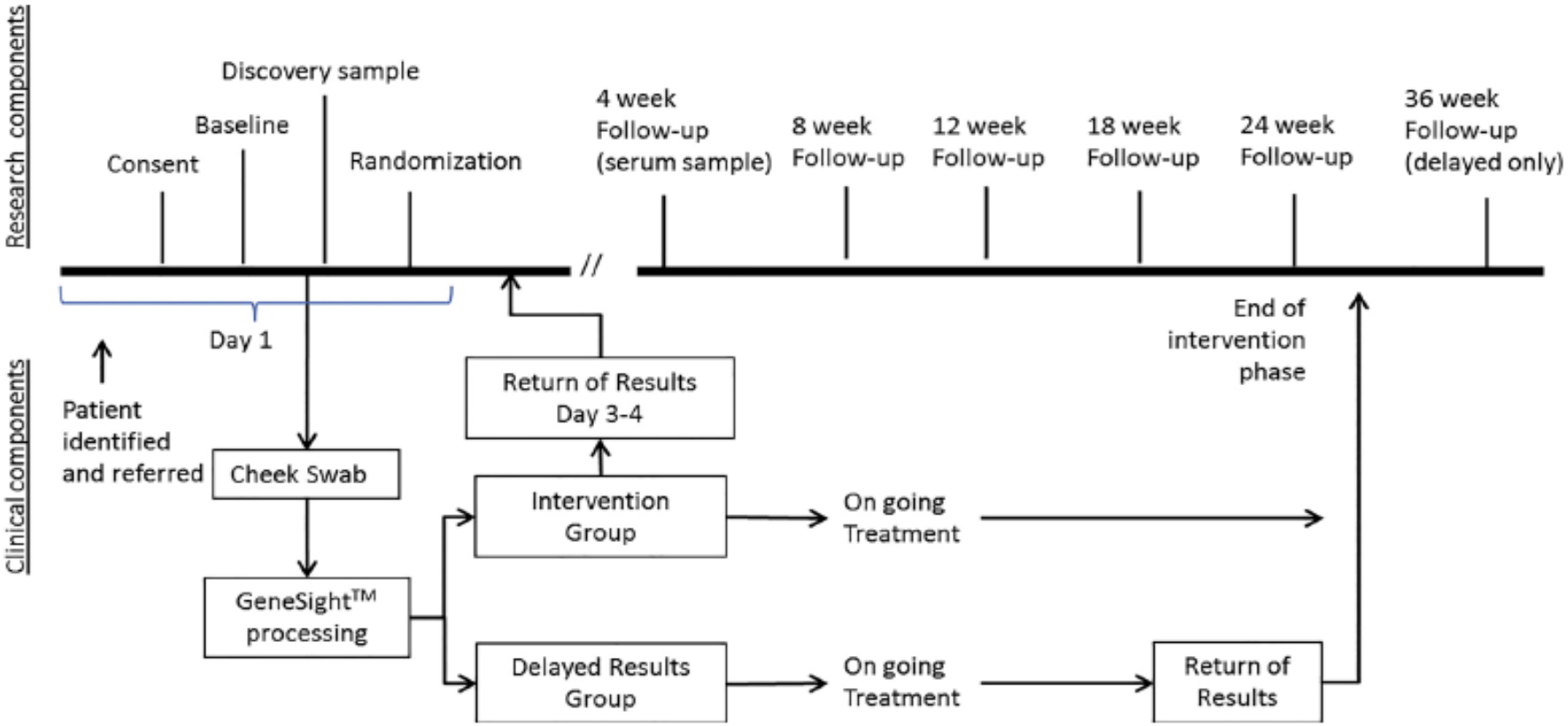


Fig. 1. Overview of study design: Interventions and assessments.

Oslin DW et al. Contemporary Clinical Trials 101 (2021) 106247

Primary care and mental health providers' perceptions of implementation of pharmacogenetics testing for depression prescribing

Bonnie M. Vest[1,2*], Laura O. Wray[1,2], Laura A. Brady[1,2], Michael E. Thase[3,4], Gregory P. Beehler[2,5], Sara R. Chapman[6], Leland E. Hull[7,8] and David W. Oslin[3,4]

Attitudes on Pharmacogenetic Testing in Psychiatric Patients with Treatment Resistant Depression

Michael J. McCarthy, MD, PhD[1,2], Yucui Chen[1,2], Anna Demodena[1], Eileen Fisher[3,4], Shahrokh Golshan[1,2], Trisha Suppes[3,4], John R. Kelsoe[1,2]

Vest BM, et al. BMC Psychiatry. 2020; 20(1): 518
McCarthy MJ, et al. *Depression and Anxiety*. 2020; 37(9):842-850.

PGx Testing Recommendations of Antidepressants

Drug	PharmGKB's interpretation of the level of action implied in FDA label	FDA Table of PGx Associations
Citalopram	Actionable	PMs in CYP2C19 results in higher systemic concentrations and adverse reaction risk (QT prolongation). The maximum recommended dose is 20 mg.
Escitalopram	Actionable	PMs, IMs and URMs of CYP2C19 may alter systemic concentrations.
Sertraline	None	Nothing reported
Paroxetine	Informative	PMs, IMs and URMs of CYP2D6 may alter systemic concentrations.
Amitriptyline	Actionable	PMs, IMs and URMs may alter systemic concentrations.
Nortriptyline	Actionable	PMs, IMs and URMs may alter systemic concentrations.
Venlafaxine	Actionable	PMs in CYP2D6 alters systemic parent drug and metabolite concentrations. Consider dosage reductions.
Vortioxetine	Actionable	PMs in CYP2D6 results in higher systemic concentrations. The maximum recommended dose is 10 mg.

https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations Accessed March 15, 2022.

Patient Case Example

CC: AJ is a 55-year-old Hispanic male who reports to the clinic with increased apathy in daily activities. Denies suicidal ideations/plan. He has been taking venlafaxine XR 150mg daily for depression for the past 4 weeks and admits to good compliance with taking his medication. AJ has failed prior antidepressants trials including citalopram and sertraline. He admits to experiencing numerous adverse effects with these two latter antidepressants even with adjustments in using lower doses of these medications.

PMH: Percutaneous coronary intervention with coronary artery stent placement 5 years ago. He has a history of hyperlipidemia and hypertension.

SH: denies alcohol, recreational drug use and smoking.

Current Medications: venlafaxine XR 150mg daily, simvastatin 20mg qhs, lisinopril 20mg daily

Current Vitals: BP 125/85, HR 75, RR 12

Labs: SCr 0.9 mg/dL, ALT 25 IU/L and AST 20 IU/L, fasting lipid panel (TC 150, HDL 45, LDL 85 and TG 90), and A1c 5.5%

His psychiatrist ordered pharmacogenomic testing to guide next steps in managing AJ's treatment-resistant depression. The PGx test comes back 4 days later (refer to next slide) and consults you regarding input on treatment recommendations.

Manchester University

FOR ACADEMIC PURPOSES ONLY - NOT FOR CLINICAL USE

PATIENT INFORMATION		SPECIMEN DETAILS		ORDERED BY
NAME:	Patient 27522	**SPECIMEN TYPE:**		
ACC #:	27522	**COLLECTION DATE:**	1/1/1900	
DOB:	1/1/1900	**RECEIVED DATE:**	1/1/1900	
SEX:		**REPORT DATE:**	2/1/2018	

Test Details

Gene	Genotype	Phenotype	Alleles Tested
CYP2C19	*2/*2	Poor Metabolizer	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *17
CYP2C9	*1/*2	Intermediate Metabolizer	*2, *3, *4, *5, *6, *11
CYP3A5	*1D/*3	Intermediate Metabolizer	*1D, *2, *3, *3B, *3C, *6, *7, *8, *9
CYP3A4	*1/*1	Normal Metabolizer	*1B, *2, *3, *12, *17, *22
VKORC1	-1639G>A A/A	High Warfarin Sensitivity	-1639G>A
Apolipoprotein E	Indeterminate	Unknown Phenotype	ε2, ε4, (ε3 is reference)
CYP2D6	*1/*2xN	Ultra-Rapid Metabolizer	*2, *3, *4, *4M, *6, *7, *8, *9, *10, *12, *14A, *14B, *17, *29, *35, *41
CYP2B6	*1/*1	Normal Metabolizer	*6, *9
SLCO1B1	521T>C T/T	Normal Function	521T>C, 388A>G
COMT	Val158Met A/A	Low COMT Activity	Val158Met
OPRM1	A118G A/A	Normal OPRM1 Function	A118G
CYP1A2	*1F/*1L	Normal Metabolizer- Possible Inducibility	*1C, *1D, *1F, *1K, *1L, *1V, *1W
MTHFR	1298A>C AA 677C>T TT	Increased Risk of Hyperhomocysteinemia	1298A>C, 677C>T
MTHFR	677C>T TT	Reduced MTHFR Activity	1298A>C, 677C>T
Factor II Factor V Leiden	20210G>A GG 1691G>A GG	No Increased Risk of Thrombosis	20210G>A, 1691G>A

Additional Test Results (added to this original report)

HLA-B*15:02	negative/negative	Negative	HLA-A*31:01	negative/negative	Negative
HLA-B*57:01	negative/positive	Positive			
HLA-B*58:01	negative/negative	Negative			

Patient Case Example

Which of the following treatment choices would you recommend as the next best step for managing AJ's depression? Select all that apply.

a. Venlafaxine
b. Desvenlafaxine
c. Amitriptyline
d. Paroxetine
e. Escitalopram
f. Fluoxetine
g. Bupropion
h. Vortioxetine

Emerging Areas of PGx and Mental Health

Drug	Gene	CPIC Level
Atomoxetine*	CYP2D6	A
Venlafaxine	CYP2D6	A/B provisional
Vortioxetine	CYP2D6	A/B provisional
Aripiprazole	CYP2D6	B provisional
Risperidone	CYP2D6	B provisional
Aripiprazole lauroxil	CYP2D6	B/C provisional
Brexpiprazole	CYP2D6	B/C provisional
Bupropion	CYP2B6	B/C provisional
Haloperidol	CYP2D6	B/C provisional
Iloperidone	CYP2D6	B/C provisional
Mirtazapine	CYP2D6	B/C provisional
Perphenazine	CYP2D6	B/C provisional
Thioridazine	CYP2D6	B/C provisional

*CPIC guideline available https://cpicpgx.org/genes-drugs/ Accessed March 14, 2022

SUMMARY TAKE HOME POINTS

- PGx test results are informative and helpful in guiding prescribing of antidepressants for patients who have underlying drug-gene interactions
- Cost-effectiveness studies support coverage of reactive PGx testing for patients who fail prior antidepressant trials
- Large clinical trials involving preemptive PGx testing and treatment of depression are currently in progress
- CPIC guidelines involving SSRIs/SNRIs and atypical antipsychotics on the horizon