Pharmacogenomic Decision Support Tools for Major Depressive Disorder

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Disclosures: Boadie W. Dunlop, MD
Personal/Professional Financial Relationships with Industry, Last 12 Months

External Industry Relationships *	Company Names	Role
Equity, stock, or options in biomedical industry companies or publishers**	None	
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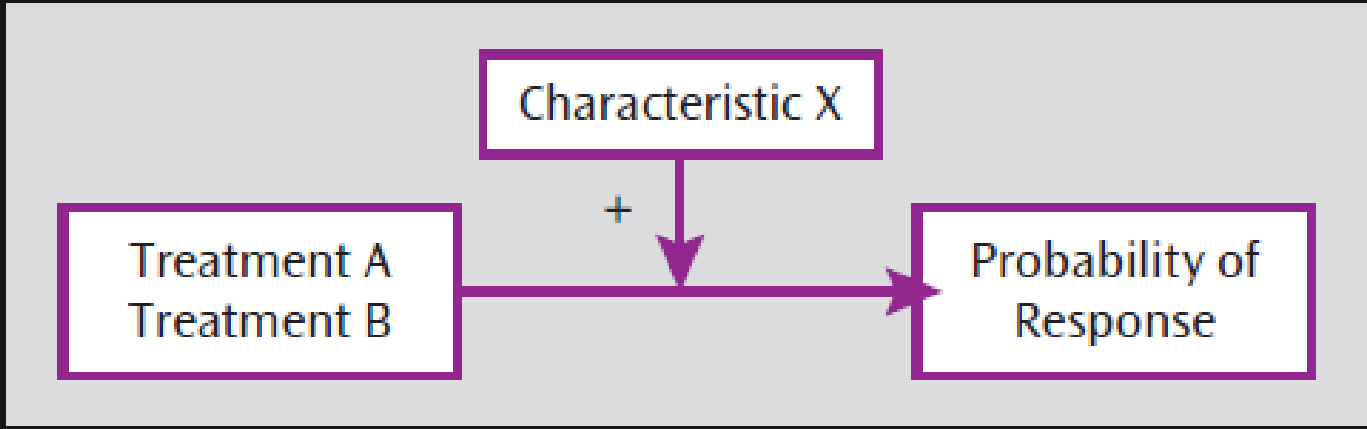
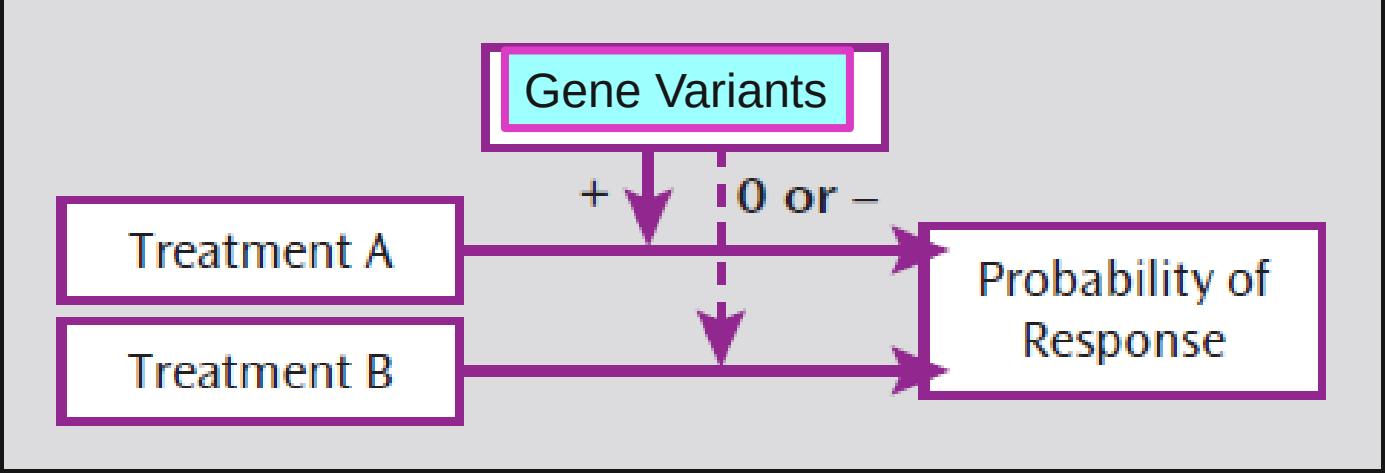
Industry funds to Emory for my research	Acadia, Aptinyx, Compass Pathways, Otsuka, Sage, Takeda, NIH	Principal investigator/Co-investigator
Other	Greenwich Biosciences, Mol Dx, Myriad Neuroscience, Sophren, Otsuka	Consultant

Precision Medicine: Predictors vs Moderators

1. **Predictor** (Non-specific)



2. **Moderator** (Treatment Specific)



Simon and Perlis, Am J Psychiatry, 2010; 167:1445-1455

Other Possible Benefits

- Optimize Dosing
- Avoid negative outcomes
  - Drop-out from treatment
  - Avoid adverse drug reactions
  - Inform medication tapering

Pharmacogenetics vs Pharmacogenomics

- **Pharmacogenetics** has historically referred to how variation in a *single* gene impacts the response to a single drug.

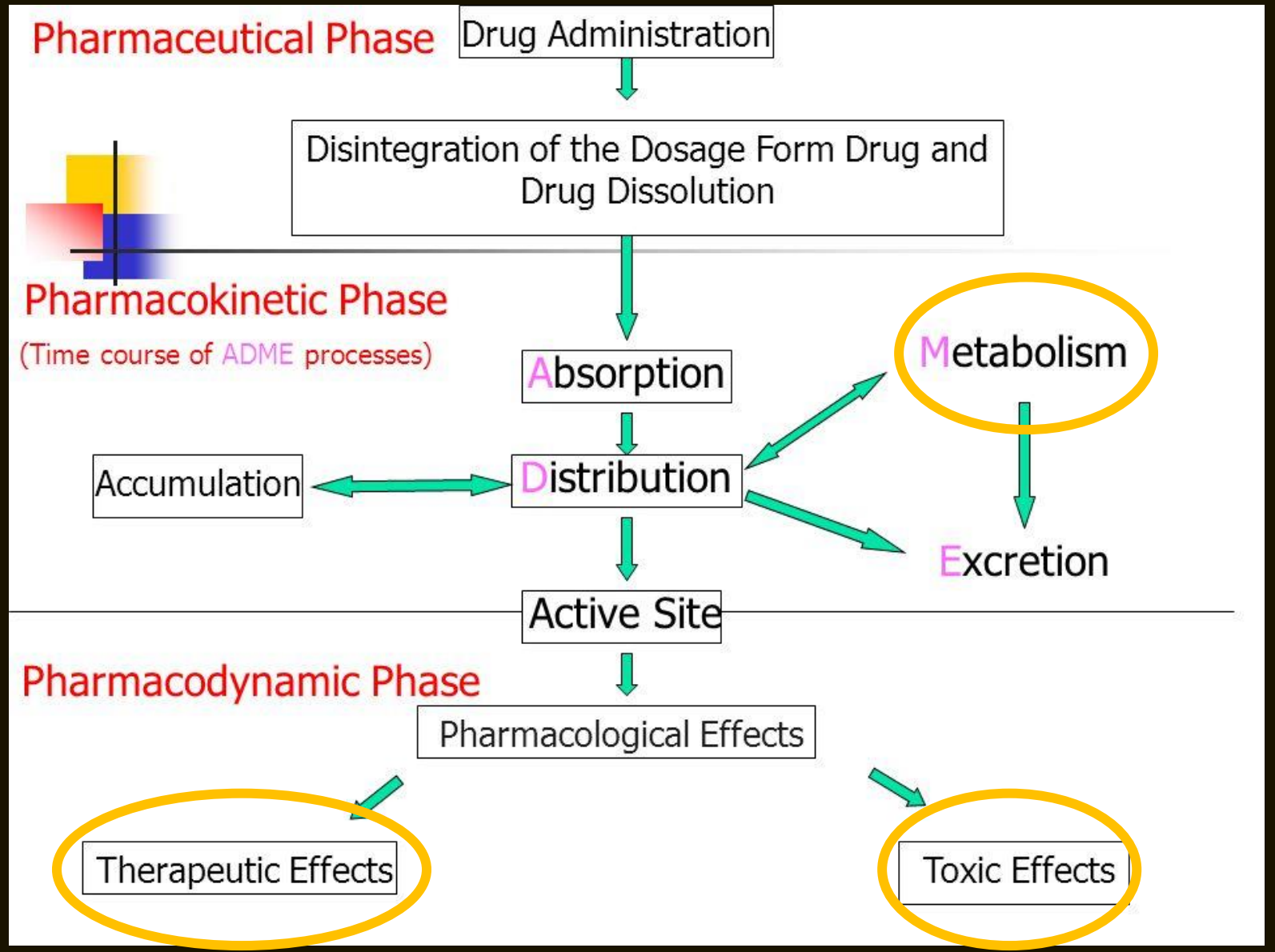
- **Pharmacogenomics** is a newer and broader term that encompasses how all of the genes of an organism (the genome) impact responses to a wide variety of drugs.

- Today these terms are often used interchangeably.

Pharmacokinetics vs Pharmacodynamics and the targets of PGx Testing

- Pharmacokinetics (PK): What the body does to the drug
  - GI, Liver, Kidney actions
- Pharmacodynamics (PD): What the drug does to the body
  - Receptors, Transporters

- Immune-Related Genes:
  - HLA-B*1502
  - HLA-A*3101



Pharmacogenomics (PGx): A Crowded Space

Professional Guidelines

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  - https://cpicpgx.org/
- Dutch Pharmacogenetics Working Group (DPWG)
  - http://upgx.eu/
- Canadian Pharmacogenomics Network for Drug Safety (CPNDS)
  - http://cpnds.ubc.ca/

Regulatory

- US Food and Drug Administration (FDA)

Industry

- PGx Decision Support Tool (DST) manufacturers

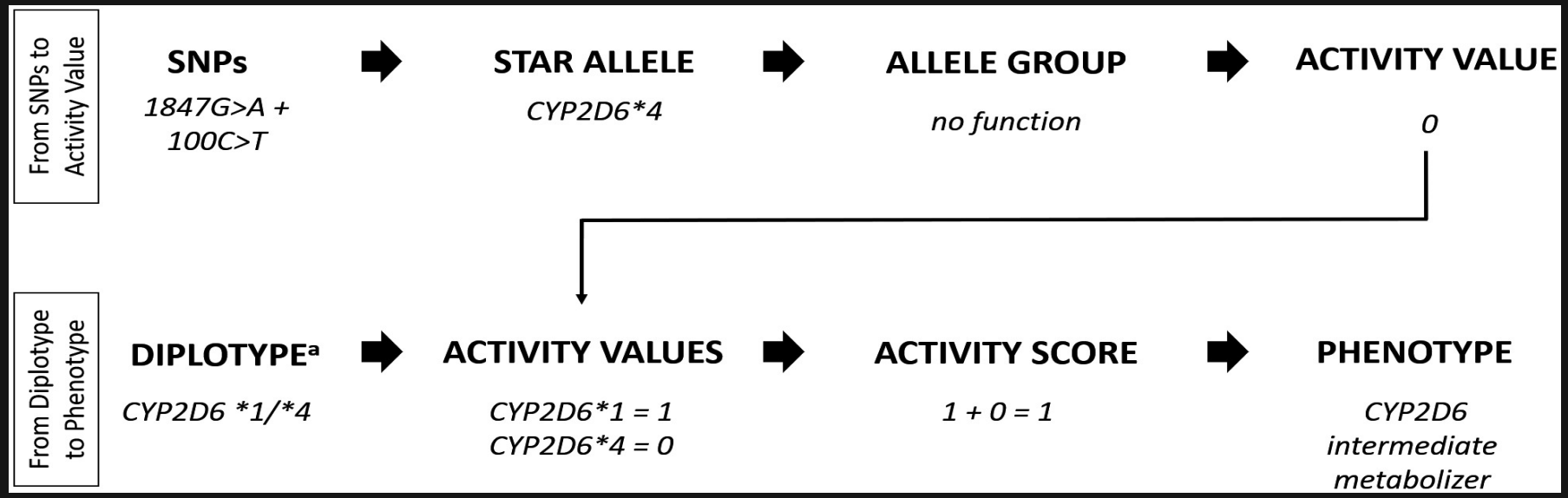
Gene-drug pairs with clinical prescribing guidelines relevant to psychiatry

Gene	Drugs
CYP2C19	amitriptyline, citalopram, clomipramine, doxepin, escitalopram, imipramine, sertraline, trimipramine
CYP2C9	phenytoin
CYP2D6	amitriptyline, aripiprazole, atomoxetine, clomipramine, desipramine, doxepin, fluvoxamine, haloperidol, imipramine, nortriptyline, paroxetine, pimozide, trimipramine, venlafaxine
HLA-A	carbamazepine
HLA-B	carbamazepine, oxcarbazepine, phenytoin

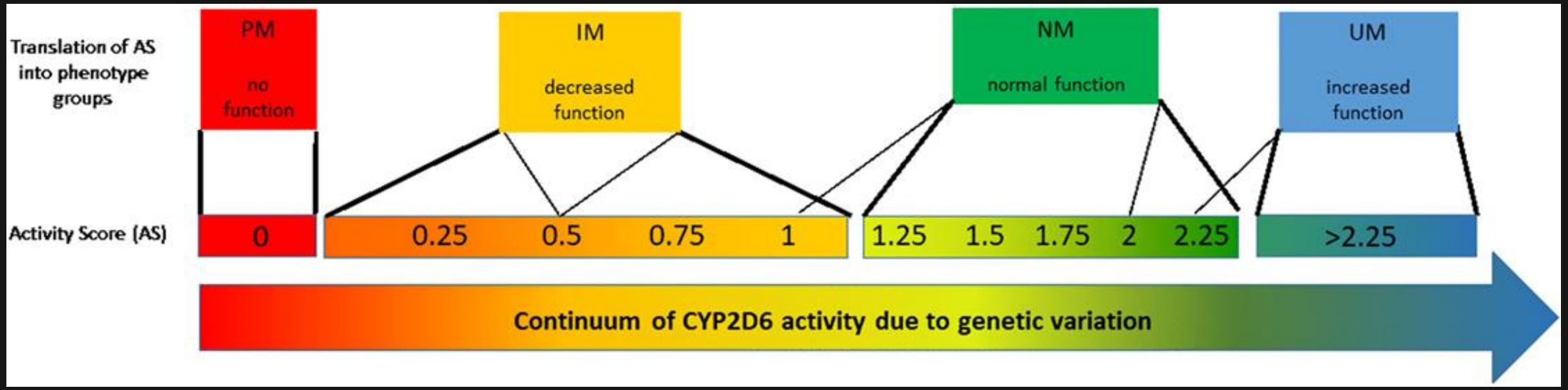
Guidelines published as of 10 September, 2019 from CPIC, DPWG, or CPNDS

Bousman, Forbes & Dunlop, *Precision Psychiatry,* 2020, in press

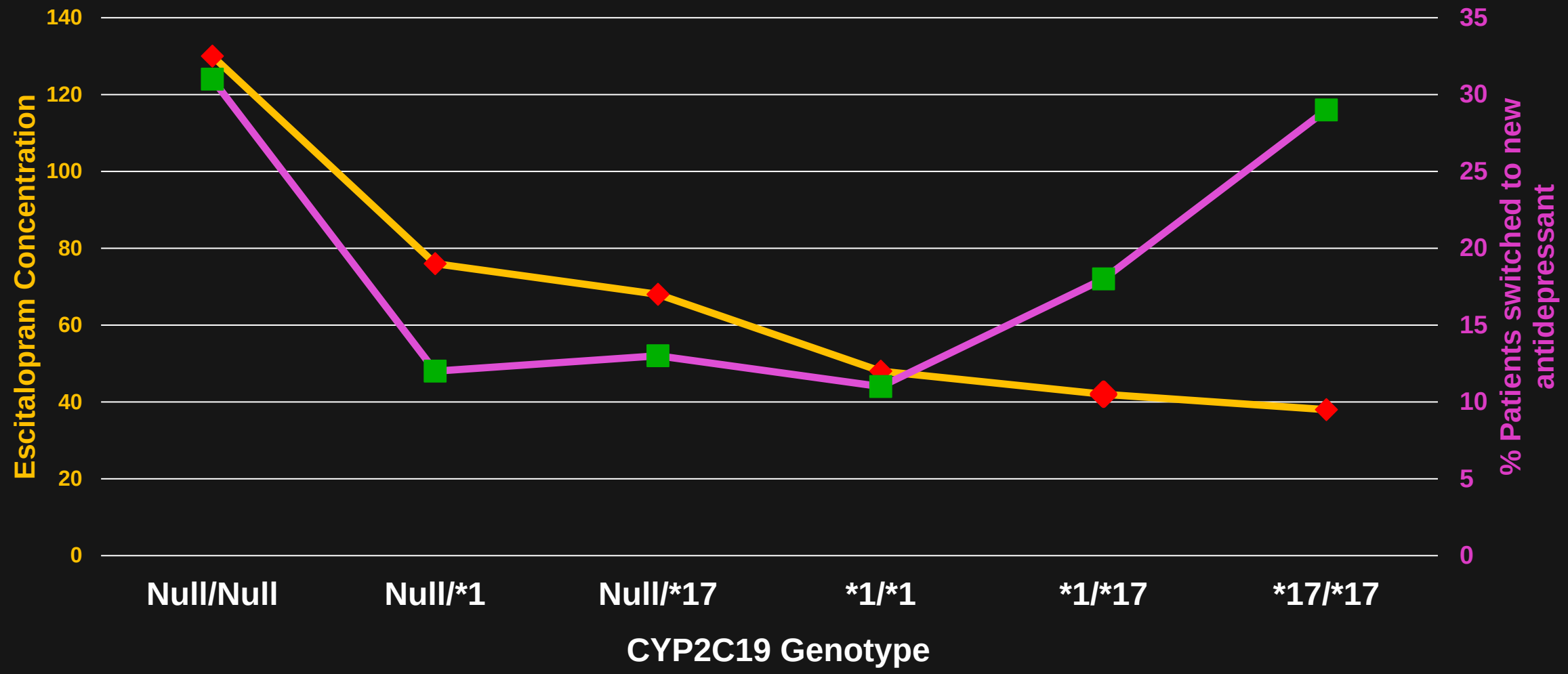
From PK Gene to Metabolizer Phenotype



Caudle et al. *Clinical & Translational Sciences*, 2020; 13:116-124

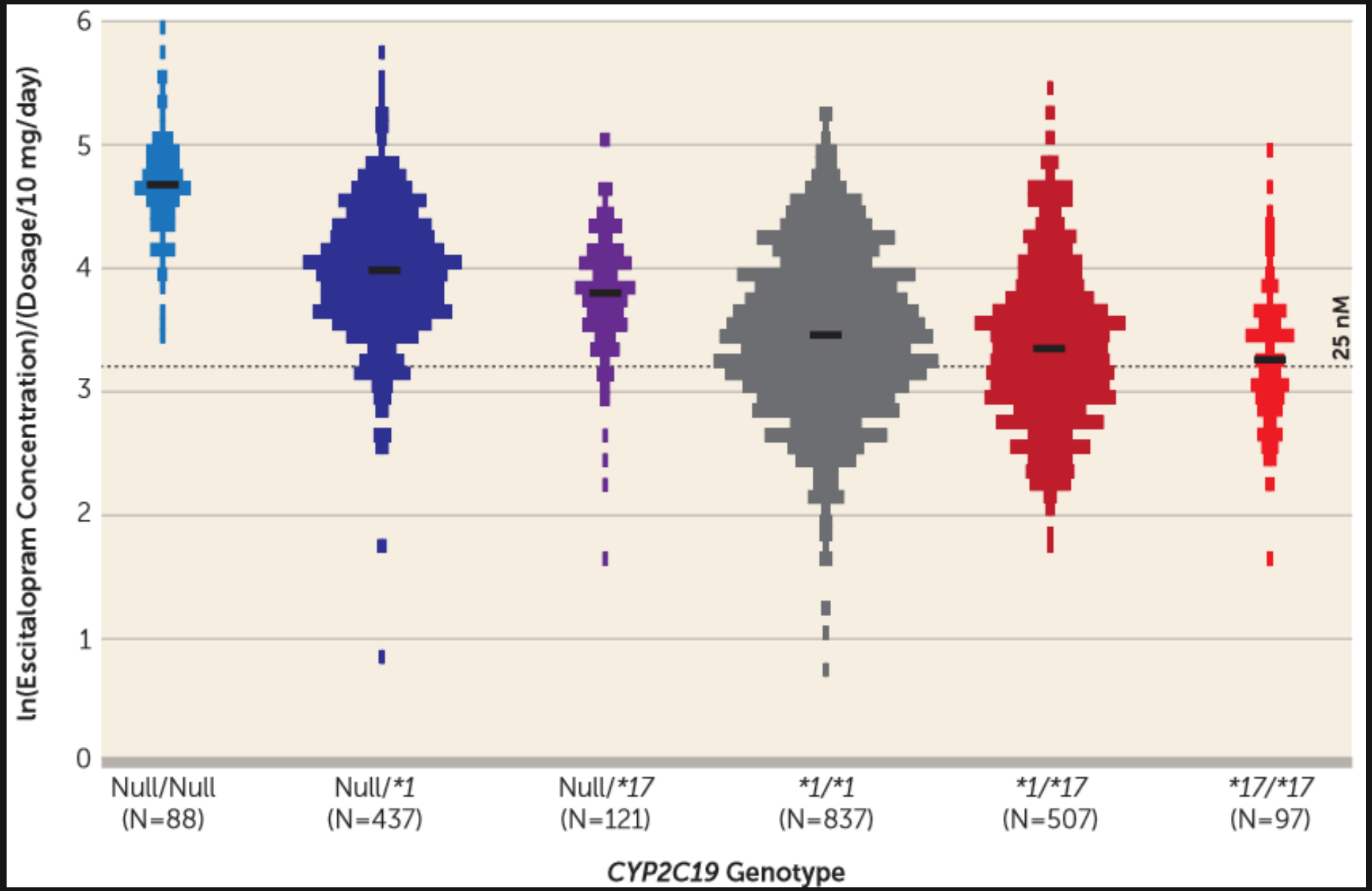


Impact of CYP2C19 on Escitalopram Exposure (Norway)



Jukic et al., *Am J Psychiatry*, 2018;175(5):463-470.

Variability in Escitalopram Concentration by CYP2C19 Genotype



Jukic et al., *Am J Psychiatry*, 2018;175(5):463-470.

Selected psychiatric drugs with gene-drug warnings on FDA label

Drug	Gene	Adverse drug reactions	Gene-Drug interaction management in PMs	Drug-drug interaction management*
Aripiprazole	2D6	Stroke, TIA, TD, agranulocytosis, hyperglycemia	Reduce dose by half	Reduce dose by half
Atomoxetine	2D6	↑HR, BP, liver injury	Start at 0.5 mg/kg/day. Titrate at 4wk intervals	Start at 0.5 mg/kg/day. Titrate at 4wk intervals
Brexpiprazole	2D6	Stroke, TIA, TD, agranulocytosis, hyperglycemia	Start at half usual dose	Start at half usual dose for 2D6 & 3A4 inhibitors
Carbamazepine	HLA-B	Stevens Johnson Syndrome/TEN	Genotype if Asian origin: HLA-B*1502: avoid using	None
Citalopram	2C19	QT prolongation	Max dose 20 mg/day	Max dose 20 mg/day
Iloperidone	2D6	QT prolongation, tachycardia, hyperglycemia, agranulocytosis	Reduce dose by half	Reduce dose by half
Pimozide	2D6	QT prolongation, TD, torsades de pointes, cardiac arrest	Genotype if use >4 mg/day. Titrate at 2 week intervals	Contraindicated
Thioridazine	2D6	QT prolongation, TD, torsades de pointes, cardiac arrest	Contraindicated	Contraindicated
Vortioxetine	2D6	Serotonin syndrome, bleeding	Max dose 10 mg/day	Reduce dose by half

Conrado et al., Pharmacogenomics 2013; 14:215-23

*If on strong CYP inhibitor

Regulatory Environment of PGx Tests is Changing

FDA is increasingly concerned that unregulated laboratory developed tests (LDTs) for genomic testing may pose a public health threat

Oct. 31, 2018

The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication

https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific

Nov. 1, 2018

Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research on agency's warning to consumers about genetic tests that claim to predict patients' responses to specific medications

https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md

April 4, 2019

WARNING LETTER

Inova Genomics Laboratory

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019

Feb. 20, 2020

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

https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic

FDA Table of PGx Interactions: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

APA Task Force for Biomarkers and Novel Treatments: Conclusion on PGx Testing for Antidepressant Selection

Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing

Zane Zeier, Ph.D., Linda L. Carpenter, M.D., Ned H. Kalin, M.D., Carolyn I. Rodriguez, M.D., Ph.D., William M. McDonald, M.D., Alik S. Widge, M.D., Ph.D., Charles B. Nemeroff, M.D., Ph.D.

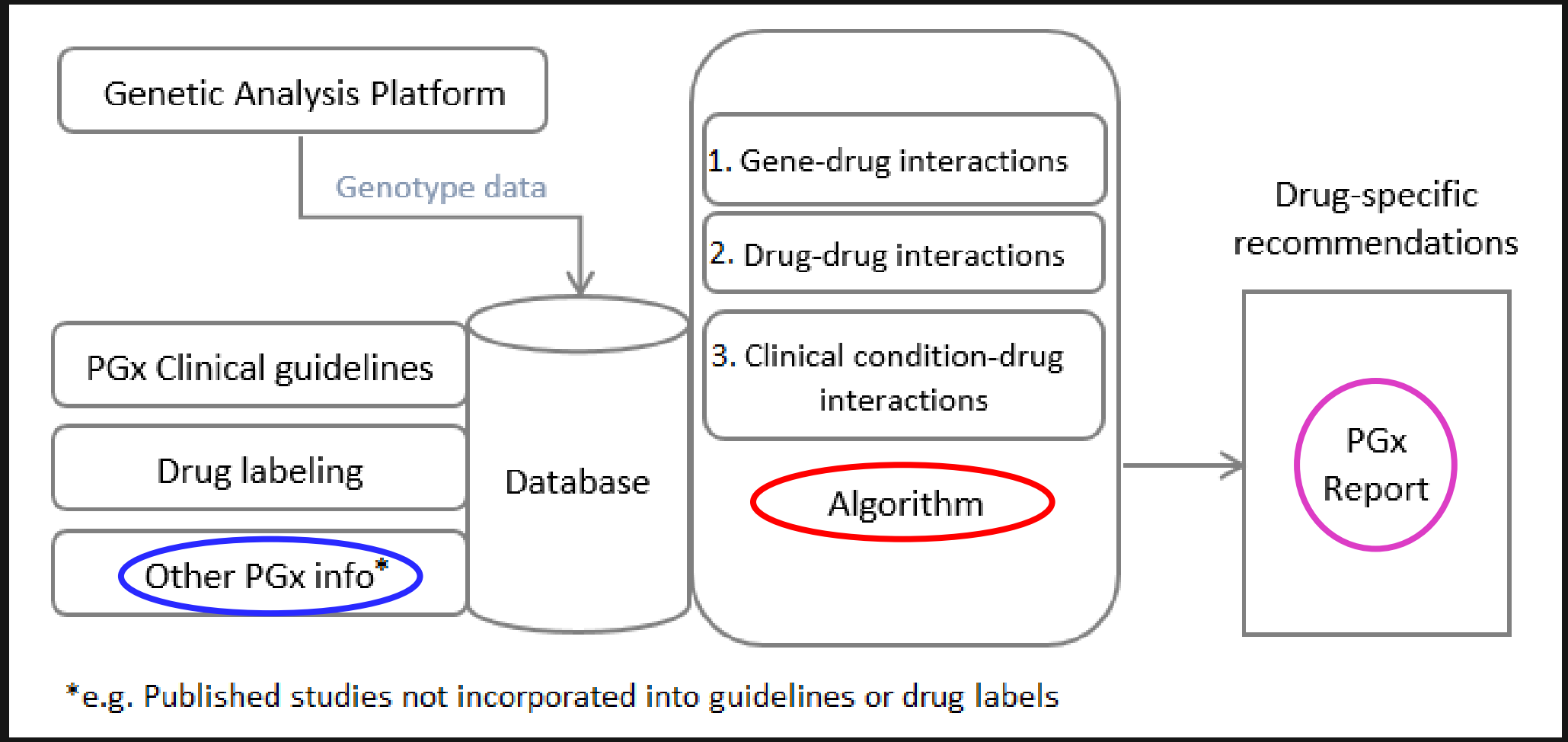
The accrual and analysis of genomic sequencing data have identified specific genetic variants that are associated with major depressive disorder. Moreover, substantial investigations have been devoted to identifying gene-drug interactions that affect the response to antidepressant medications by modulating their pharmacokinetic or pharmacodynamic properties. Despite these advances, individual responses to antidepressants, as well as the unpredictability of adverse side effects, leave clinicians with an imprecise prescribing strategy that often relies on trial and error. These limitations have spawned several combinatorial pharmacogenetic testing products that are marketed to physicians. Typically, combinatorial pharmacogenetic decision support tools use algorithms to integrate multiple genetic variants and assemble the results into an easily interpretable report to guide prescribing of antidepressants and other psychotropic medications. The authors review the evidence base for several combinatorial pharmacogenetic decision support tools whose potential utility has been evaluated in clinical settings. They find that, at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.

AJP in Advance (doi: 10.1176/appi.ajp.2018.17111282)

Zeier et al., Am J Psychiatry. 2018 Sep 1;175(9):873-886

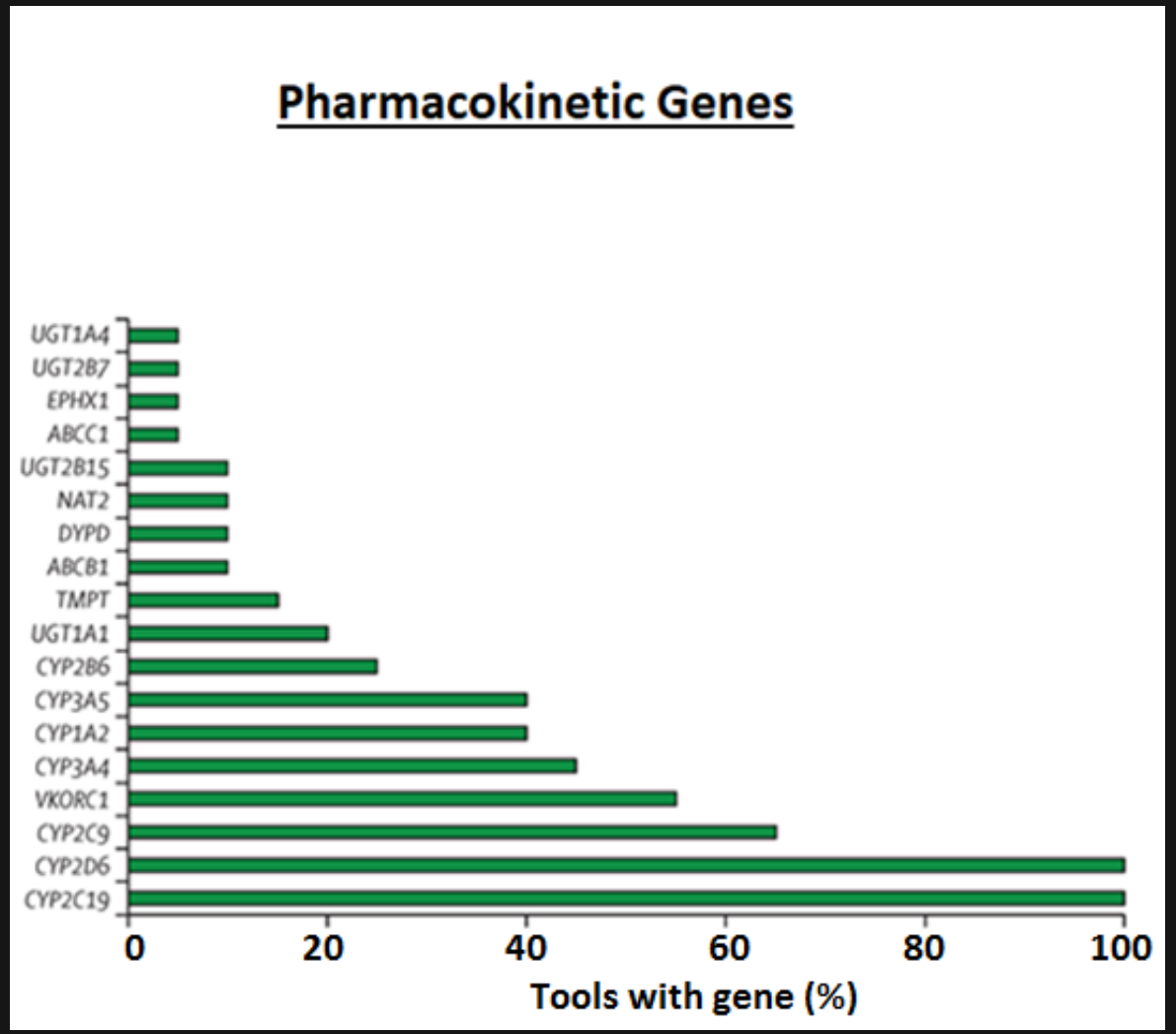
Commercially Available PGx Decision-Support Tools

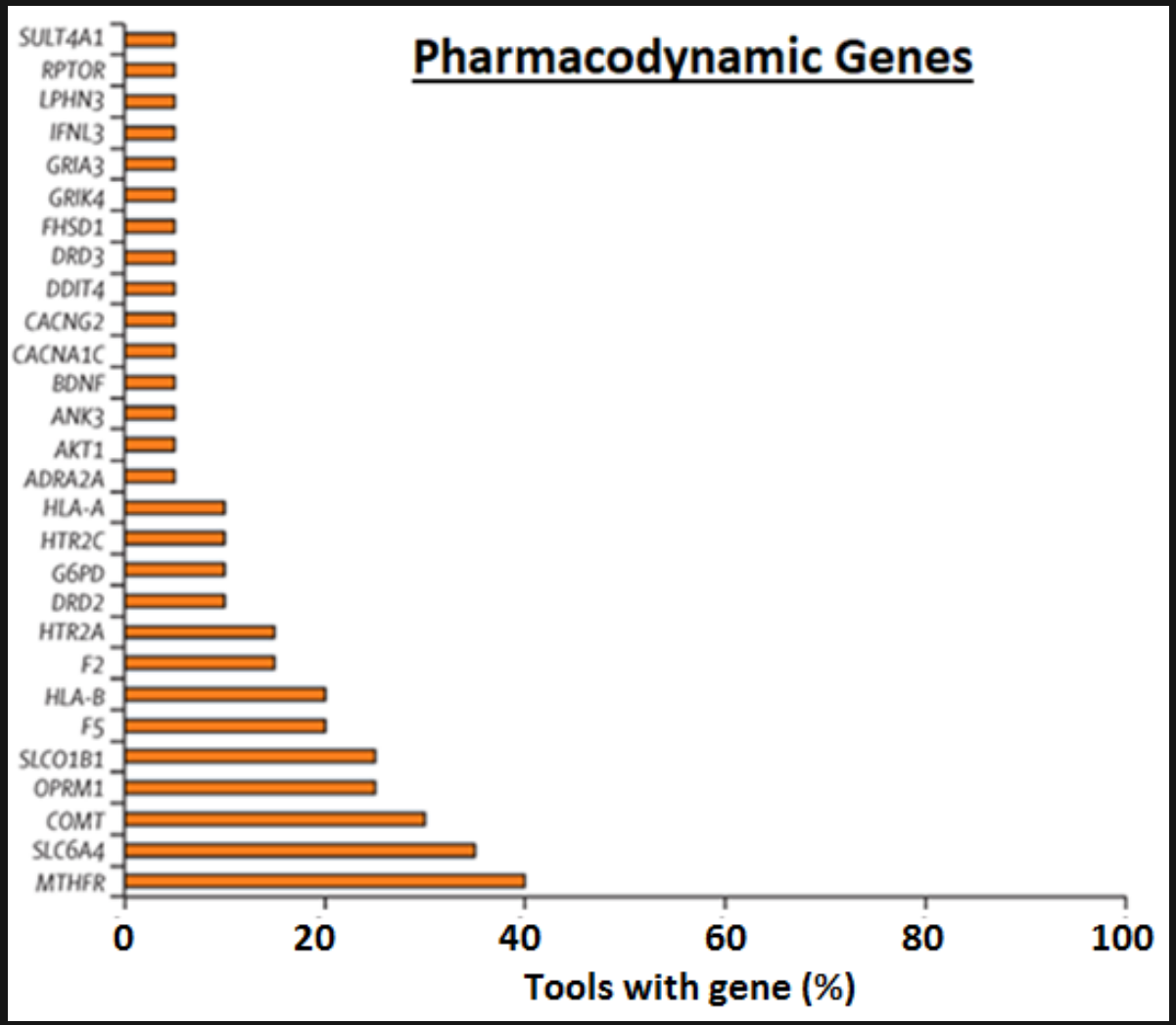
Overview of PGx Report Generation



Perez et al., BMC Psychiatry, 2017; 17:250

Genes Analyzed across PGx Tests Vary Substantially

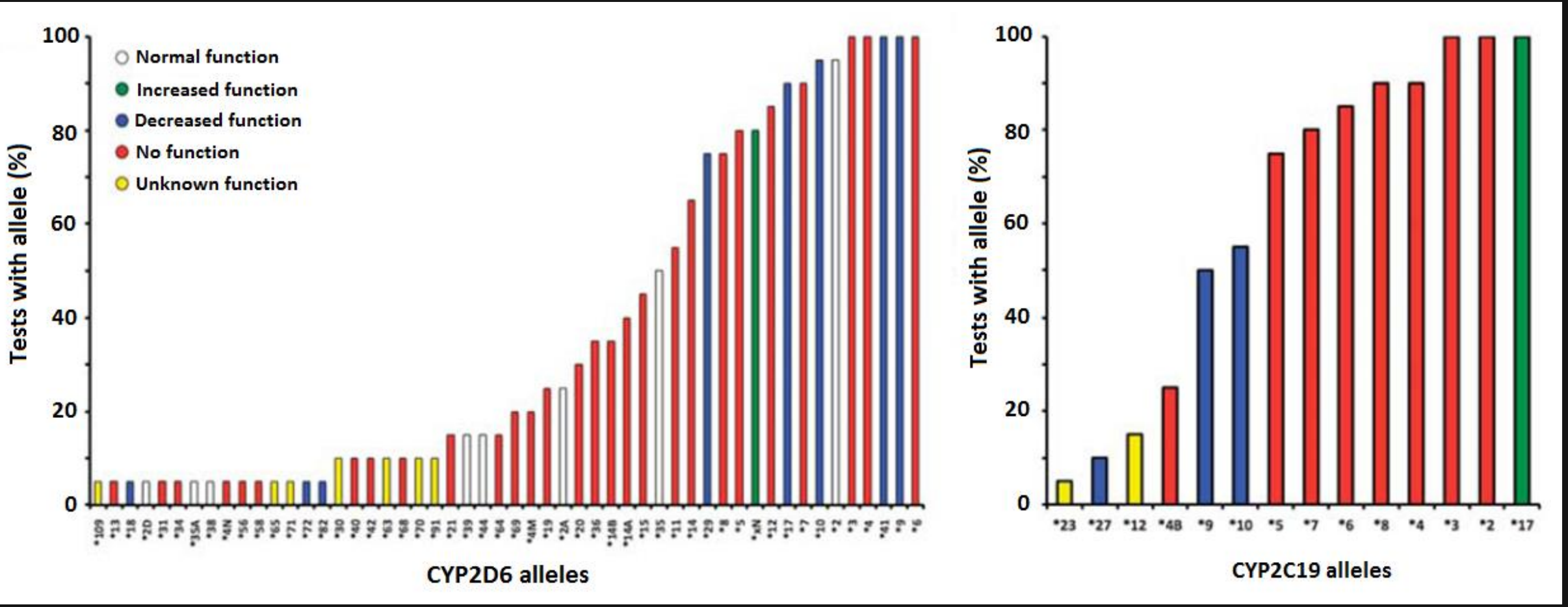




Bousman & Hopwood, Lancet Psychiatry, 2016; 3:585-90

Even if including same genes, DSTs may differ in the specific allele variants tested

CYP2D6 and 2C19 Star Alleles across PGx Tests



Bousman et al., Pharmacogenet Genomics, 2017; 27: 1-6.

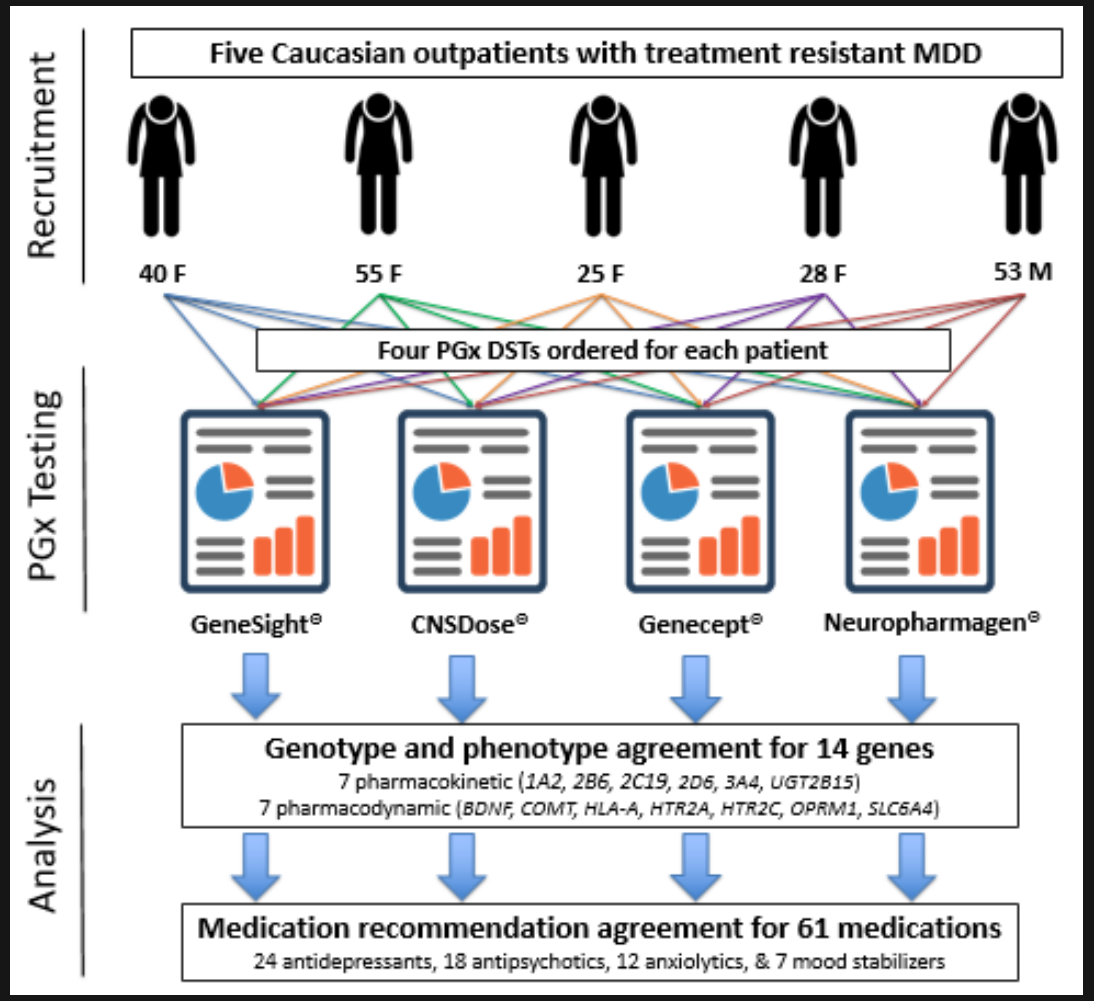
Commercial PGx Tests with RCT data

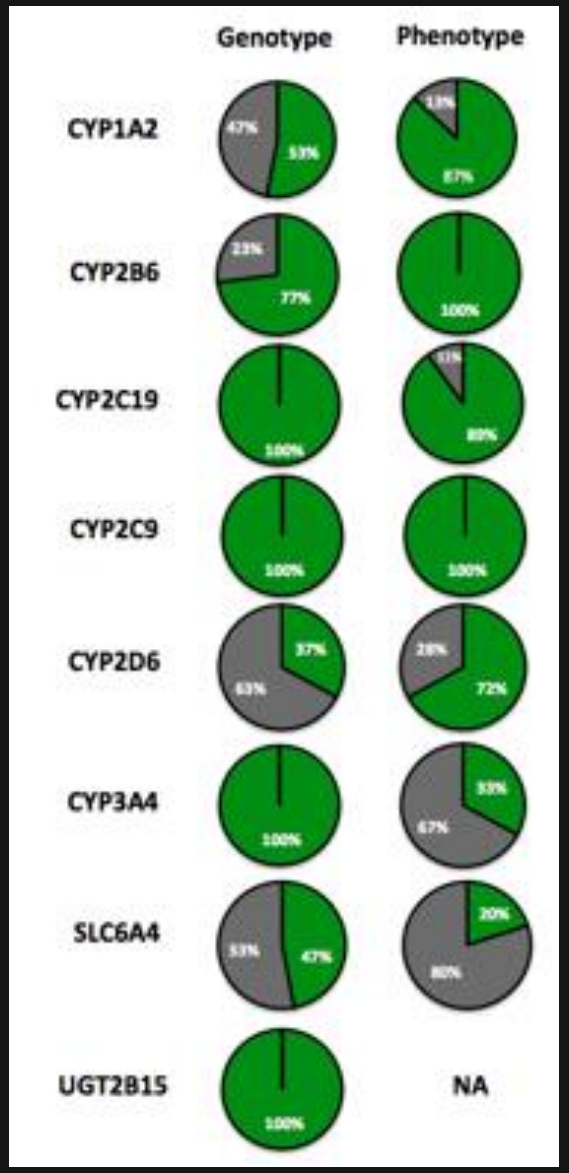
PGx Test Name	Manufacturer	Number of MDD RCTs	Incorporates Drug-Drug-Gene Interactions?	Recommendations
Amplis	Luminus (CNS Dose)	1	No	1. Lower dose 2. Average dose 3. Higher dose
Genecept Assay	Genomind	1	Yes	1. Use as Directed/Therapeutic Options 2. Use with Caution
GeneSight Psychotropic	Myriad Neuroscience	2	No	1. Use as Directed 2. Use with Caution 3. Use with Caution and ↑ Monitoring
NeuroIDgenetix	AltheaDx	1	Yes	1. Use as Directed 2. Use with Caution or ↑ Monitoring
Neuropharmagen	AB Biotics	2	No	1. Increased response or ↓ risk of ADRs 2. Standard response 3. Reduced response or ↑ Monitoring 4. ↑ Risk of adverse drug reactions (ADRs)

Genes Included in Specific PGx DSTs

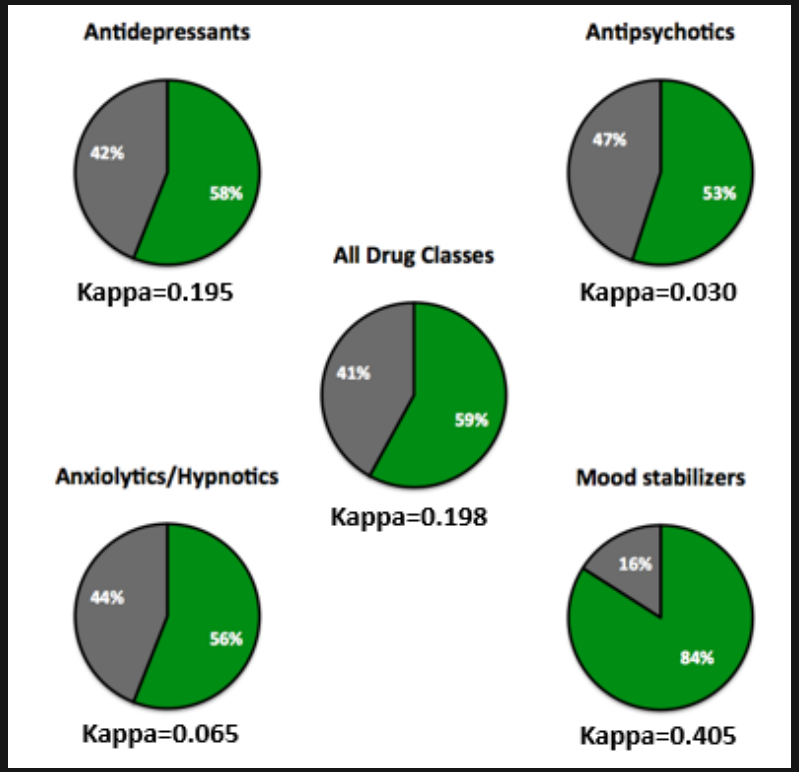
	Gene	Amplis	Genesight	NeuroIDGenetix	Genecept v.2.0	Neuropharmagen
PHARMACO-KINETIC	CYP1A2		x	x	x	x
	CYP2B6		x		x	x
	CYP2C19	x	x	x	x	x
	CYP2C9		x	x	x	x
	CYP2D6	x	x	x	x	x
	CYP3A4		x	x	x	x
	CYP3A5			x	x	
	ABCB1	x				x
PHARMACO-DYNAMIC	SLC6A4		x	x	x	x
	5HT2A		x	x		x
	5HT2C				x	X
	COMT			x	x	x
	BDNF				x	x
	MTHFR			x	x	
	Others				7	17

How Interchangeable are PGx DSTs?





Medication Recommendations



Bousman & Dunlop, *The Pharmacogenomics Journal*, 2018; 18(5):613-622

Summary Outcomes

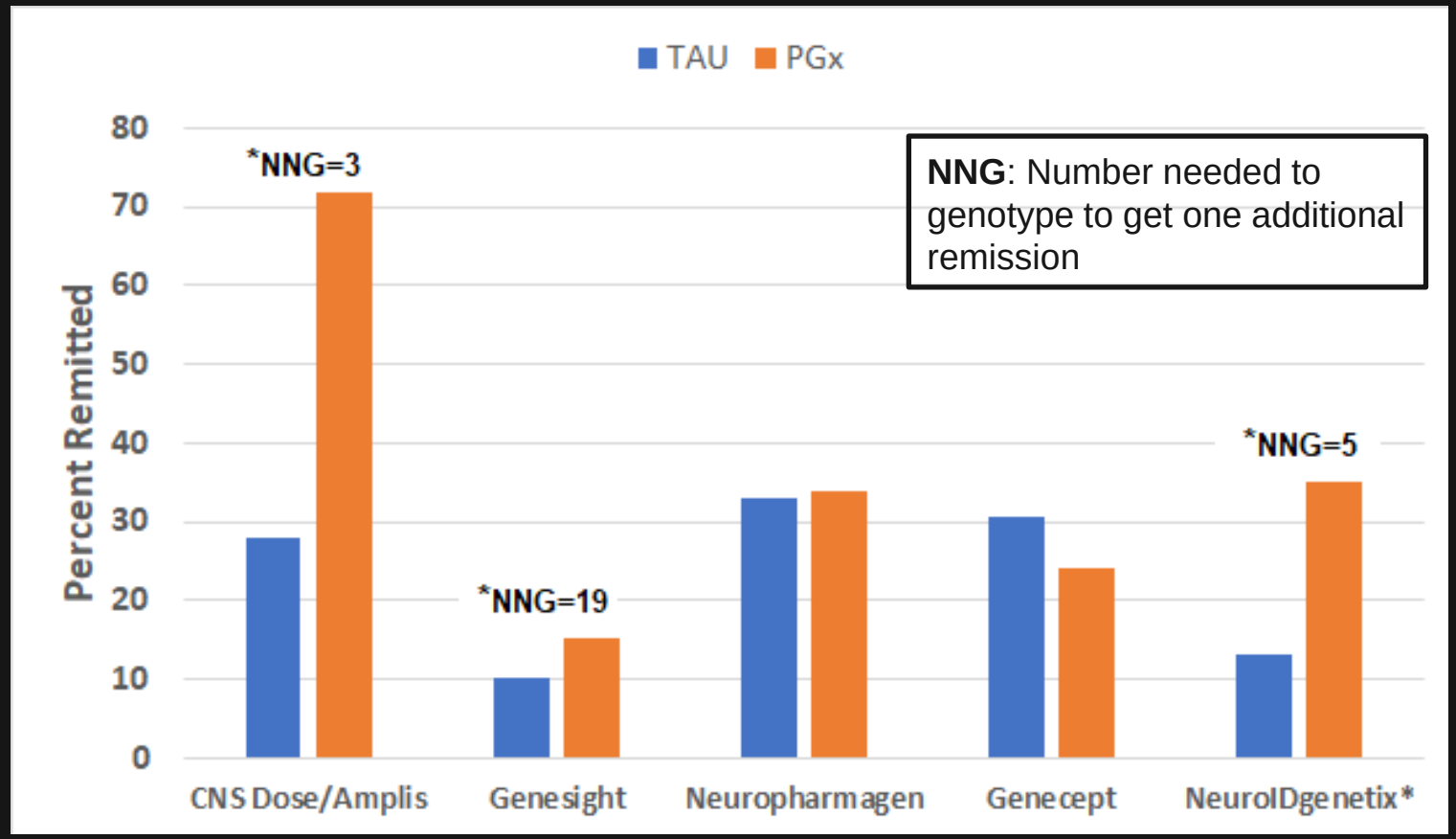
Except for the Amplis/CNS Dose test, each company's largest trial failed to achieve statistical significance on the pre-specified primary outcome:

- Mean symptom change (Genesight, Genecept)
- Adverse drug reaction frequency (Neuropharmagen, NeruoIDgenetix)

PGx DST	Significant Continuous Outcome	Significant Remission and/or Response Rate
Amplis/CNS Dose	n.r.	Yes
Genesight	No	Yes
Neuropharmagen	No	Yes
Genecept	No	No
NeuroIDgenetix - *"Severe" subset*	n.r./No	Yes

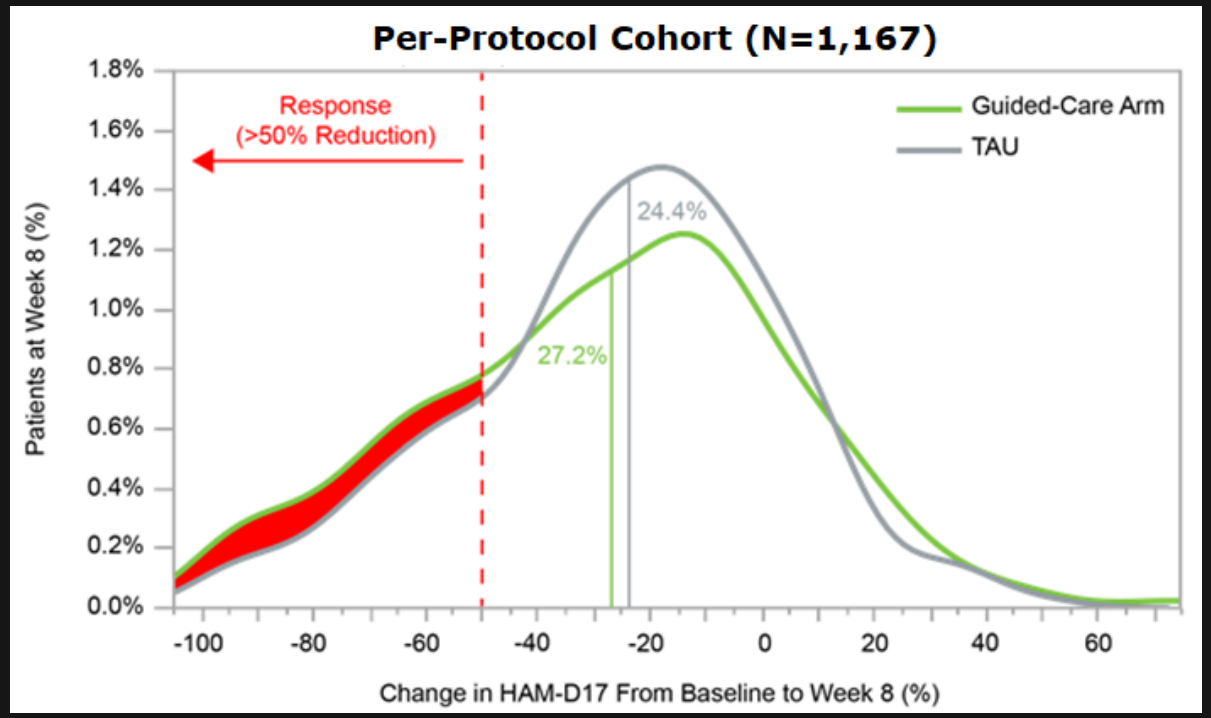
Remission Rates across 5 PGx DSTs

PGx DST	N Analyzed	Mean # Drug Failures
CNS Dose/Amplis	148	n.r.
Genesight	1,167	3.5
Neuropharmagen	316	2.5
Genecept	296	1.4 (est.)
NeuroIDgenetix	93 *("Severe" subset)	n.r.

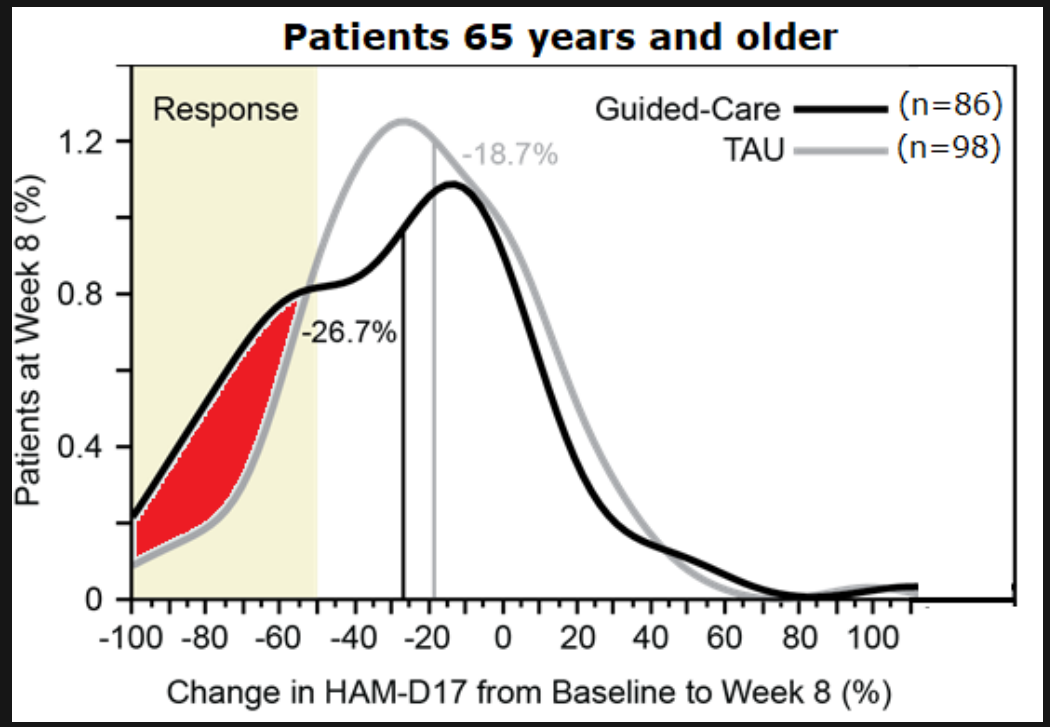


CNS Dose/Amplis: Singh, *Clin Psychopharmacol & Neurosci,* 2015:150-156
Genesight: Greden et al., *J. Psychiatr Res,* 2019, 111:59-67
Neuropharmagen: Perez et al., *BMC Psychiatry,* 2017; 17:250
Genecept: Perlis et al., *Depress Anxiety,* 2020, epub.
NeuroIDgenetix: Bradley et al., *J Psychiatr Res,* 2018; 96:100-107

Distributions of % Change in GUIDED Trial

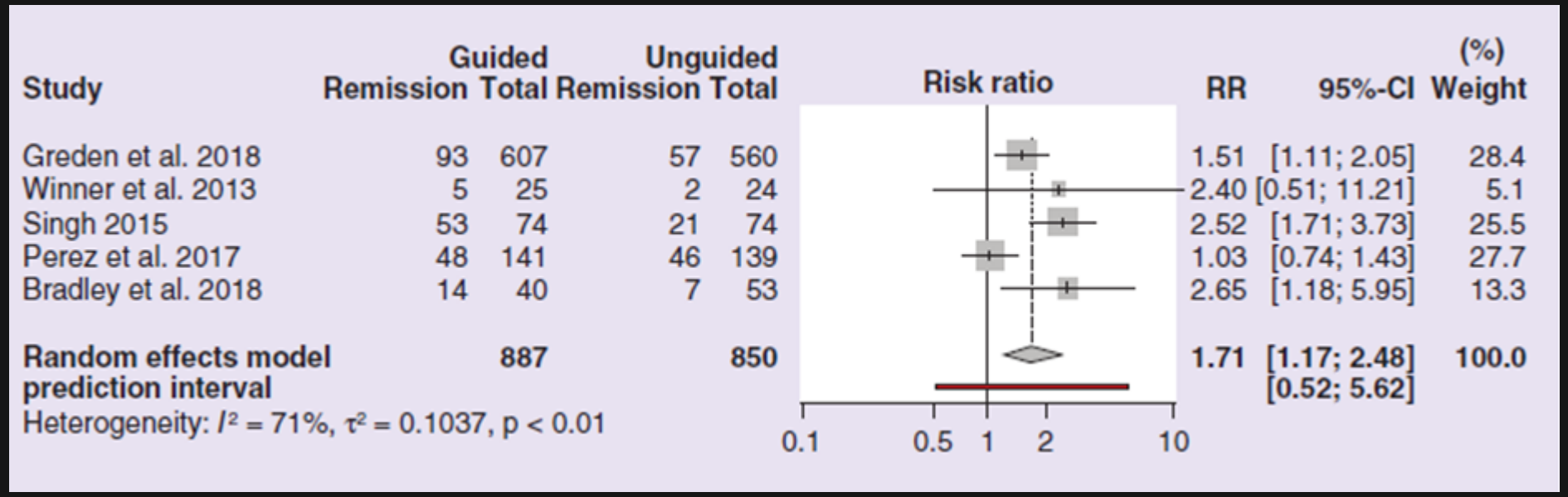


Greden et al., *J. Psychiatr Res*, 2019, 111:59-67 (suppl)



Forester et al., *Am J Geriatr Psychiatry*, 2020, epub

Meta-Analysis of PGx RCTs for MDD Remission



NOTE:
Omits Perlis et al. Genecept RCT, *Depression & Anxiety,* May 2020, epub.

Bousman et al. *Pharmacogenomics*, 2019; 20(1):37-47.

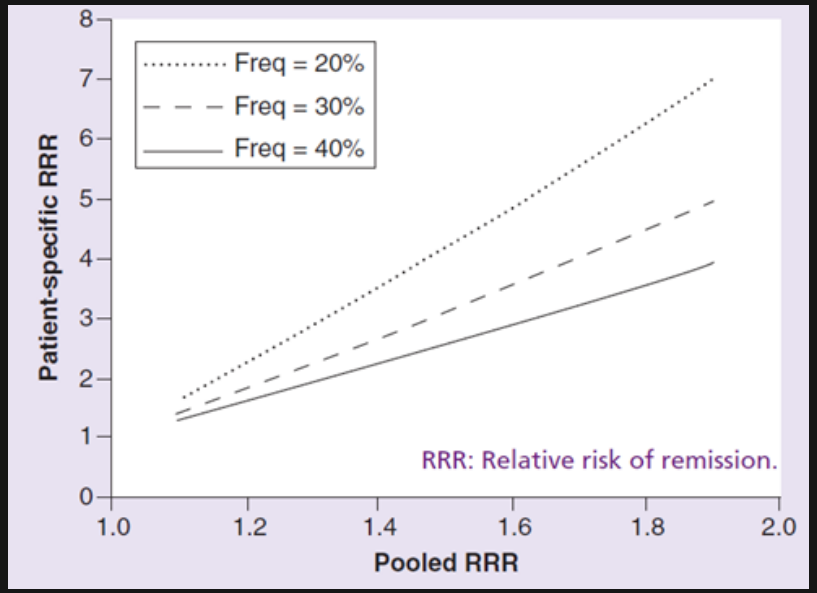
Relative Risk for Remission with PGx Testing
'Patient-specific RRR' vs 'Pooled RRR'

"Patient-specific RRR": Benefit of PGx-informed prescribing for an individual with an actionable genotype

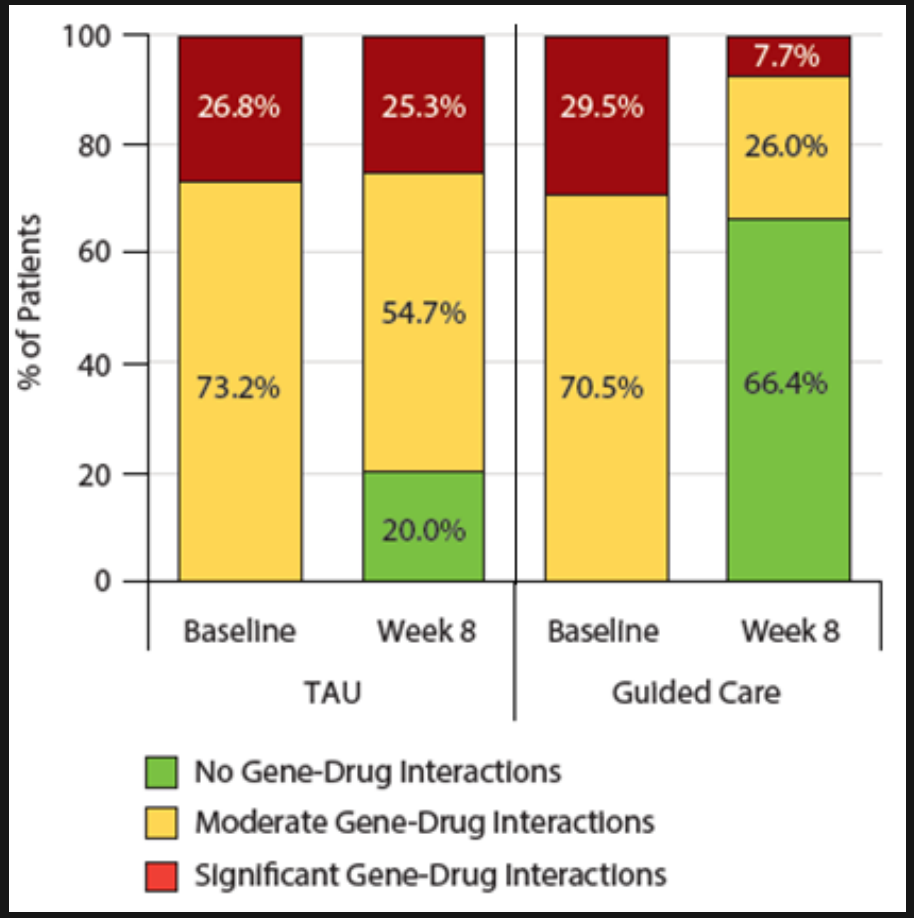
"Pooled RRR": Benefit in entire cohort (dilutes patient-specific RRR)

Relationship is a function of the frequency of actionable genotypes

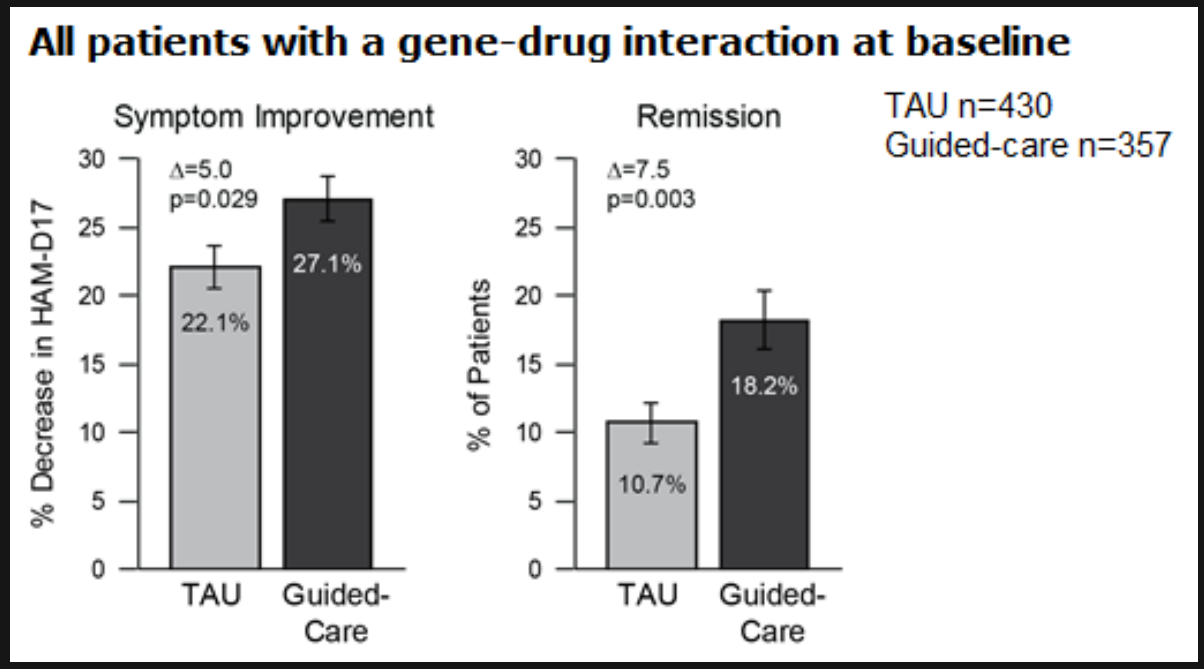
Suthers & Polasek, *Pharmacogenomics*, 2019; 20:1061-62

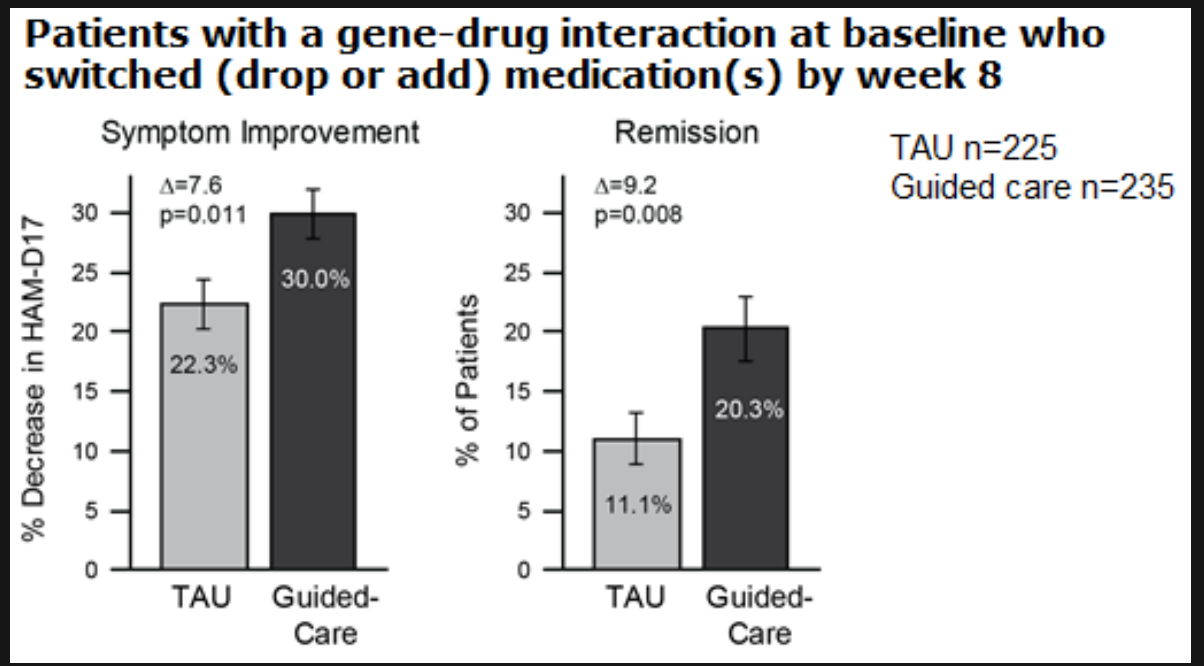


Effect of PGx Guided Treatment in Patients with an identified Gene-Drug Interaction



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





Conclusions 1

- Determining the utility and clinical timing of conducting PGx testing to inform drug prescribing is a work in progress
  - FDA regulation of PGx LDTs is likely to increase
- Variability across PGx DST's gene profiles and trial outcomes limits making generalizable testing recommendations.
- A critique common to all PGx RCTs is the lack of blinding of the treating clinician to treatment arms
  - Cannot rule out expectancy/placebo or therapeutic zeal effects
- The remarkable finding of non-significant mean improvement, but higher remission rates, suggest PGx DSTs have a sizeable benefit in a small proportion of all tested patients, which is insufficient to drive average overall change.

Conclusions 2

- RCTs of PGx DSTs demonstrate the challenge of developing biologically-based precision-medicine approaches to MDD
  1. Difficult to show differences in RCTs comparing two arms with active treatment (i.e., no placebo)
  2. PGx RCTs are a blend of efficacy and effectiveness trial designs, in that prescribers do not need to follow the testing recommendation. Indeed, many do not.
  3. For the majority of patients PGx test results are not informative for antidepressant selection, greatly reducing statistical power.
- Clinical Conundrum:
  - Patients who are on a genetically-incongruent medication are mostly likely to benefit from PGx-guided care
  - BUT: Can’t know if genetically incongruent until tested!