Precision Medicine in Mental Health Care: Can Pharmacogenomic Testing Improve Antidepressant Outcomes?

VISN 4 MIRECC
Mental Illness Research, Education and Clinical Center

VA HEALTH CARE | Defining EXCELLENCE in the 21st Century

Faculty Disclosure: Past Three Years

- **Consultant**—Acadia, Inc., Akili, Inc., Alkermes, Inc., Gerson Lehrman Group, Inc., Guidepoint Global, LLC, Janssen Pharmaceuticals, Inc., H. Lundbeck A/S, MedAvante, Inc., moksha8 Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., Sage Pharmaceuticals, Sunovion Pharmaceuticals Inc., Takeda Pharmaceutical Company Ltd.;
- **Employment (spouse)**—Peloton Advantage (does business with several pharmaceuticals)
- **Grant/Research**—Acadia, Inc., Alkermes, Allergan, Inc., AssureRx Health, Inc., Axome, Inc., Intracellular Inc., Janssen Pharmaceuticals, Inc., Patient Centered Outcomes Research Institute
- **Royalties**—American Psychiatric Foundation, Guilford Publications, Herald House, W.W. Norton & Company, Inc.

Agenda

- Unmet needs in depression care
- Rationale for pharmacogenomics
- Introduction to genomic testing
- Sample test results
- Examining the evidence
- Reasons for skepticism
- PRIME Care Primer

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Background: Public Health Significance

- Depression is one of the world's great public health problems
- At least 1 in 7 Veterans is currently suffering from a depressive disorder
- Untreated/poorly treated depression is implicated in 75% of suicides
- Untreated/poorly treated depression amplifies the burden of all common chronic medical illnesses
- Although many effective therapies are available, only about 1/3rd remit with the first course of medication and 1/3rd will remain depressed despite multiple treatment trials

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Background: Unmet Needs Pertaining to Antidepressants (ADs)

- Intent-to-treat response rates for first- and second-line antidepressant drugs (ADs) are no higher than 50%
- Only about 2/3rds of new prescriptions for ADs are refilled
- At least 10% of new Rx fail because of side effects
- Each unsuccessful course of AD is associated with a 10-20% risk of dropping out of care
- Odds for successful treatment decrease and risk of intolerable side effects increases with each failed trial
- There are no reliable clinical tools to match each patient with the AD that is the most likely to be effective
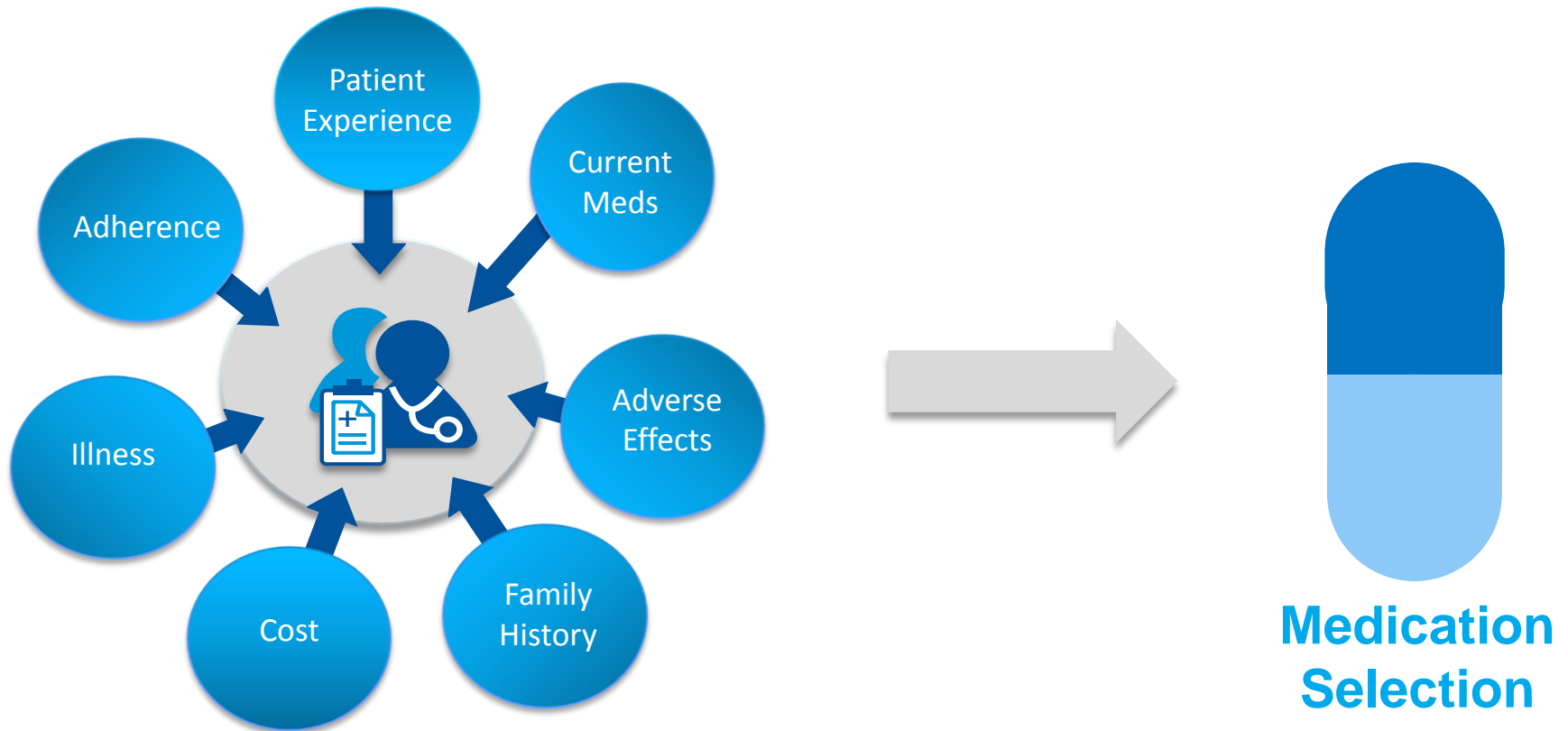
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Pharmacogenomics Defined

Pharmacogenomics uses information about a person's genetic makeup, or genome, to choose the medications or doses of medicine that are likely to work best for that particular person.

National Institutes of Health

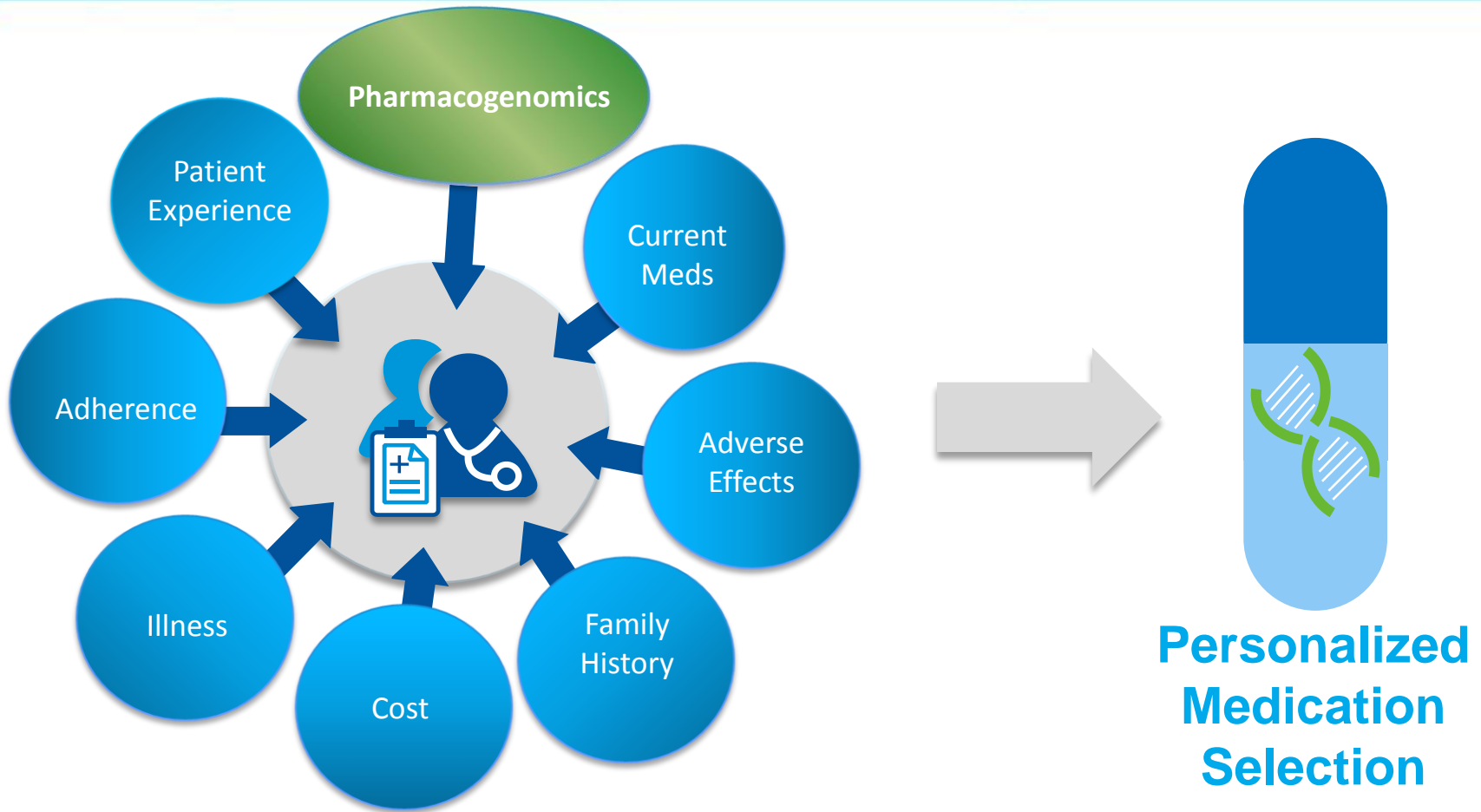National Human Genome Research Institute

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Background

- Pharmacogenetic testing (PGx)
  - Pharmacokinetics (PK): genes that affect drug metabolism
  - Pharmacodynamics (PD): genes that affect drug action
- FDA now requires testing new drugs' PK profile
  - Ultra rapid, rapid, or slow metabolism via polymorphisms of Cytochrome P450 enzymes
- Several companies have introduced PGx batteries

  FDA does not approve/endorse the actual tests

  FDA does monitor/advise re. claims of therapeutic effects
- Clinical practice guidelines
  - VA/DoD and HSRD reviews (2016) concluded that there is not enough evidence yet to incorporate into routine practice
  - American Psychiatric Association review (2018) echoed this conclusion
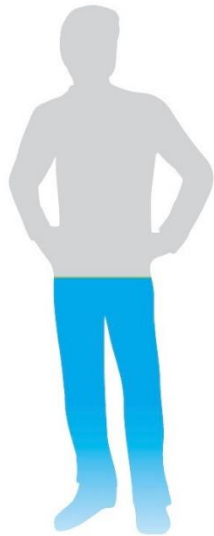
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Current Medication Decision Factors

Patient Experience

Current Meds

Adherence

Adverse Effects

Illness

Family History

Cost

Medication Selection

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Personalized Medication Selection Factors

Pharmacogenomics

Patient Experience

Current Meds

Adherence

Adverse Effects

Illness

Family History

Cost

Personalized Medication Selection

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How Genetics Can Affect Medication Blood Levels

EXTENSIVE (NORMAL) METABOLIZER

Breaks down medications normally. Has normal amounts of medication at normal doses.

ULTRARAPID METABOLIZER

Breaks down medications rapidly. May not get enough medication at normal doses.

INTERMEDIATE METABOLIZER

Breaks down medications slowly. May have too much medication at normal doses.

POOR METABOLIZER

Breaks down medications very slowly. May experience side effects at normal doses.

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Selected Polymorphisms Relevant to Antidepressant Response

Pharmacokinetic

CYP2D6

CYP2C19

CYP2C9

CYP1A2

CYP2B6

CYP3A4

UGT1A4

UGT2B15

Pharmacodynamic

SLC6A4 (serotonin transporter)

5HTR2A (serotonin 2A receptor)

HLA-B*1502 (Human Leukocyte Antigen)

*HLA-A*3101 (Human Leukocyte Antigen)*

MTHFR (methylfolate reductase)

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Key Pharmacogenomic Polymorphisms Result in Almost Infinite Possibilities

- One commercially available battery that includes 8 genes that influence AD response yields more than 300,000 different reports!
- These 8 genes are mapped on 6 chromosomes indicated by the arrows
- As a result of this almost random pattern of distribution, having one abnormal polymorphism is almost unrelated to having another
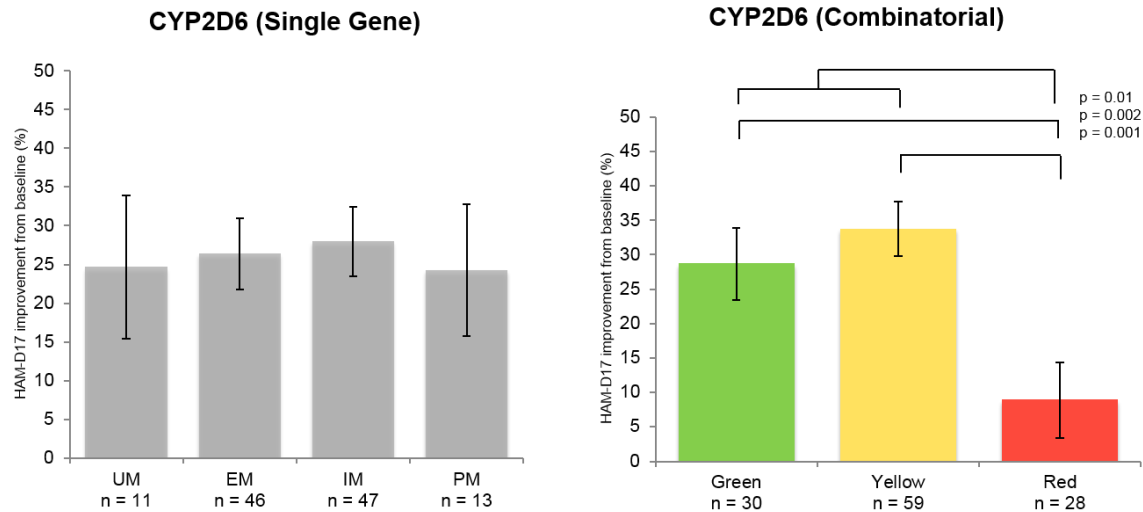
PRIME Care **12**
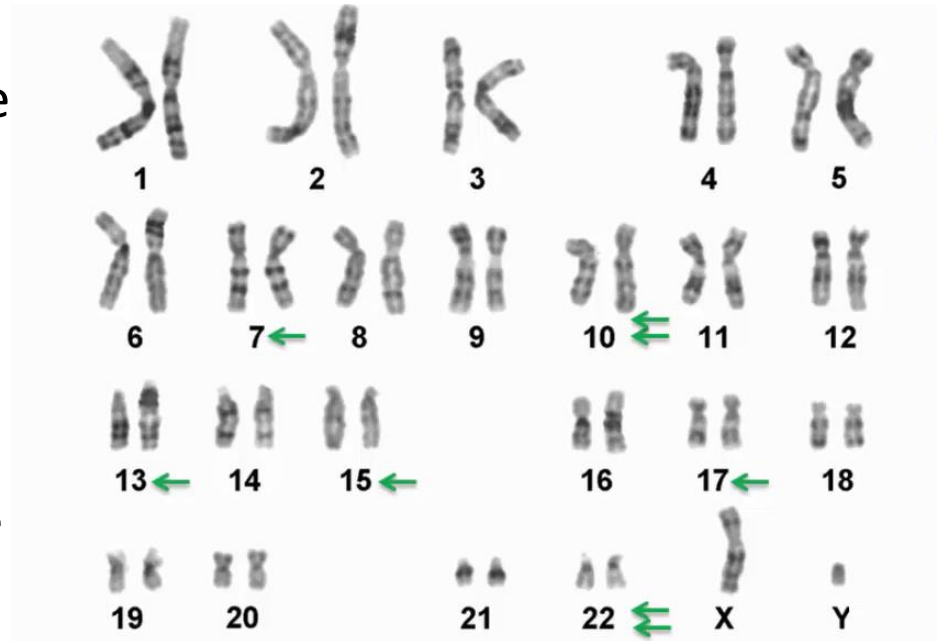
PGx Profiles Using Combinatorial Pharmacogenomics

Complex algorithms based on proprietary research, pharmacology, and results from nearly one thousand published studies involving 50+ medications
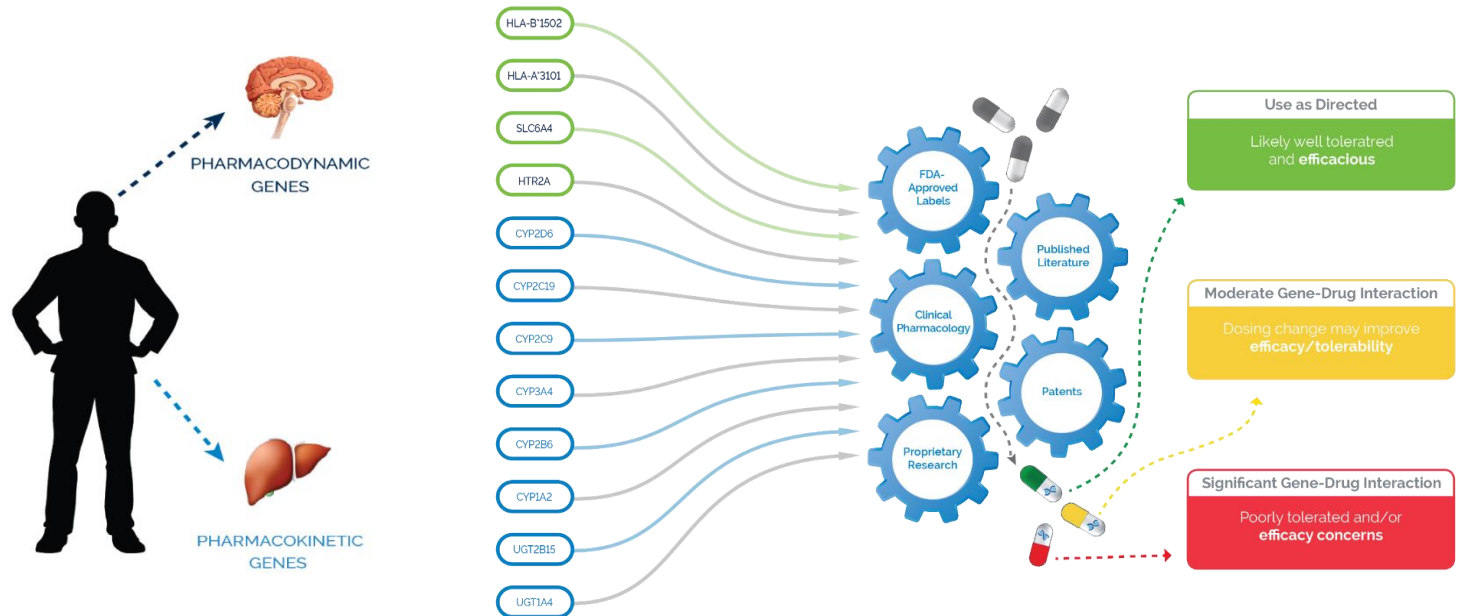
Single Gene vs Combinatorial Approach

Altar CA, et al. *Pharmacogenomics Journal.* 2015.

Using the Test Results in Practice: A Case Example

- 32 y/o male with MDD and periods of problem drinking; current PHQ9 = 15

- Had some exposure to IED explosions but no TBI; subthreshold PTSD

- Currently not drinking; smokes ~1.5 packs of cigarettes each day

- Did not respond to sequential adequate trials of citalopram (40 mg/day) and sertraline (100 mg/day)

- PGx profile reveals multiple findings of interest

GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

genesight

Patient, Sample
DOB: 7/22/1984
Order Number: 9907
Report Date: 6/3/2016
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION		SIGNIFICANT GENE-DRUG INTERACTION	
desipramine (Norpramin®)	fluoxetine (Prozac®)	3	bupropion (Wellbutrin®)	1,6
nortriptyline (Pamelor®)	sertraline (Zoloft®)	1,4	duloxetine (Cymbalta®)	2,7
vortioxetine (Trinellix®)	desvenlafaxine (Pristiq®)	1,8	fluvoxamine (Luvox®)	2,7
	levomilnacipran (Fetzima®)	1,8	paroxetine (Paxil®)	1,4,6
	trazodone (Desyrel®)	1,8		
	vilazodone (Viibryd®)	1,8		
	amitriptyline (Elavil®)	2,7		
	doxepin (Sinequan®)	2,7		
	imipramine (Tofranil®)	2,7		
	selegiline (Emsam®)	2,7		
	citalopram (Celexa®)	3,4		
	escitalopram (Lexapro®)	3,4		
	clomipramine (Anafranil®)	3,7		
	venlafaxine (Effexor®)	3,8		
	mirtazapine (Remeron®)	3,7,8		

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Caveats and Other Considerations for PGx

- Medications classified in the "Red Zone" can be both effective and well-tolerated
- Medication effects on CYP enzymes can mimic or amplify inherited differences in drug metabolism
- Pharmacogenomic differences often are overshadowed by factors such as nonadherence and unaddressed co-morbidities
- Other relevant factors that influence medication response, both inherited and acquired, will likely be identified in the future
- Various PGx batteries are not interchangeable
- The actual cost of a PGx battery is subject to change and society has not yet determined the proper "price point"

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Effect of pharmacogenomic testing on response rates during antidepressant treatment of MDD: A meta-analysis
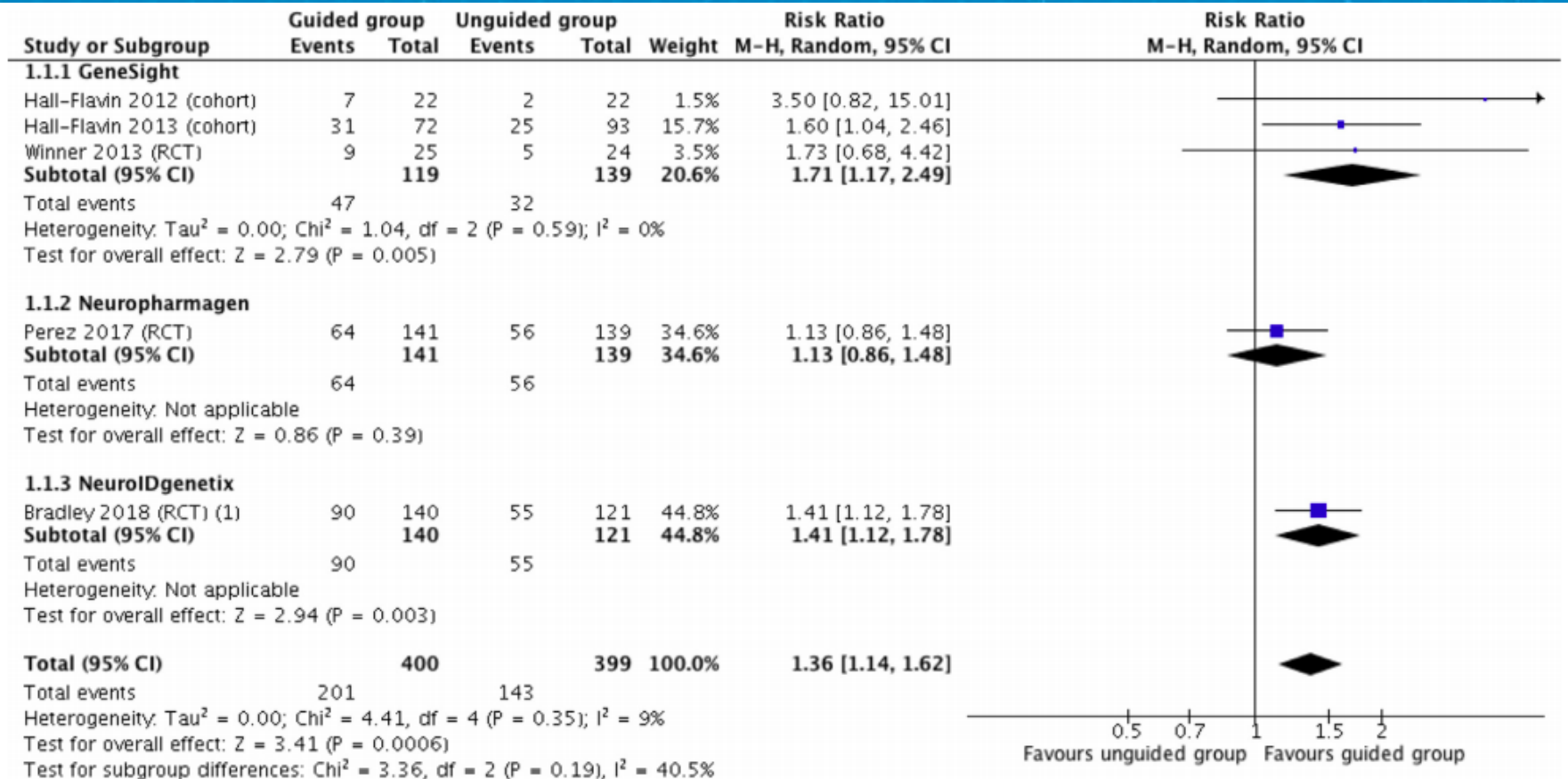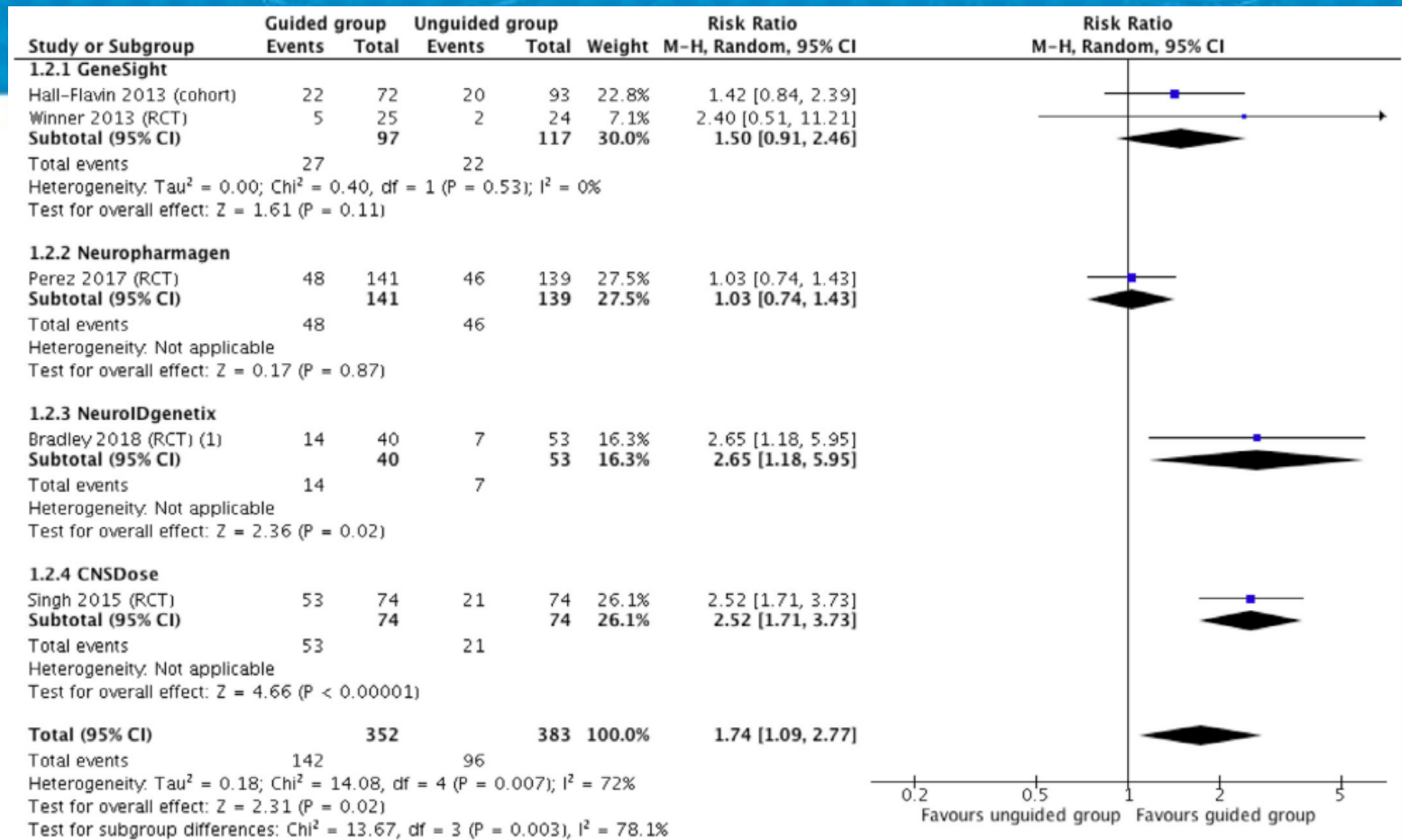

Fig. 3. Pooled risk ratio (RR) of response rates comparing pharmacogenomic guided treatment versus unguided treatment (i.e., treatment as usual).

Effect of pharmacogenomic testing on remission rates during antidepressant treatment of MDD: A meta-analysis

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

GUIDED: Large Scale Pragmatic Trial of PGx in Treatment-Seeking Patients with MDD

- Multi-center trial (60 participating sites) led/coordinated by investigators from the National Network of Depression Centers
- Funded by AssureRx (now Myriad): GeneSight PGx battery
- 1167 consenting adults with MDD who had failed at least one 8 week trial of an AD in the current episode
- Random assignment, double blind assessment (patients and raters)
- Outcomes evaluated over 12 weeks
- Primary and secondary hypotheses specified, exploratory tests in "congruent" and "incongruent" subgroups

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GUIDED: Main Findings

Treatment guided by pharmacogenomic testing resulted in a 50% improvement in remission rates and a 30% increase in response rates at week 8 compared to TAU. Symptom improvement in the guided-care arm trended toward significance at week 8 compared to TAU.
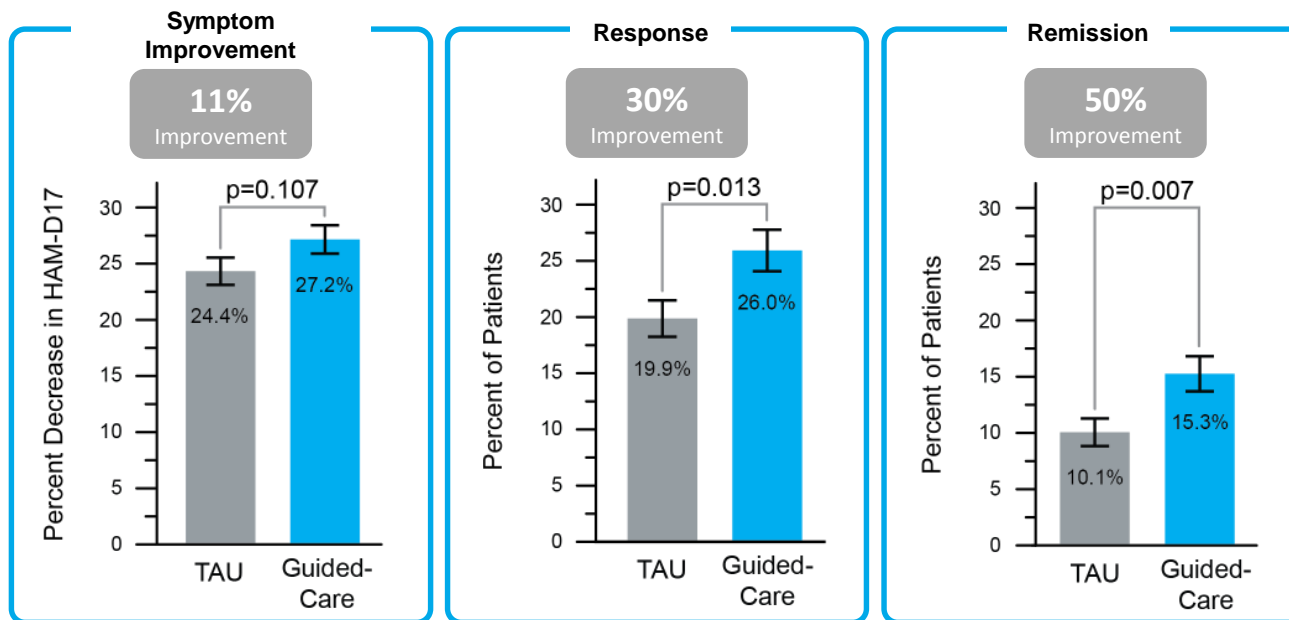
Greden JF et al. *J Psych Res*. 2019 (in press)

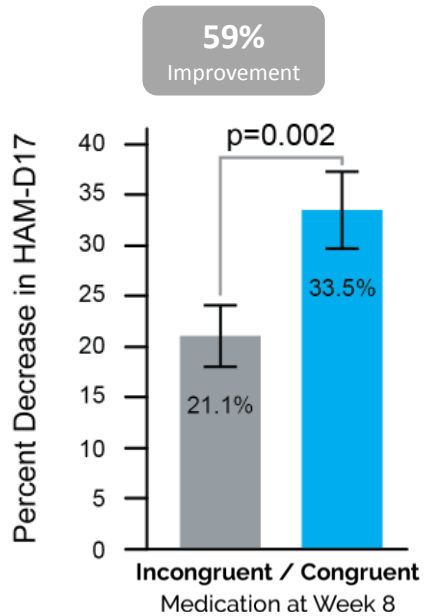# Increased Congruence in the Guided-Care Arm

Medication congruency with the pharmacogenomic test increased 11.8% in the guided-care arm while it stayed constant for the TAU arm (note scale is not 0 – 100%).
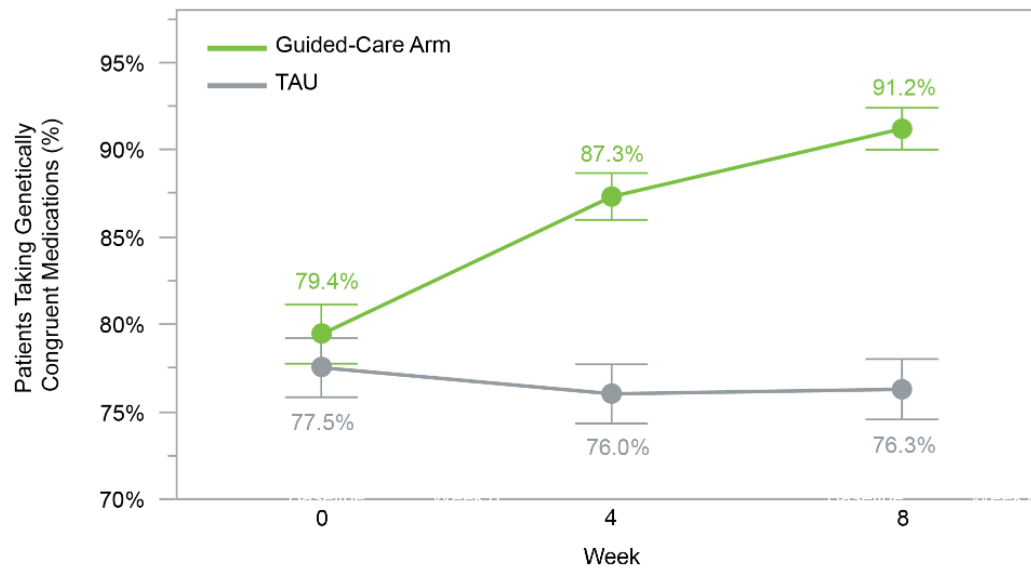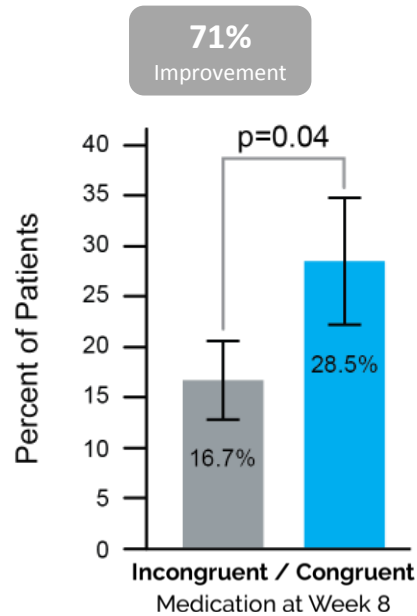

Greden et al. *J Psych Res*. 2019

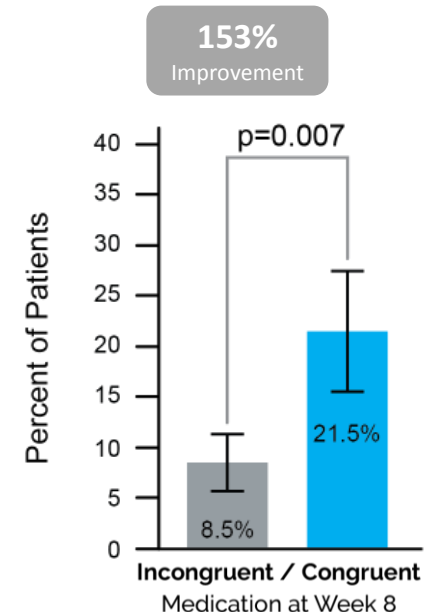# The Value of PGx Explained by the Subgroup of Patients Taking Incongruent Medications

Greden JF, et al. *J Psych Res.* 2019

Further Caveats Based on the State of the Evidence in 2019

- Incremental value of PGx testing is modest in 4 studies of MDD (i.e., 5%-10% absolute increase in response/remission) and would not justify widespread use
- Many patients have no "actionable" findings
- Value of testing when other drugs (mood stabilizers, stimulants or second generation antipsychotics) are included and longer periods of treatment are permitted has not been tested
- Lock-step adherence to color-coded simplifications could cause some patients not to receive medications that could be effective
- Cost-effectiveness has not been established and will change as the efficiency of testing results in lower costs

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Testing the Value of PGx in Depressed Veterans: Precision Medicine in Mental Health Care (PRIME Care)

- Principal Investigator: David Oslin, MD

- Operational Partners / Advisory Board: Office of Mental Health Operations and VINCI, plus advisory board members from QUERI, Genomic Medicine Program, Bioinformatics, Million Veteran Program, and Specialty Care Services among others

- Funding Support for this Program Project: VA HSR&D SDR 16-348

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- Five cores: Implementation, Methods, Discovery, Value Assessment, Knowledge Translation

- About 20 study sites; 2000 depressed patients

- Randomization to Immediate or Delayed PGx Results

- In Delayed group, prescribers will receive information six month later than Immediate group

- Outcomes assessed monthly by independent evaluators for 6 months

- Study not quite at mid-point – if your site is participating, sign up now!

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Pharmacogenomics: Take Home Points

- There are great unmet needs in depression therapeutics
- Some aspects of antidepressant tolerability and response are mediated by inherited/genetic factors
- It is hoped that applied pharmacogenetics can improve care by personalizing drug selection
- Several studies indicate that outcomes can be improved by 5%-10% using PGx profiles to guide drug selection
- There is great controversy about cost-effectiveness
- PRIME Care will help to answer important questions about using PGx in VA care settings

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