

Pharmacogenetics trial of depression: A focus on suicidal thoughts

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PRIME
Care

Disclosures



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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

Poll



For antidepressant prescribing, which of the following best represents how PGx testing might be helpful?

- A. Selecting the most efficacious medication for a patient
- B. Selecting a medication that will have fewer side effects
- C. Provide information of the metabolism of selected medications
- D. There is no evidence that PGx testing is helpful in choosing an antidepressant



Background

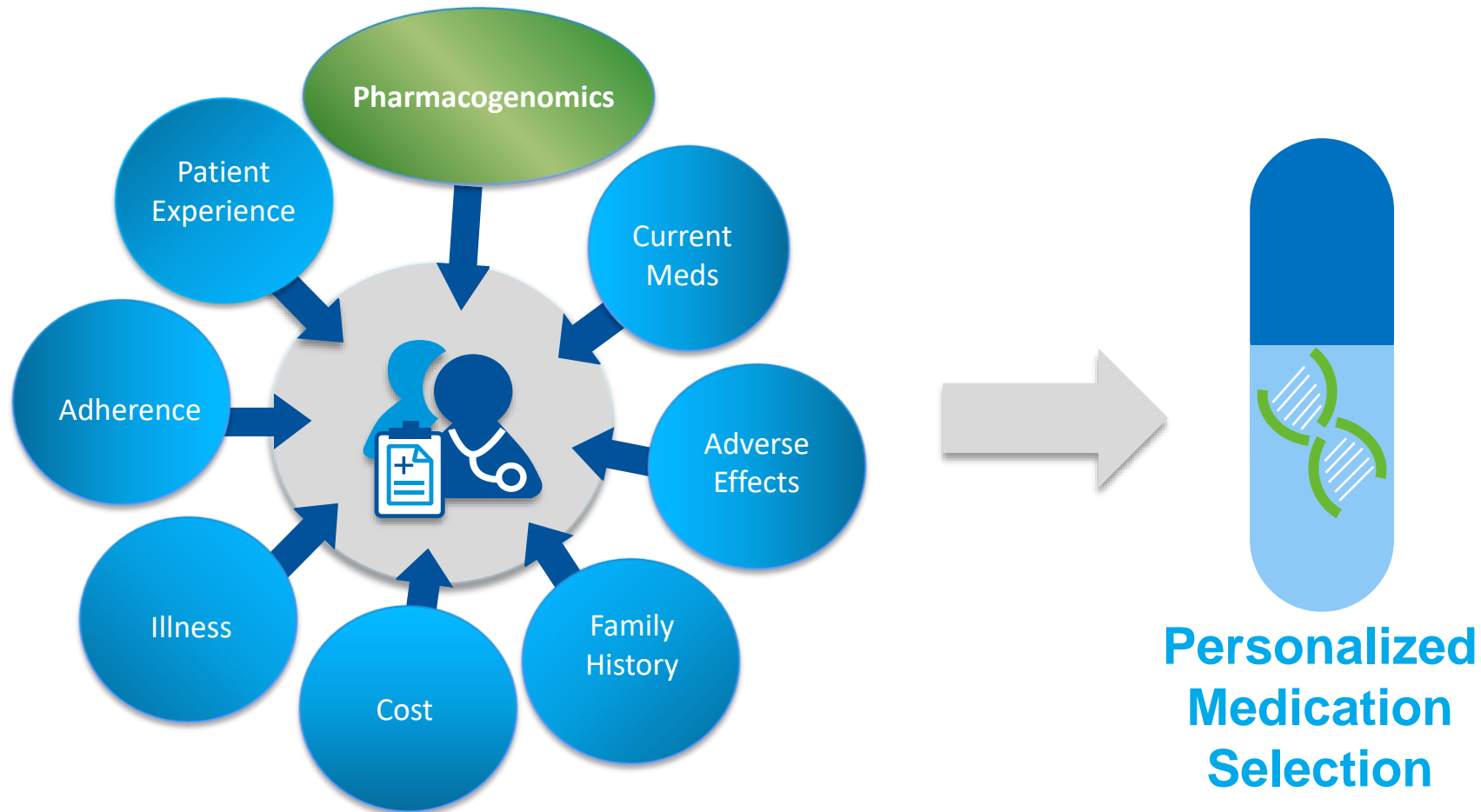
- Pharmacogenetic testing is commercially available – now!
- The VA is embarking on a clinical project to provide testing to 250,000 Veterans
- MVP is beginning to experiment with returning select genotypes
- FDA does not approve or endorse the actual tests

Pharmacogenetics vs. Disease Genetics



- Disease genetics – often easier to understand and is familiar
 - Examples: Huntington's, Cancer profiling, Alzheimer's
- Pharmacogenetics
 - Pharmacokinetics
 - Pharmacodynamics
- FDA now recommends profiling medications for actionable genetic modifiers of metabolism

Personalized Medication Selection Factors



How Genetics Can Affect Medication Blood Levels (mostly what we have in psychiatry)



**ULTRARAPID
METABOLIZER**

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



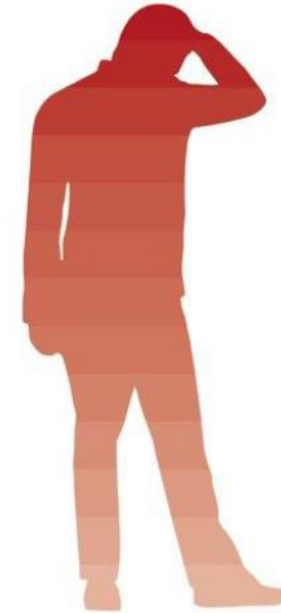
**EXTENSIVE (NORMAL)
METABOLIZER**

Breaks down medications normally. Has normal amounts of 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.



How Might PGx be Helpful in Psychiatry?

- First line AD response rates are no higher than 50%
- 1/3rd of new prescriptions for ADs are not 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



Current State of Evidence

- Several small trials and non-randomized
- 4 randomized trials of reasonable size
 - Bradley et al. 2017 – 685 subjects, NeuroIDgenetix
 - Perez et al. 2017 – 280 subjects, Neuropharmagen
 - Greden et al. 2019 – 1167 subjects, Genesight
 - Perlis et al. 2020 – 304 subjects, Genecept

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



- Multi-center trial (60 participating sites)
- 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

The Test Result



GeneSight® Psychotropic
COMBINATORIAL PHARMACOGENOMIC TEST

Patient, Sample

DOB: 7/22/1984
Order Number: 9904
Report Date: 10/23/2015
Clinician: Sample Clinician
Reference: 1456CIP

Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

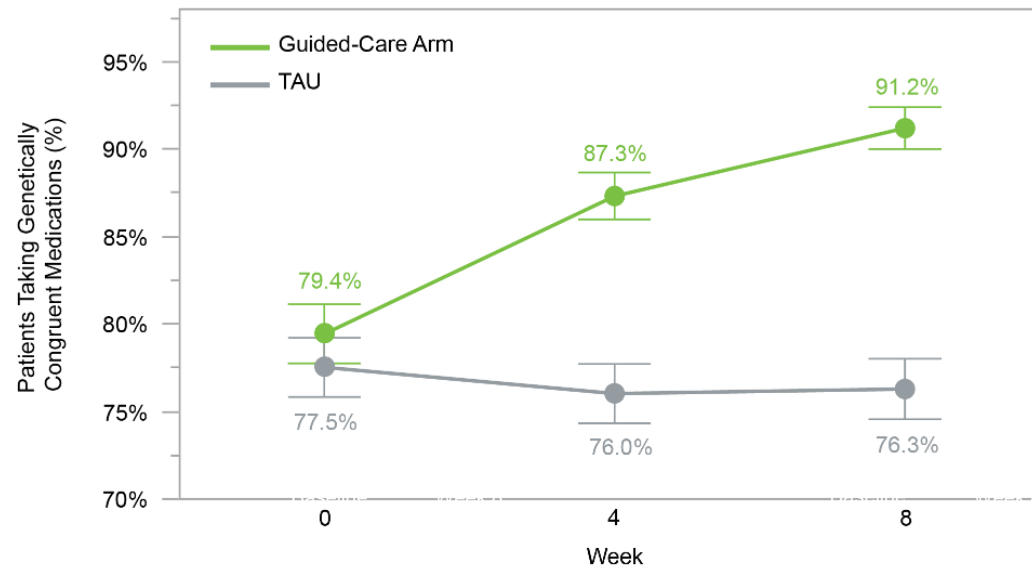
ANTIDEPRESSANTS

USE AS DIRECTED	MODERATE GENE-DRUG INTERACTION	SIGNIFICANT GENE-DRUG INTERACTION
desvenlafaxine (Pristiq®)	trazodone (Desyre®) 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 (Brintellix®) 1,6,8
		fluvoxamine (Luvox®) 1,4,6,8
		paroxetine (Paxil®) 1,4,6,8

Increased Congruence in the Guided-Care Arm

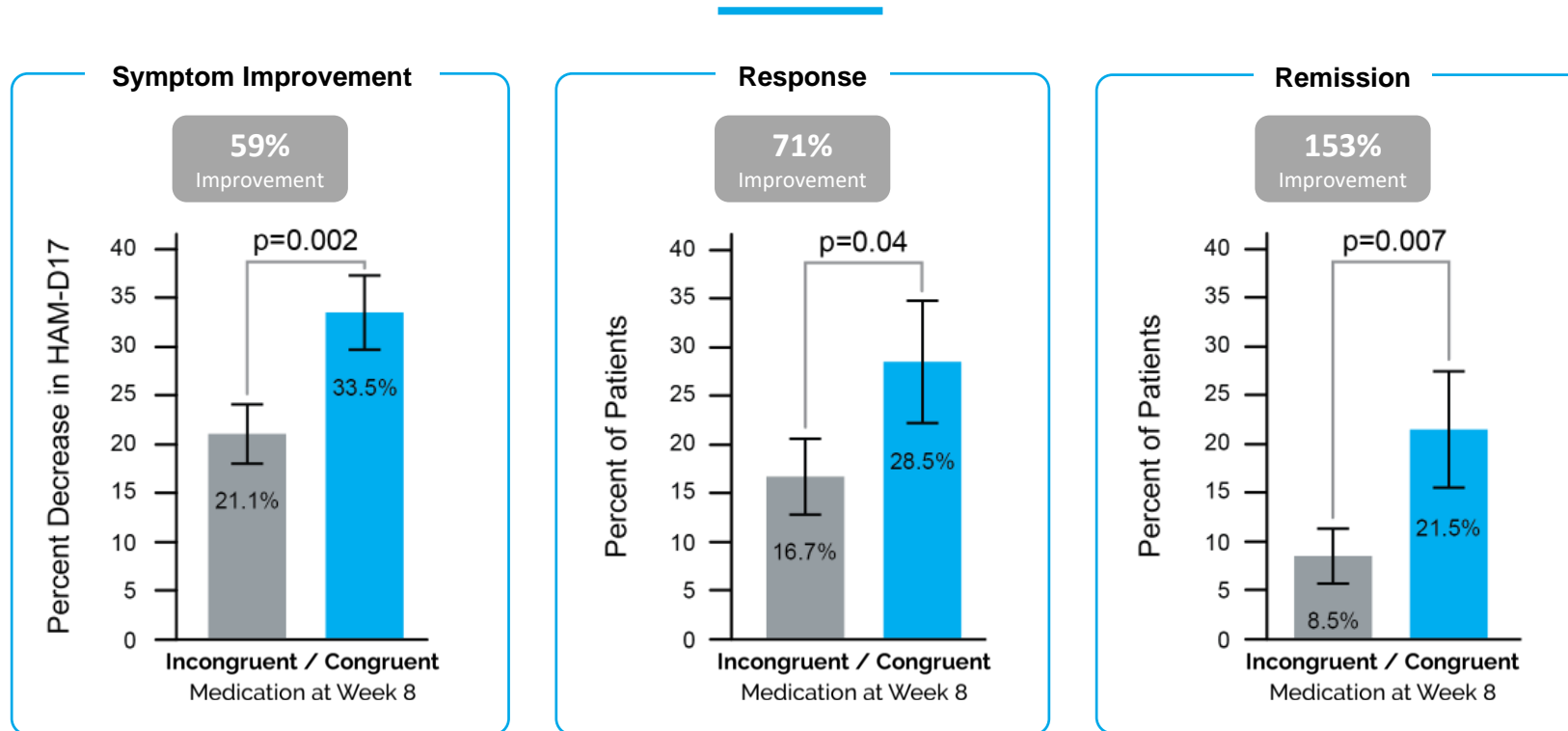


Medication congruency with the pharmacogenomic test increased 11.8% in the guided-care arm while it stayed constant for the TAU arm (note scale is not 0 – 100%).



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



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PRIME Care Study



- A VA-funded multi-site RCT (n=2,000 depressed patients enrolled at 22 sites)
- Patient/provider dyads will be randomly assigned to:
 - Intervention Group: receives results of the PGx battery right after randomization
 - Delayed Results Group: receives results after 6 months of treatment as usual
- Outcomes measured over 6 months from randomization by centralized outcome group (by telephone)

Primary Hypotheses



- Provider/patient dyads in the intervention group will use fewer contraindicated medications based on established PGx criteria than in the delayed results group
- Veterans with MDD whose care is guided by the results of the PGx battery (the intervention group) will have higher rates of depression remission than the delayed results group
- Secondary outcomes related to returning genetic results, alternate outcomes (suicide ideation), and knowledge discovery

VA Study Sites



- Albuquerque, NM**
- Ann Arbor, MI**
- Baltimore, MD
- Boston, MA
- Buffalo, NY*
- Charleston, SC
- Cincinnati, OH
- Cleveland, OH
- Denver, CO
- Houston, TX*
- Little Rock, AR**
- Miami, FL
- Minneapolis, MN
- Palo Alto, CA

- Philadelphia, PA
- Pittsburgh, PA
- Puget Sound, WA
- Richmond, VA**
- Salisbury, NC
- Salt Lake City, UT*
- San Francisco, CA
- West Haven, CT
- W. Los Angeles, CA**
- Wilmington, DE

*non-recruiting sites

**closed to recruitment



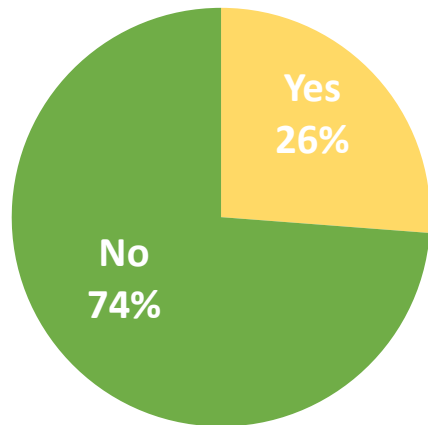
Inclusion Criteria: Pragmatic Trial

- Determined by Provider (Referral Form handout):
 - Symptomatic MDD (Single or Recurrent)
 - Starting an antidepressant
 - On monotherapy
 - Cannot have schizophrenia, bipolar disorder, active SUD
 - Doesn't require hospitalization or urgent care services at the outset of treatment
- Determined by self report / chart review
 - PHQ-9 >9
 - Age 18 - 80

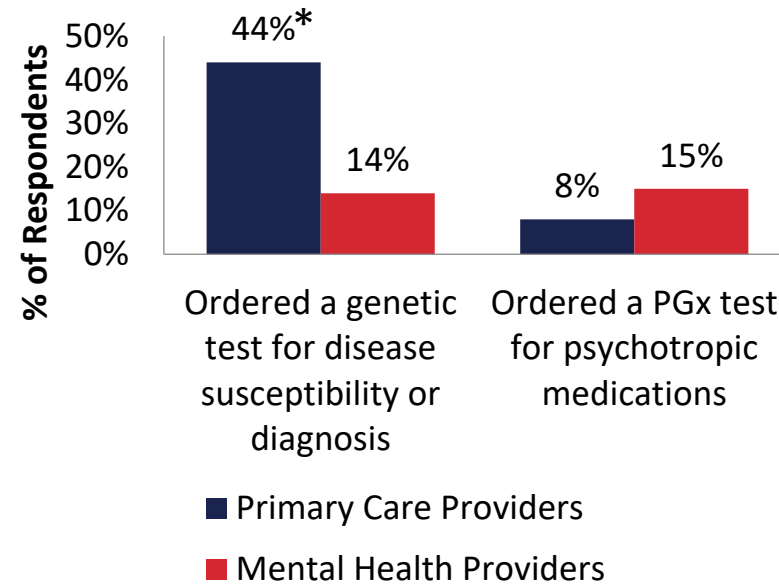


Initial Provider Impressions

Are you aware that the FDA has revised drug labels to include information about PGx (All Providers)?



Experiences ordering a genetic test in the past year



VA Primary Care and Mental Health Providers' Comfort with Genetic Testing: Survey Results from the PRIME Care Study. [Hull LE](#), [Lynch KG](#), [Oslin DW](#). *J Gen Intern Med*. 2019 34:799-801

* Denotes $p < 0.05$



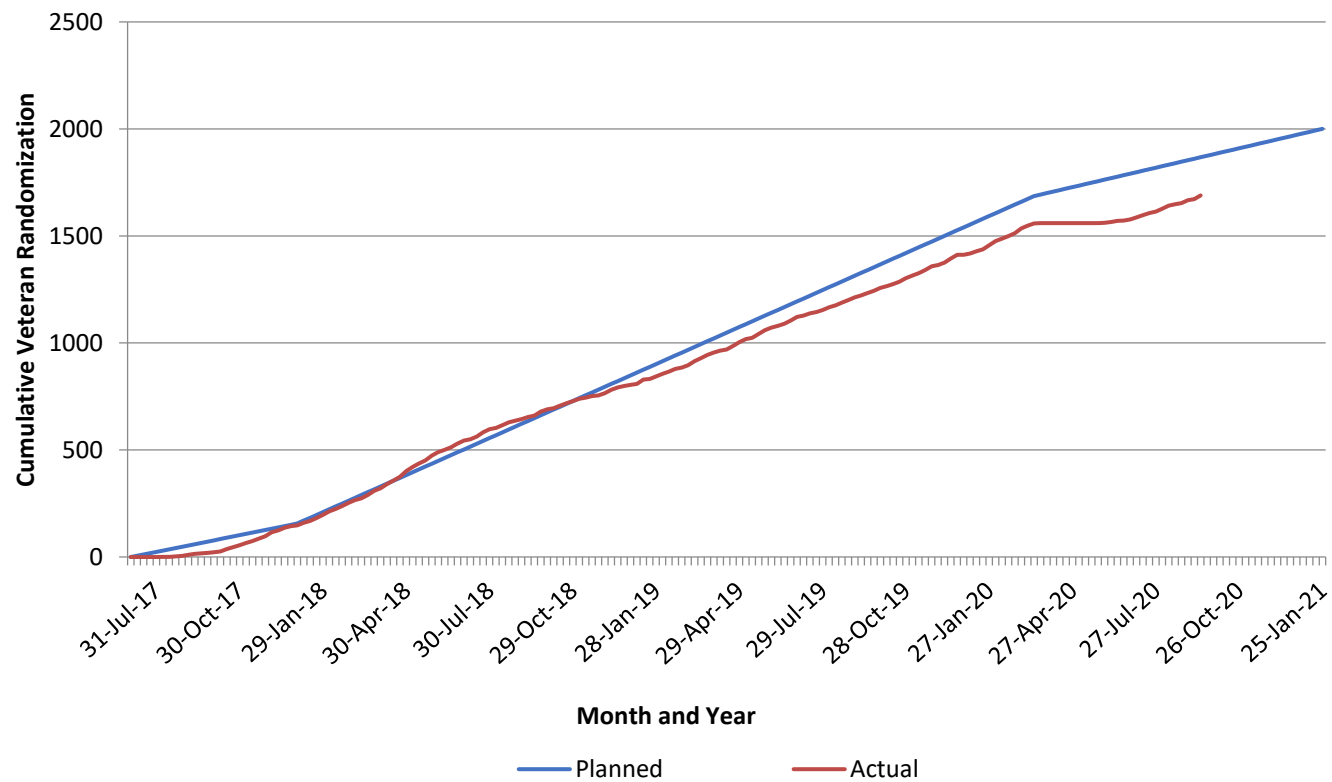
Opportunities Addressed by the Study

- We developed a training program for patients and providers (https://www.mirecc.va.gov/visn4/PrimeCare/PRIME_Care.asp)
- We developed subject matter experts at each site
- We developed a recruitment strategy for engaging front line providers
- We created a robust outcomes call center with a mechanism for addressing high risk patients

Cumulative Recruitment



Cumulative Veteran Randomization - All Sites



Baseline Characteristics of Randomized Sample



Sample Size (n=1560)	
Age	48 ± 15
Race (% Caucasian)	68 %
(% African American)	19 %
Ethnicity (% Hispanic)	11 %
Sex (% female)	25 %
Post 2001 (%)	33 %
Financial status (% can't make ends meet)	13 %

Provider Type	
MH	67 %
PCP	29 %
Other / unknown	4 %

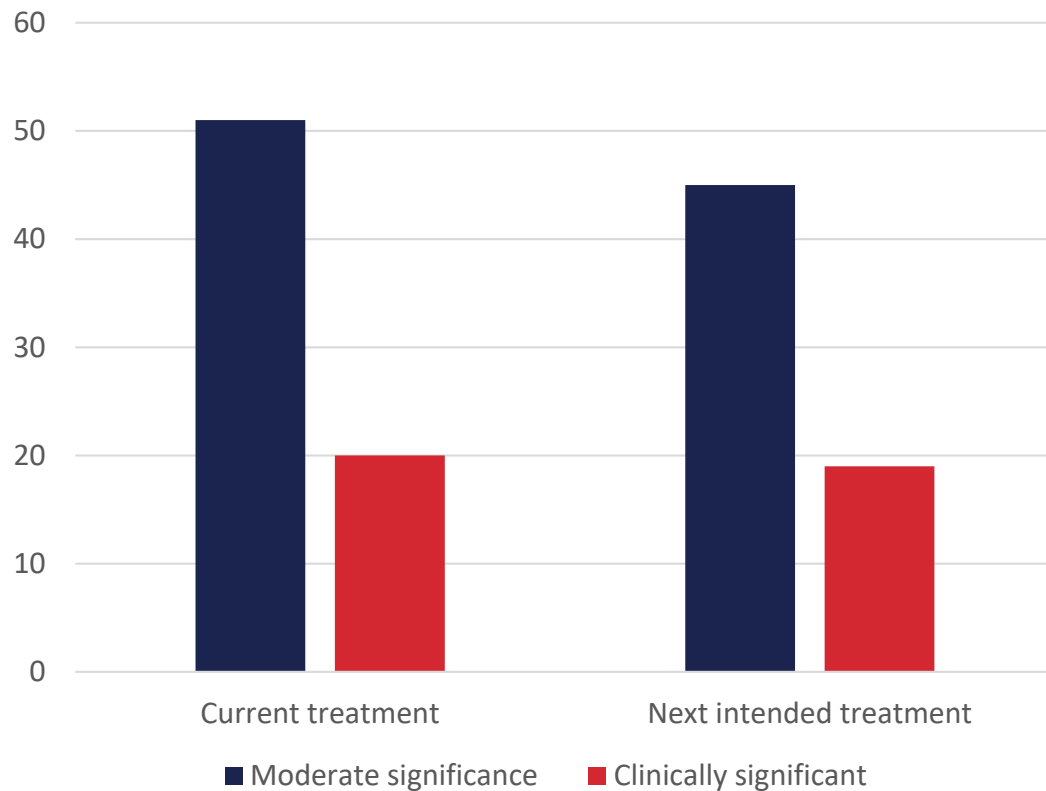
Sample Size (n=1560)	
PHQ-9 score (SD)	17.4 (4.3)
% with PTSD (trauma >36)	58%
PCL score (SD) – in those with PTSD	53.1 (10.4)
GAD-7 (SD)	14 (4.9)
Alcohol use (% at risk)	24 %
Marijuana (% recent use)	24 %
Other drugs (% recent use)	4 %
Tobacco (% with any use)	27 %

Test Utility



- **Methods**
 - Current medications – we examined the proportion of patients who were taking medications prior to randomization that were characterized as having moderate and clinically significant gene-drug interaction potential.
 - Next intended medication - we examined the proportion of patients whose next intended medication (without know PGx results) was characterized as having moderate and clinically significant gene-drug interaction potential.
 - We examined the impact on prior treatment on the odds of having a next intended medication with a clinically significant medication potential.

Outcomes



- Past treatment with an antidepressant predicted a greater likelihood of the next intended medication being one with a high potential for clinical significance (OR: 1.59, 95% CI: 1.08, 2.35)
- Ramsey et al. (under review)

Suicidality

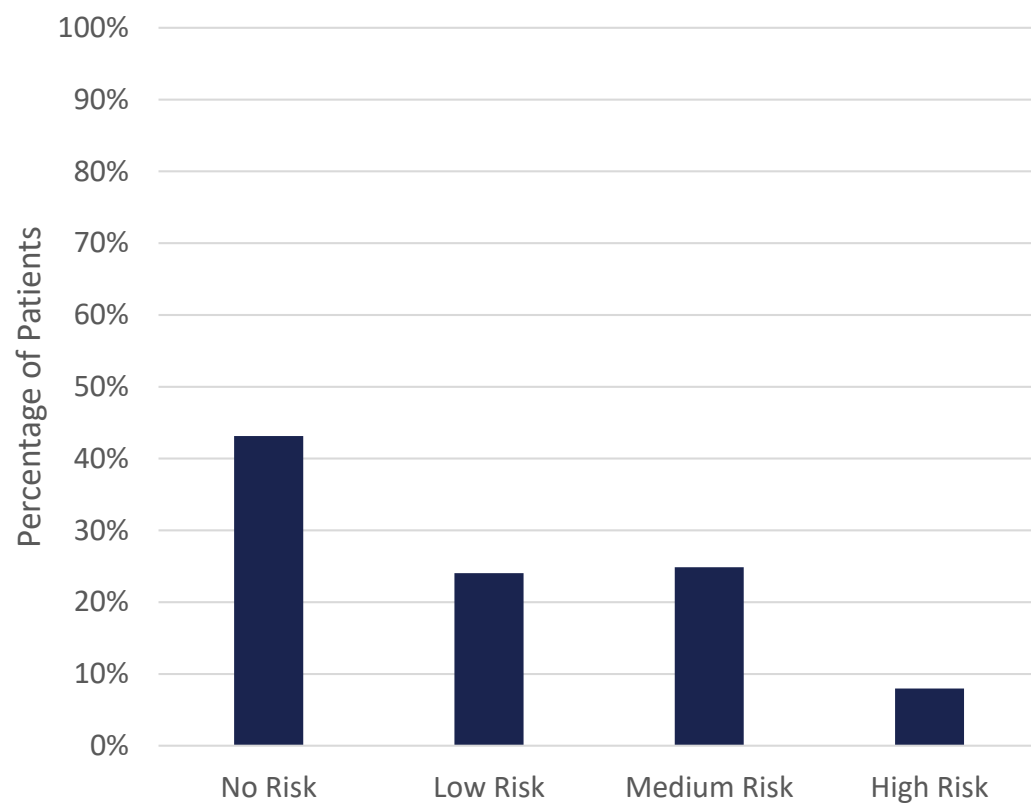


- Suicidal Ideation
 - High correlation with major depression
- Opportunity
 - CSSRS was added to the research battery at baseline and at all outcome assessments (added about one year into the study)
 - We conduct a risk assessment for anyone positive on the CSSRS or with a positive PHQ9 on item 9 (2 or 3).
 - There will be an opportunity to look at suicidal ideation as an outcome and as a phenotype.

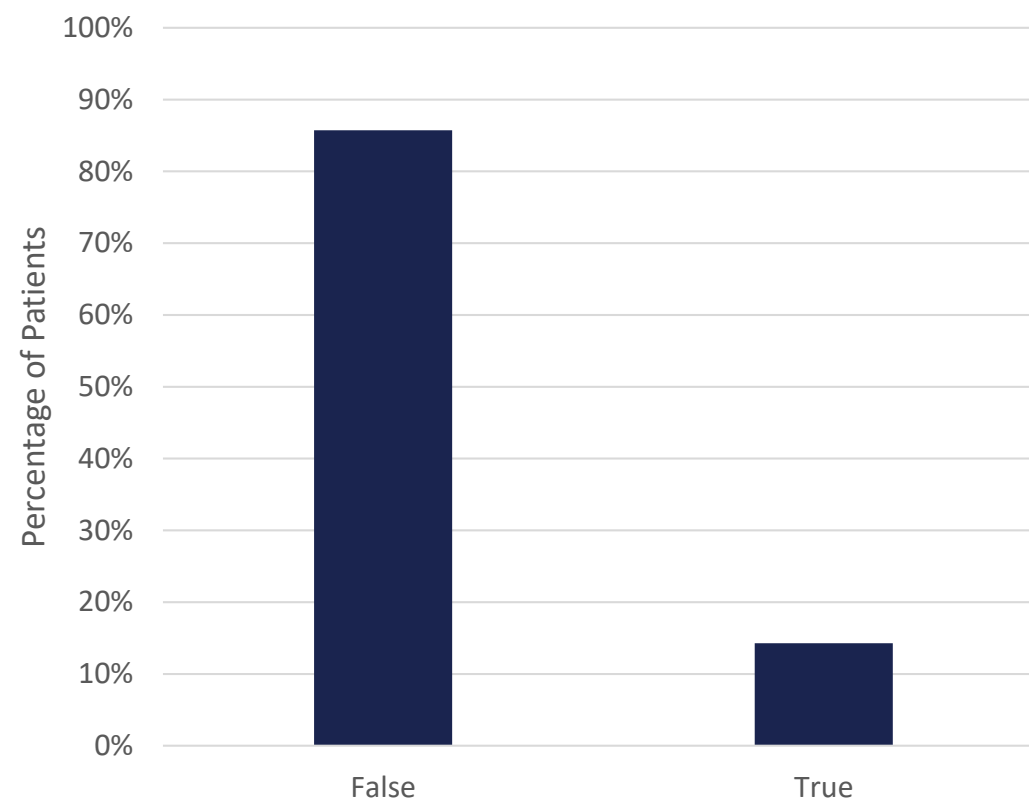


C-SSRS Risk Level Baseline

Baseline C-SSRS Risk Level



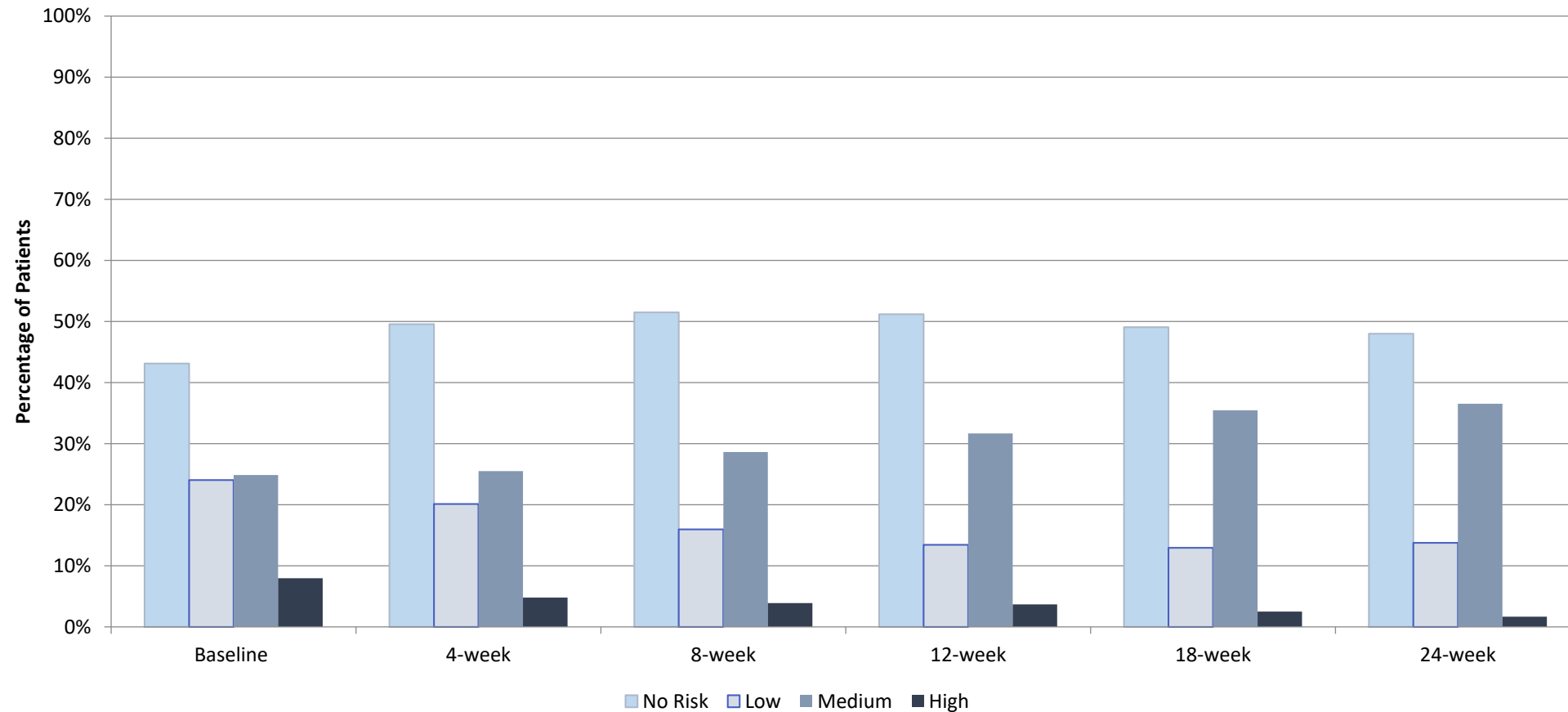
Baseline C-SSRS Screening



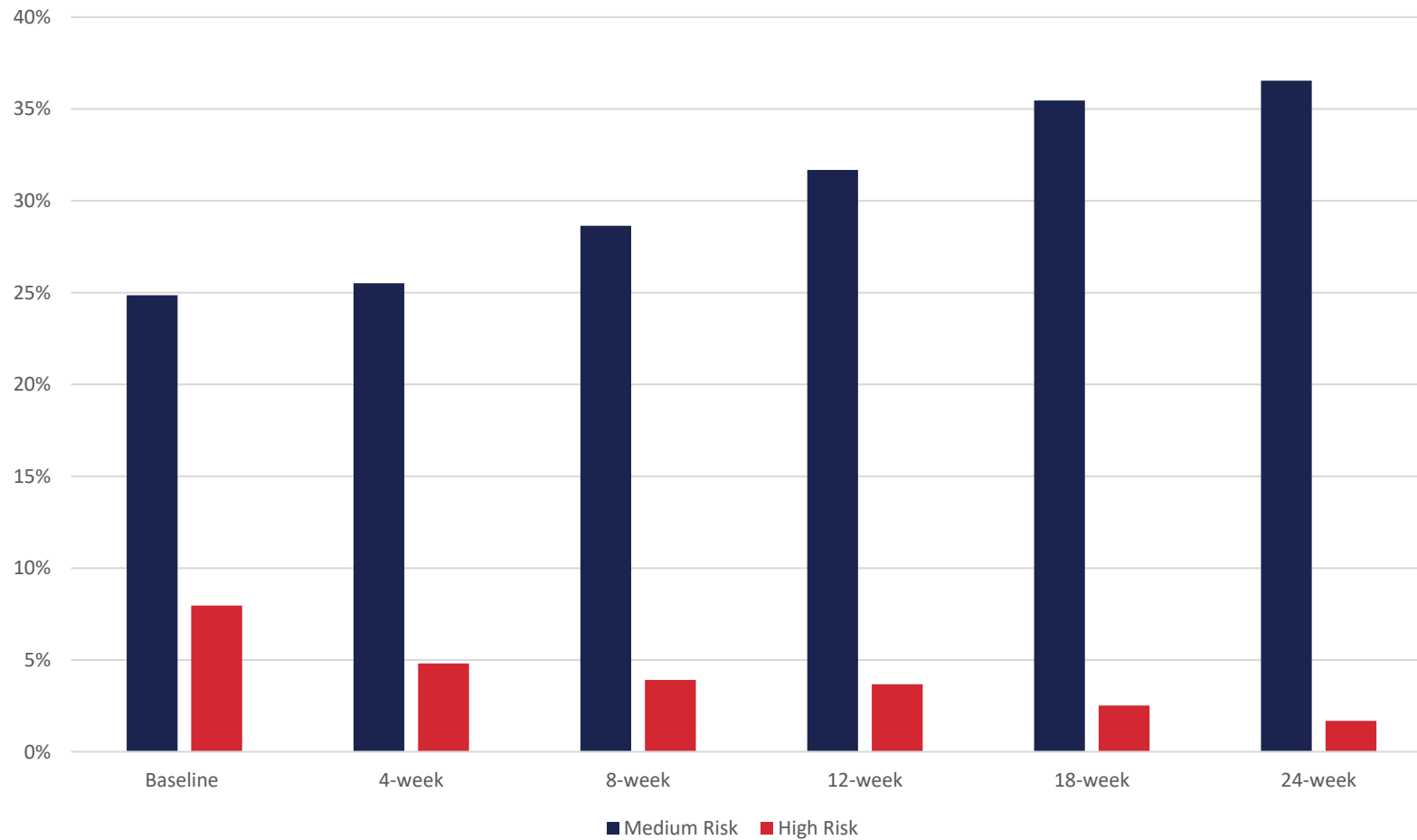
C-SSRS Over Time



C-SSRS Risk Levels



C-SSRS Medium and High Risk



Thank You.



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