# Pharmacogenetics trial of depression: A focus on suicidal thoughts

David W Oslin, MD
Professor of Psychiatry
Crescenz VA Medical Center
VISN 4 MIRECC Director
Perelman School of Medicine, University of Pennsylvania

PRIME Care

# Disclosures

- Consultant: Janssen Pharmaceuticals Inc.
- Employment: none
- Grants: NIH, VA, Janssen Pharmaceuticals Inc., DOD, Myriad Genetics

# 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

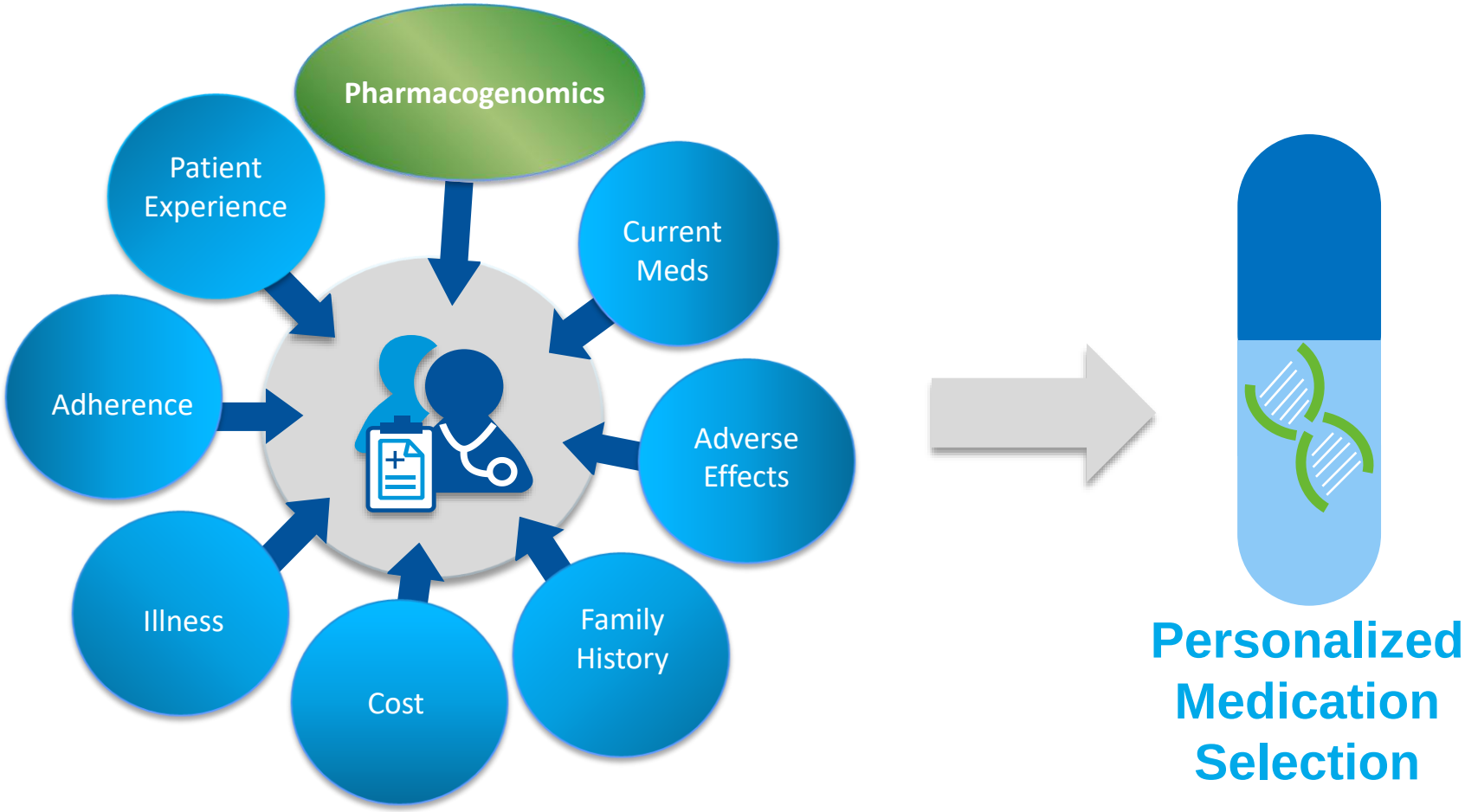
# Background

- 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

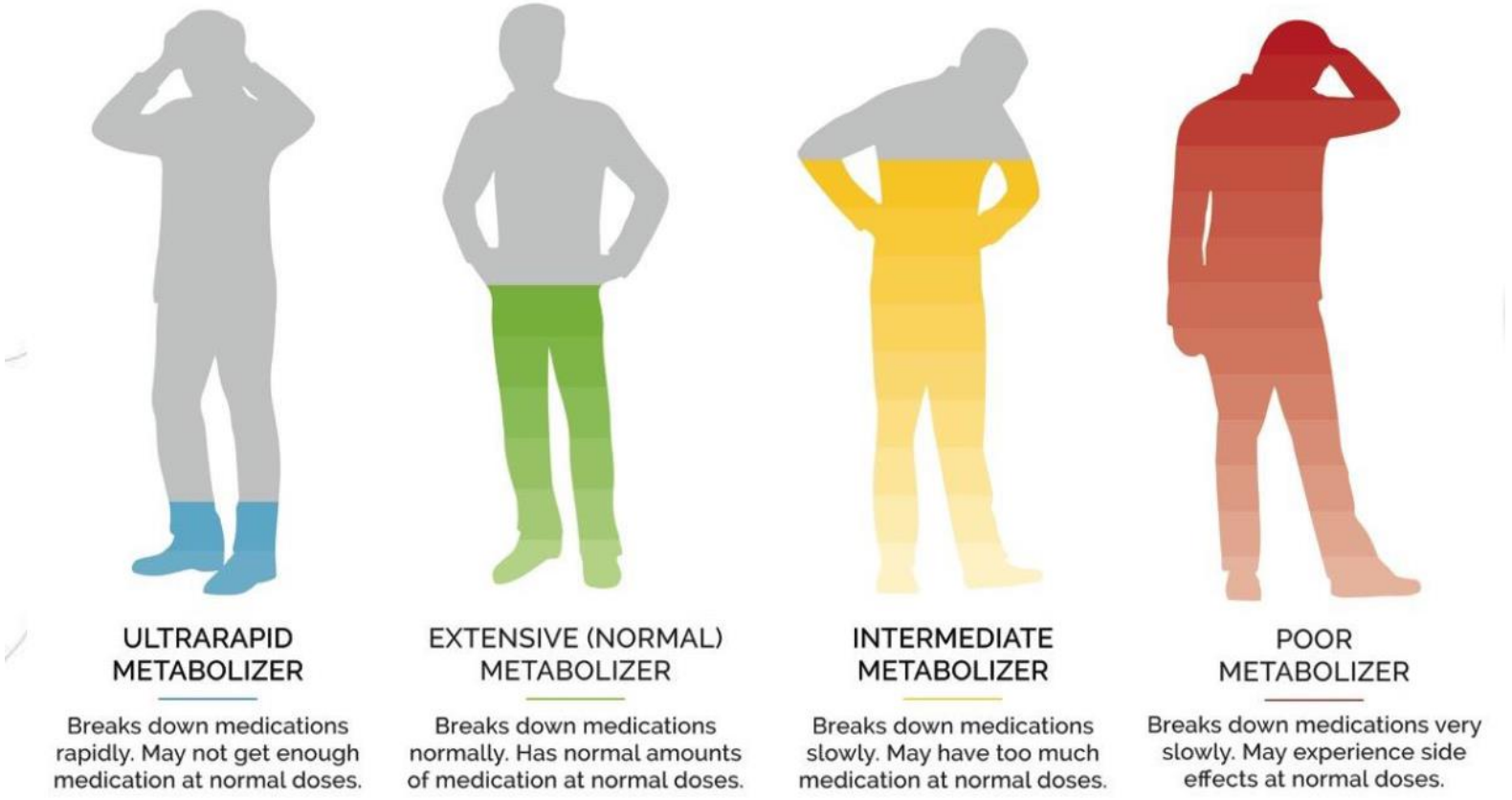
# Pharmacogenetics vs. Disease Genetics

- 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)



# 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

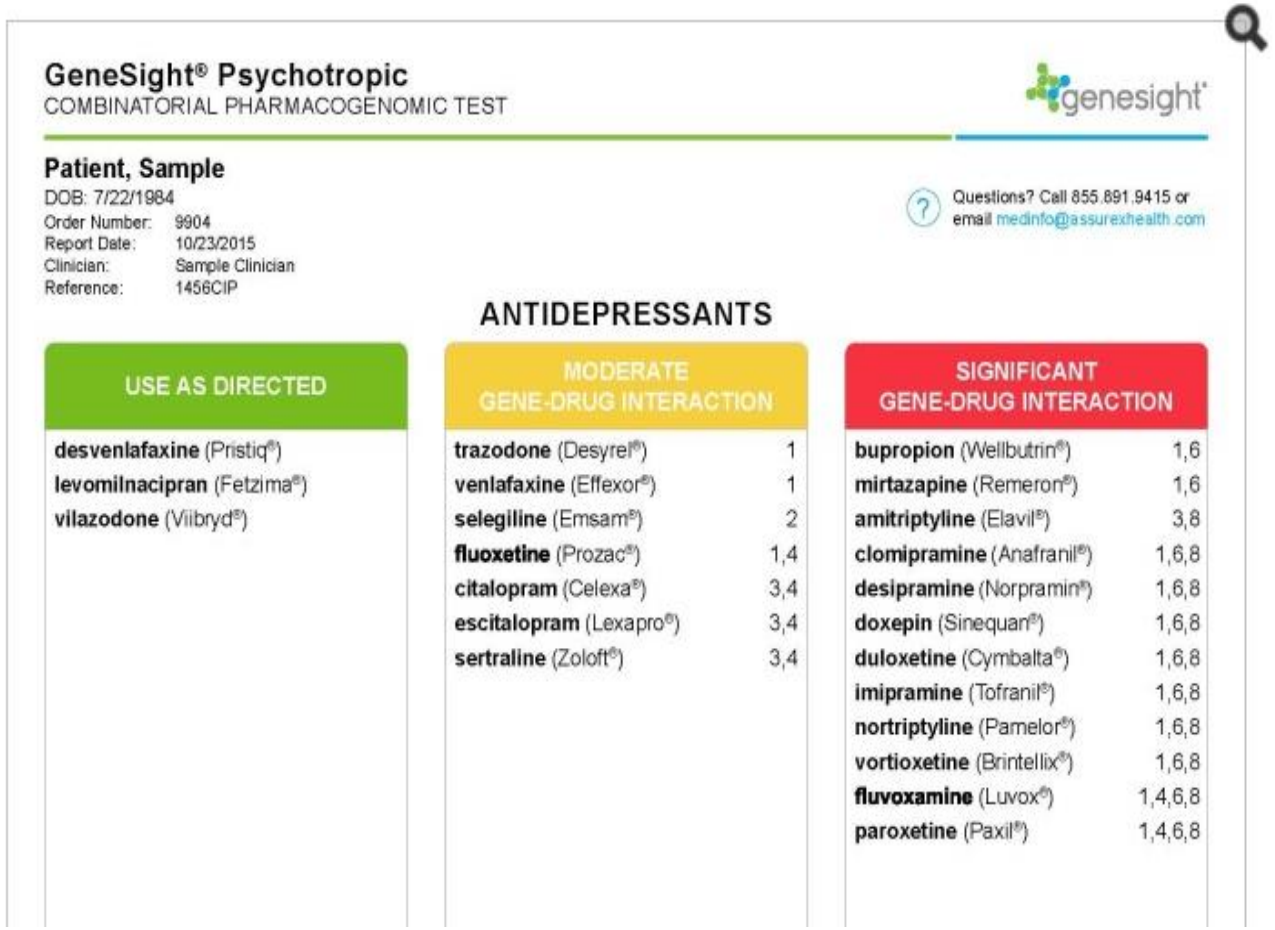
- Several small trials and non-randomized

- 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

genesight

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

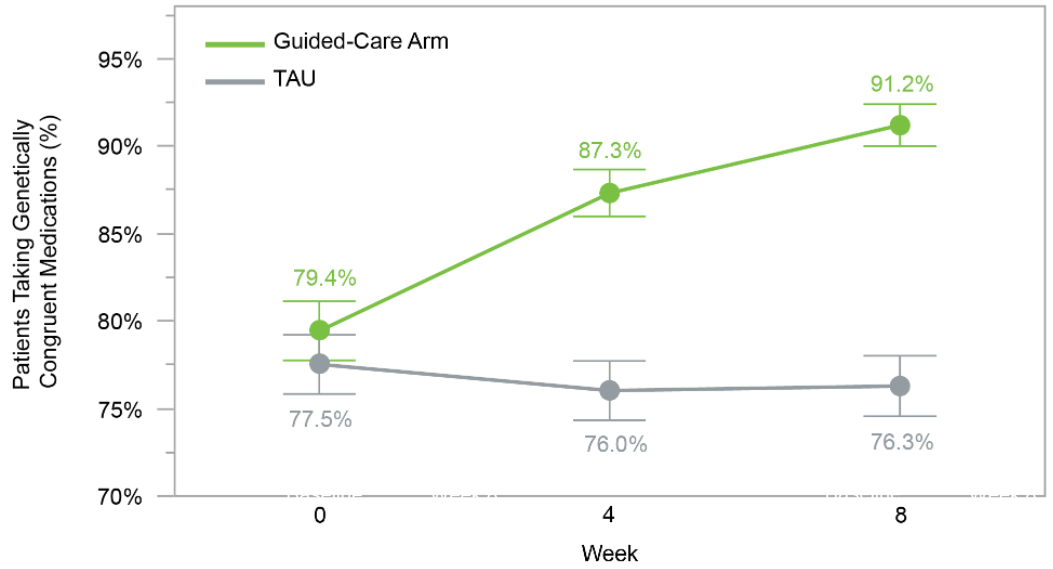
Questions? Call 855.891.9415 or email medinfo@assurexhealth.com

## ANTIDEPRESSANTS

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

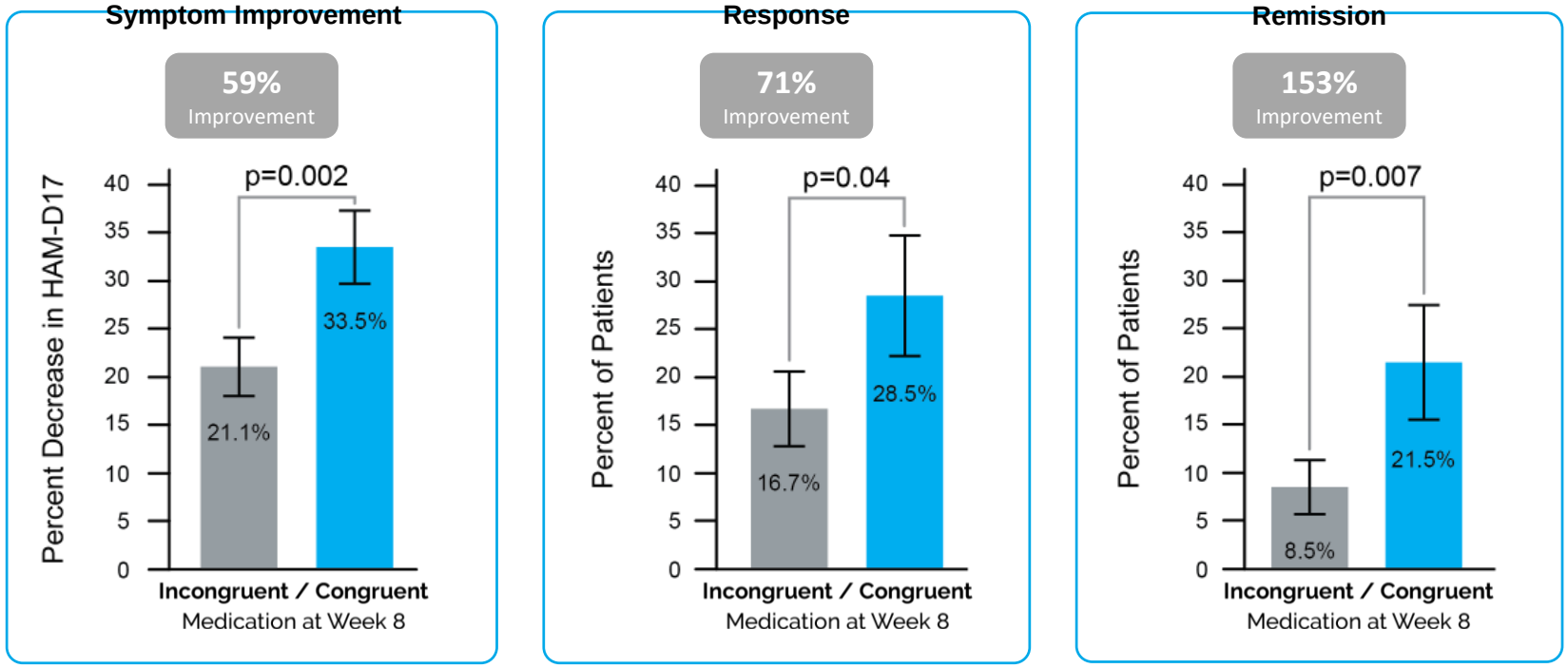
# Increased Congruence in the Guided-Care Arm

**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

# 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

# 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

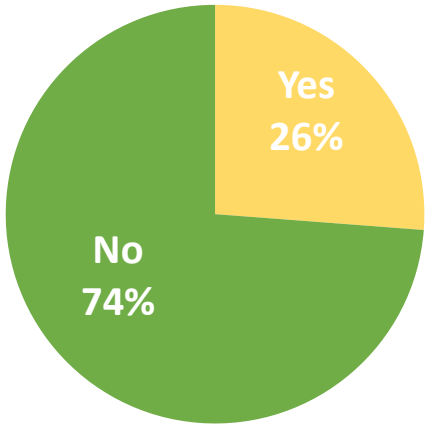
# Inclusion Criteria: Pragmatic Trial

- 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

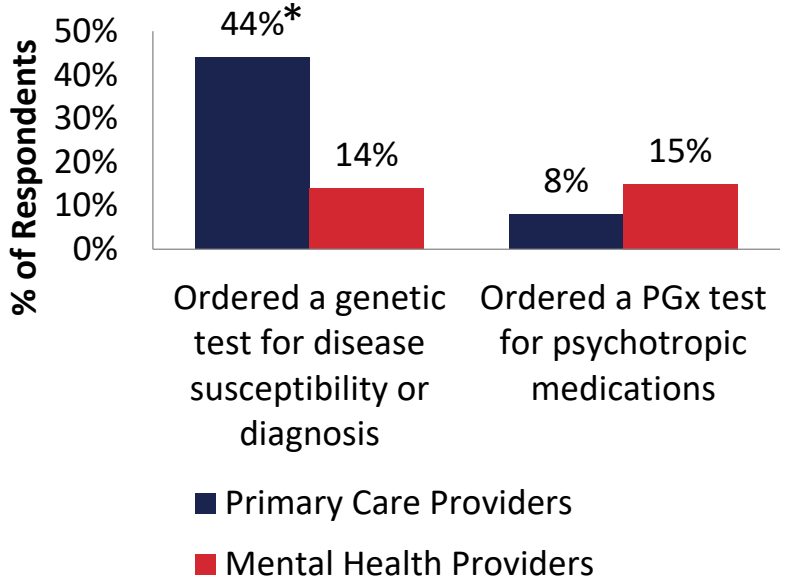
- Determined by self report / chart review
  - PHQ-9 >9
  - Age 18 - 80

# 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



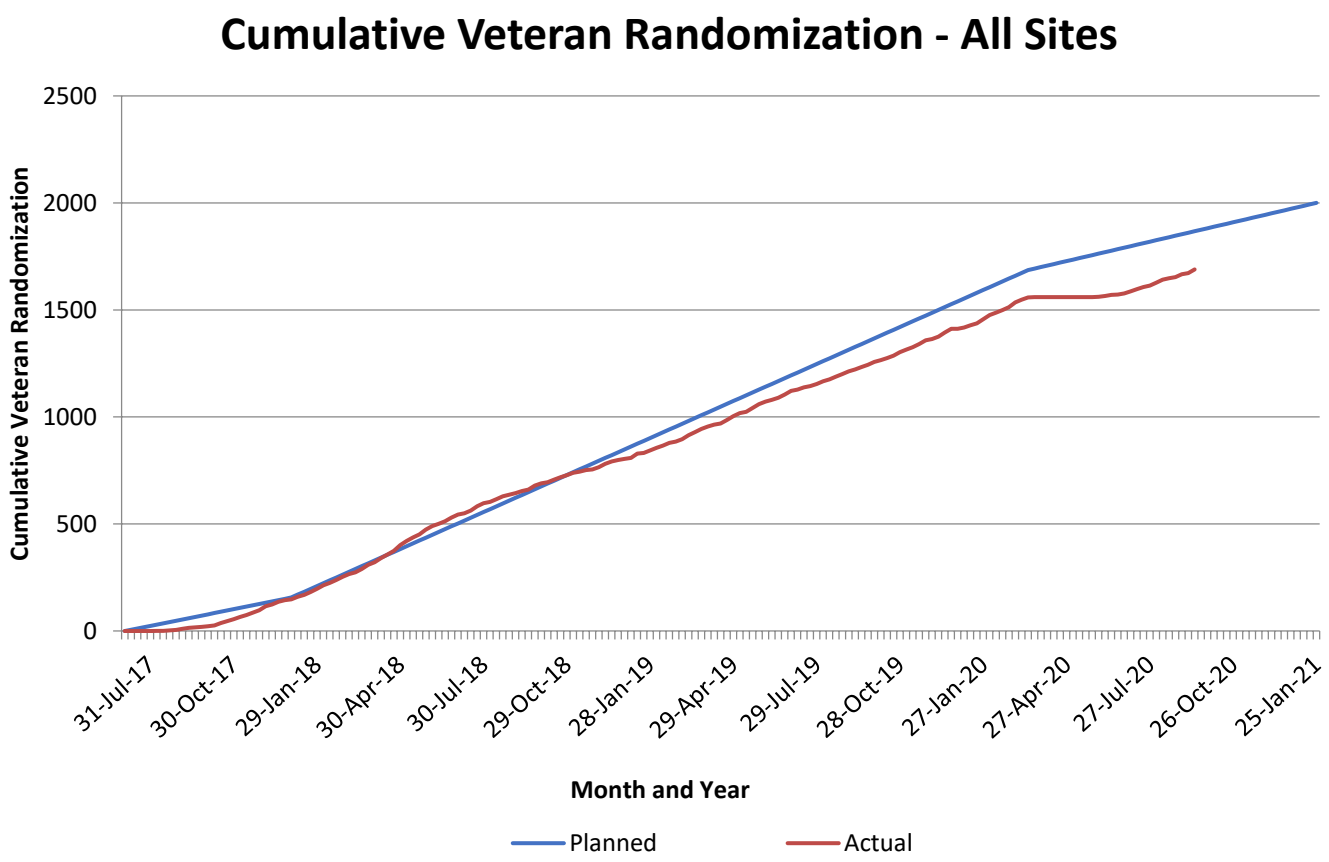

**VA Primary Care and Mental Health Providers' Comfort with Genetic Testing: Survey Results from the PRIME Care Study.** Hull LE, Lynch KG, Oslin DW. J Gen Intern Med. 2019 34:799-801

* 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



# 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 % |

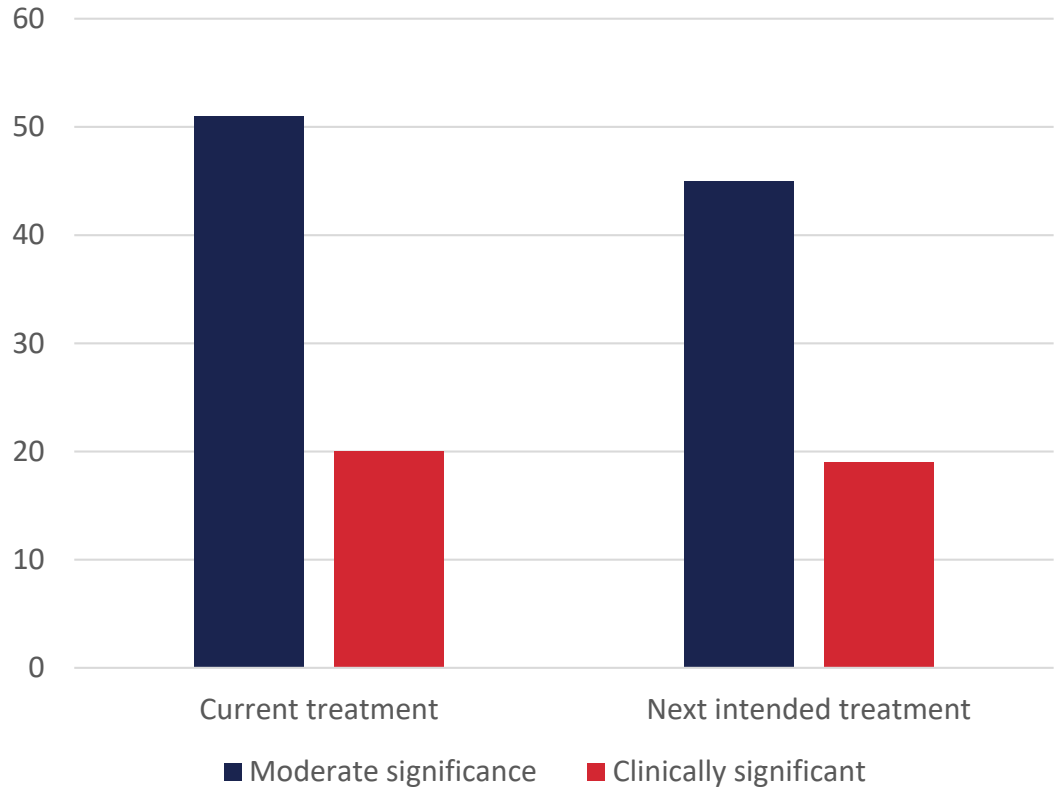
| Provider Type | |
|---|---|
| MH | 67 % |
| PCP | 29 % |
| Other / unknown | 4 % |

| 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)

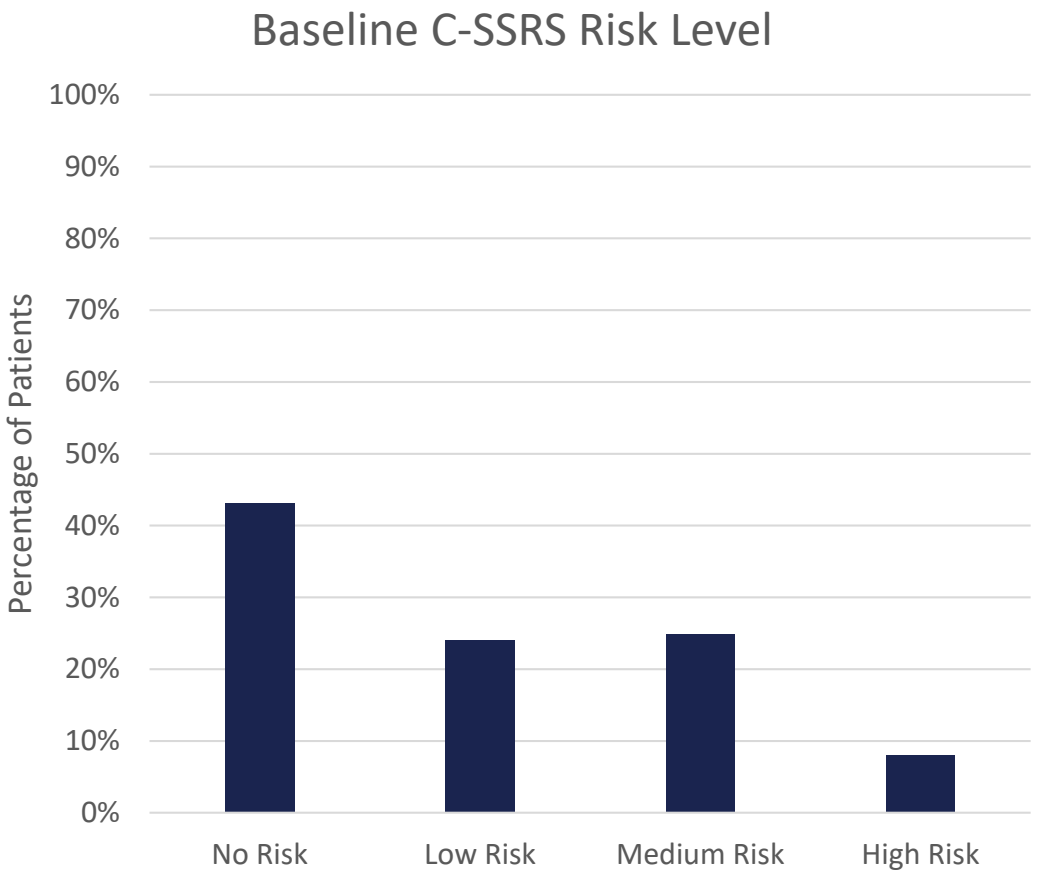
- Ramsey et al. (under review)

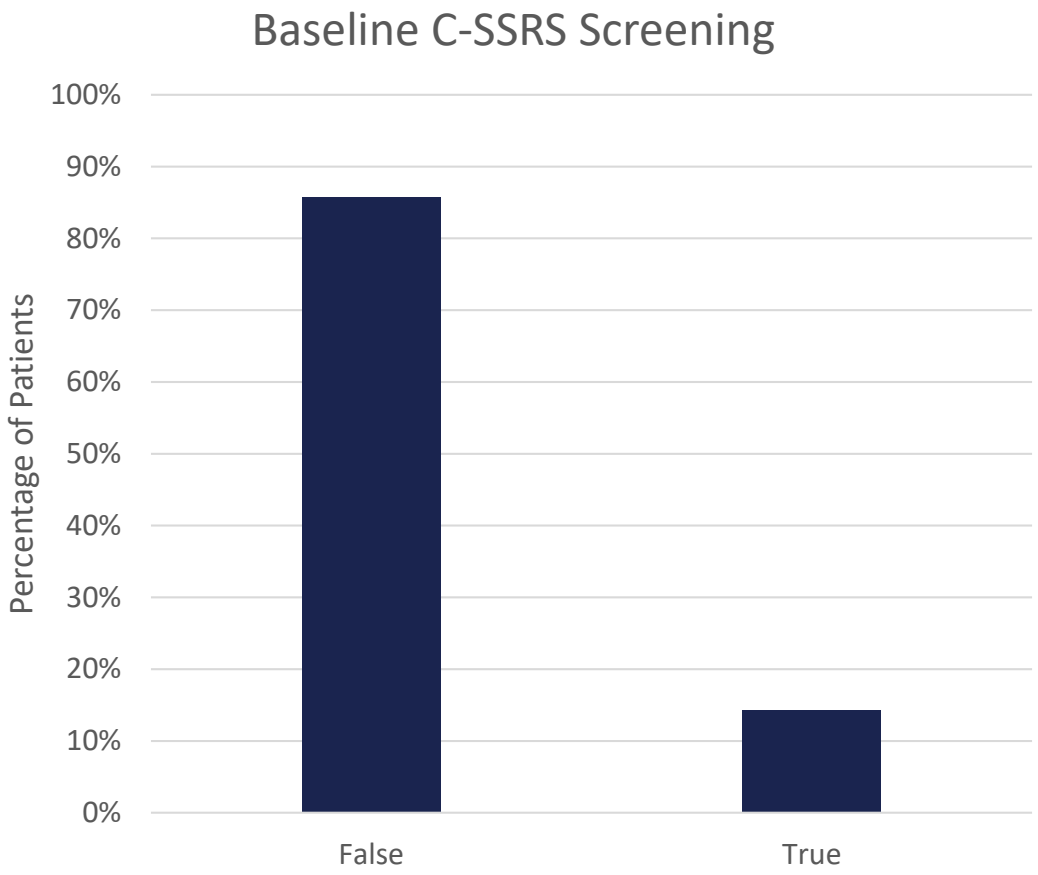
# Suicidality

- Suicidal Ideation
  - High correlation with major depression

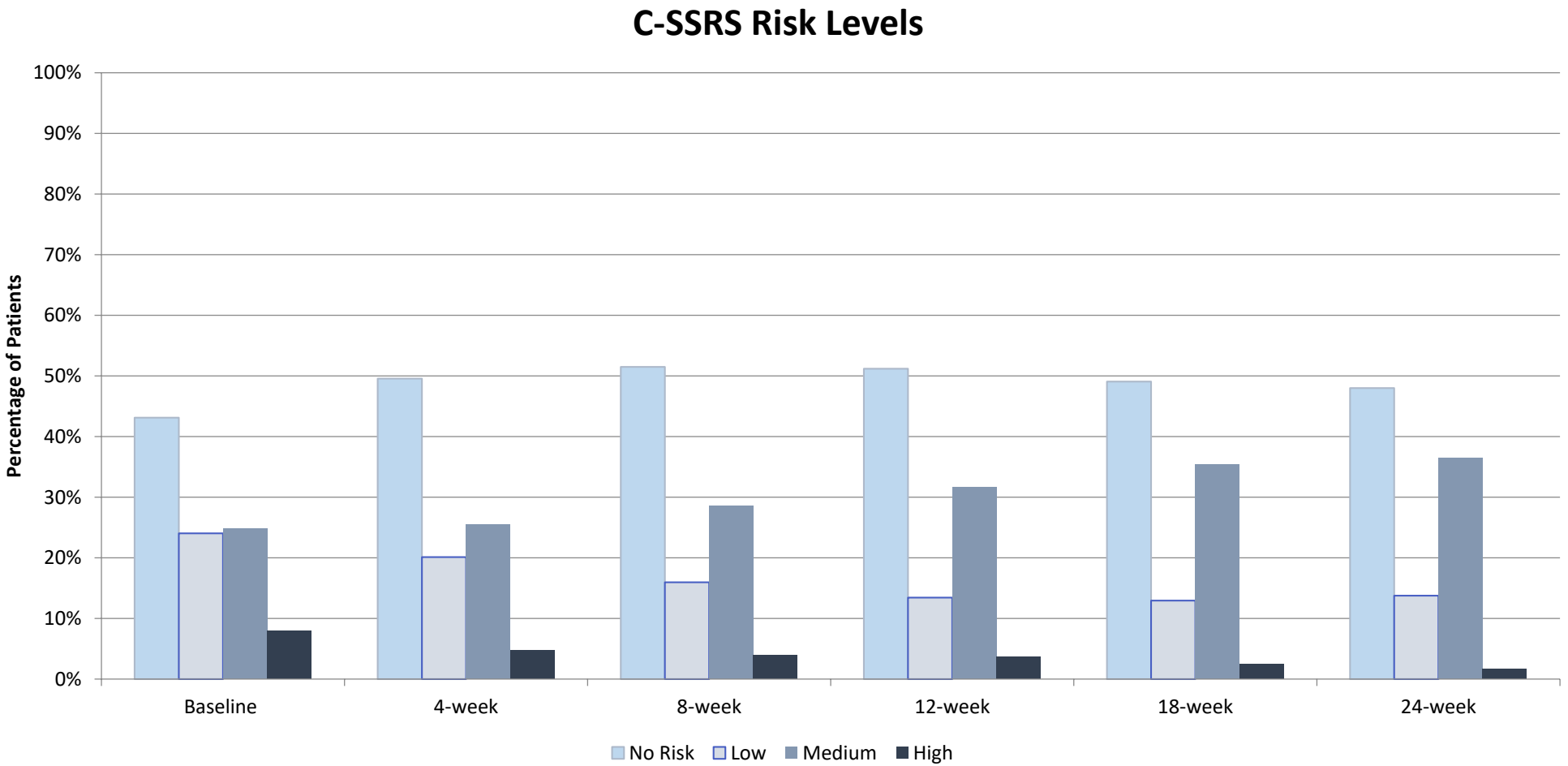
- Opportunity
  - CSSRS was added to the research battery at baseline and at all outcome assessments (added about one year into the study)
  - We conduct a risk assessment for anyone positive on the CSSRS or with a positive PHQ9 on item 9 (2 or 3).
  - There will be an opportunity to look at suicidal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

# C-SSRS Risk Level Baseline

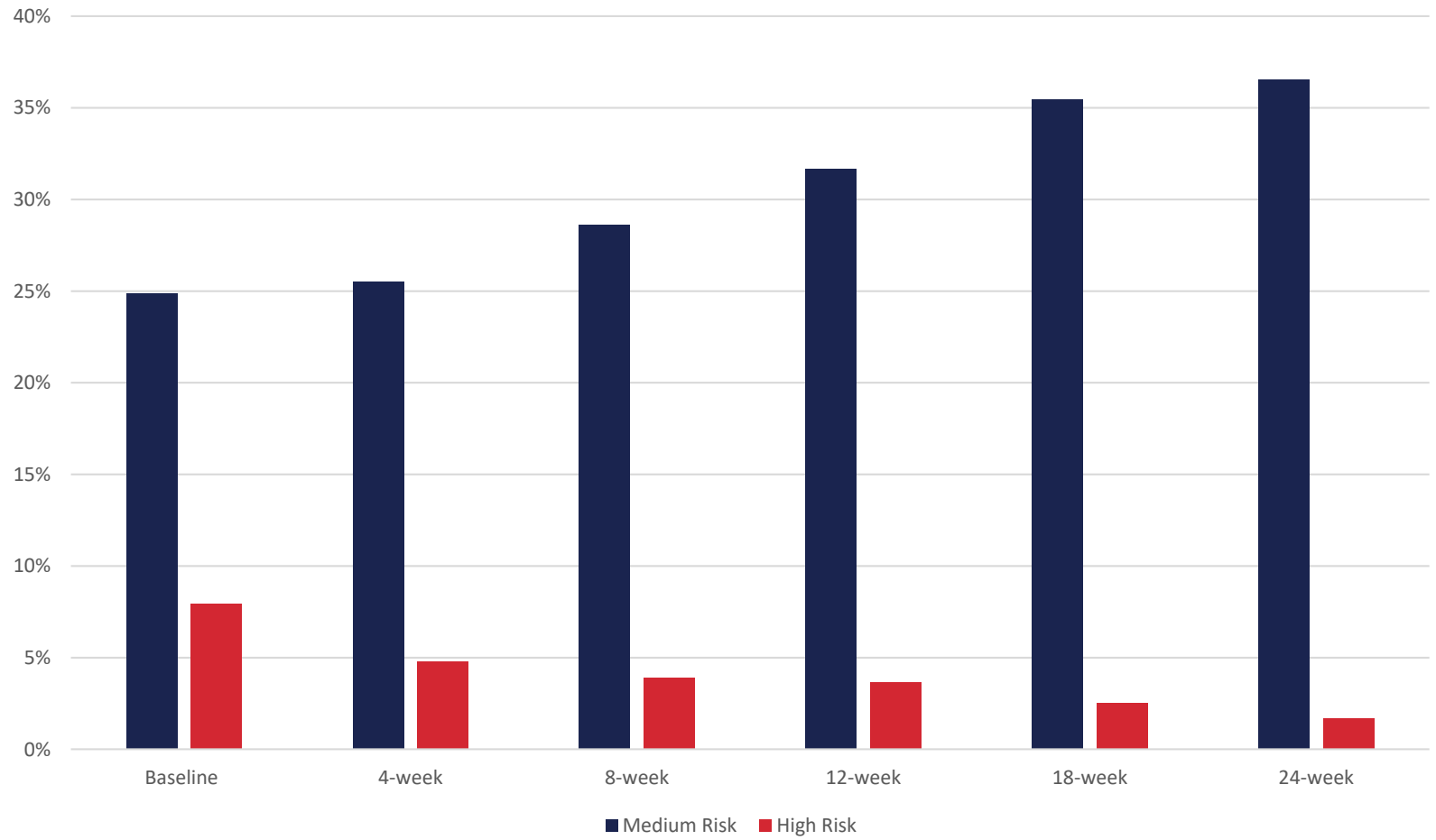


# C-SSRS Over Time



# C-SSRS Medium and High Risk



# Thank You.

PRIME Care