PRIME Care

Precision Medicine in Mental Health Care:

Incorporating Implementation Science into a Large Scale RCT

VISN 4 MIRECC
Mental Illness Research, Education and Clinical Center

CIH
Center for Integrated Healthcare

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Presenters

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PRIME Care: Principle Investigator

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PRIME Care: Knowledge Translation Core, Co-Director

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Acknowledgements

- HSR&D, Service Directed Research (SDR 16-348)
- Myriad Genetics provides in kind testing support of the PRIME Care study

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Objectives

- Study Overview
- Implementation Support of RCT
- Prepare for National Implementation

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Poll #1 (Select one)

- What is your primary role in the VA?
  - Student, trainee, or fellow
  - Clinician
  - Researcher
  - Administrator, manager or policy-maker
  - Other

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Poll #2
(select all that apply)

- What is your familiarity with pharmacogenetics (PGx) testing?
  - None, this is all new to me.
  - Some familiarity, I've read about it.
  - I've ordered PGx for patients.
  - I've had my own PGx (e.g., 23andMe).

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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

Pharmacogenomics Defined

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

National Institutes of Health
National Human Genome Research Institute

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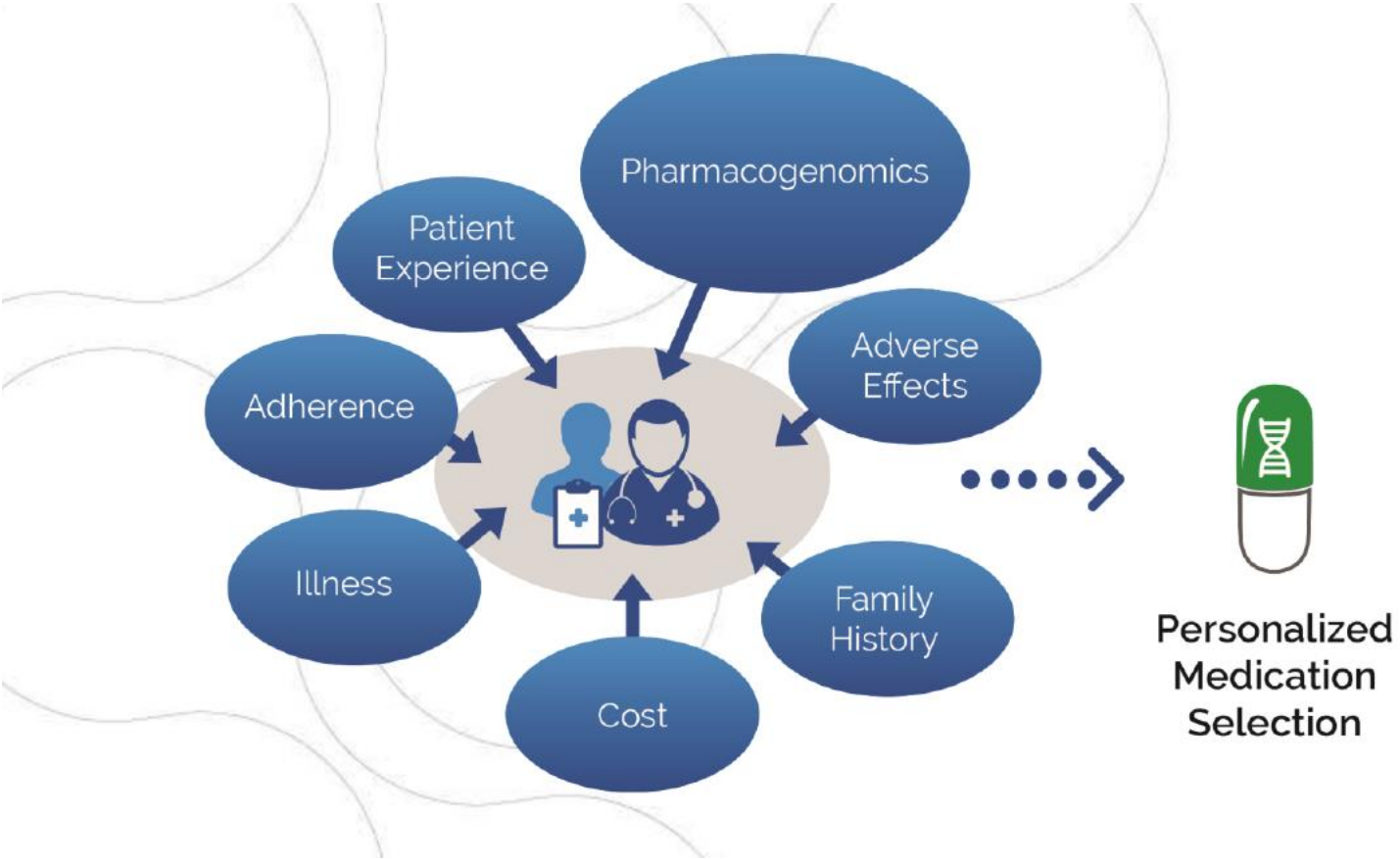
Personalized Medication Selection Factors



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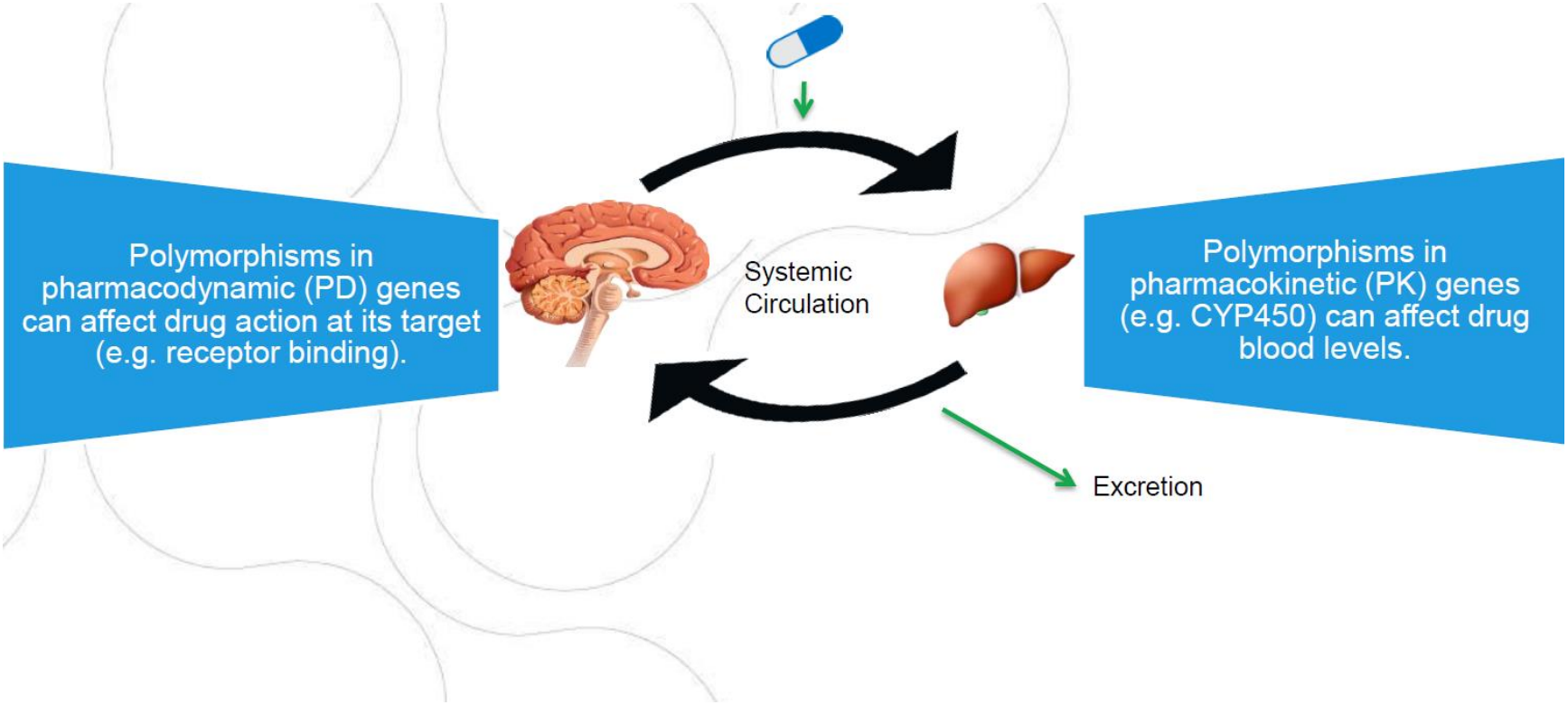
Pharmacodynamics and Pharmacokinetics



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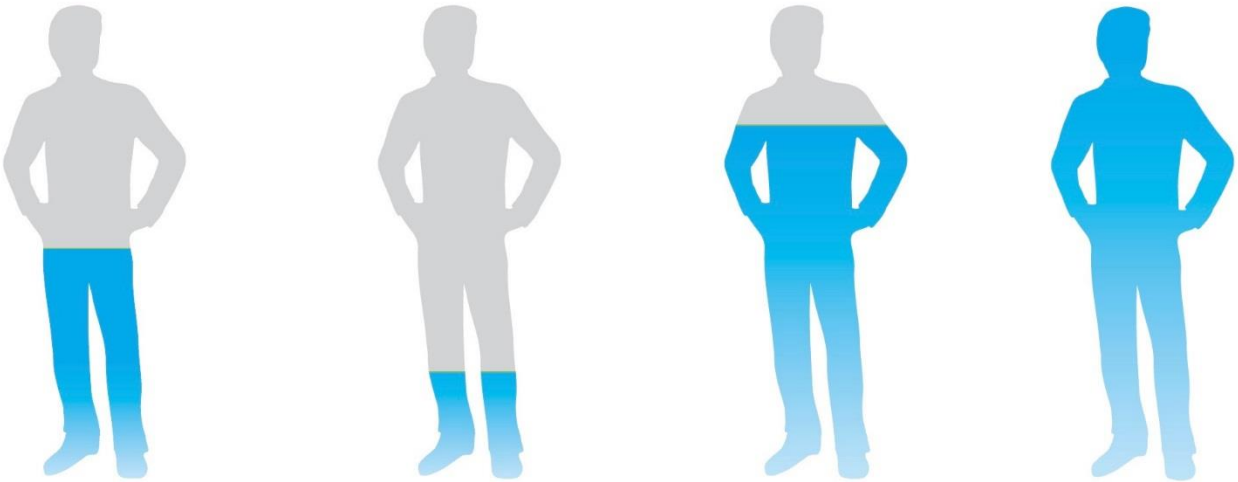
How Genetics Can Affect Medication Blood Levels



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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Evidence Synthesis*

- Lack of overall evidence to recommend for clinical care
- Call to action for more research and specifically on Veterans
- Recommended design considerations
  - selection of genetic variants
  - format of pharmacogenomics results delivery
  - education
  - ethical, legal, and social considerations
  - patient populations and outcome assessment methods.
- Based on HSR&D Evidence-based Synthesis Program

*Peterson, K., et al., *Evidence Brief: The Comparative Effectiveness, Harms, and Cost-effectiveness of Pharmacogenomics-guided Antidepressant Treatment versus Usual Care for Major Depressive Disorder*. 2016, Department of Veterans Affairs: Washington, DC.

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Precision Medicine in Mental Health Care (PRIME Care)

- Program Project
- Principal Investigator: David Oslin, MD
- Operational Partners / Advisory Board: Office of Mental Health and Suicide Prevention, VINCI, plus advisory board members from QUERI, Genomic Medicine Program, Bioinformatics, Million Veteran Program, Pharmacy Benefits Management, and Specialty Care Services among others
- Funding Support: VA HSR&D SDR 16-348

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- Program project grant with 5 cores
  - Implementation
  - Methods
  - Discovery
  - Value Assessment
  - Knowledge Translation
- Activities center around the conduct of a randomized clinical trial to test the “utility” of genetic testing

Clinical Trial Design

- Multi-site RCT (n=2,000 depressed patients enrolled at 19 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)

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Primary Hypotheses

- Provider/patient dyads in the intervention group will use fewer contraindicated medications or doses of medication based on established PGx criteria than in the delayed results group

- Veterans with Major Depressive Disorder 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

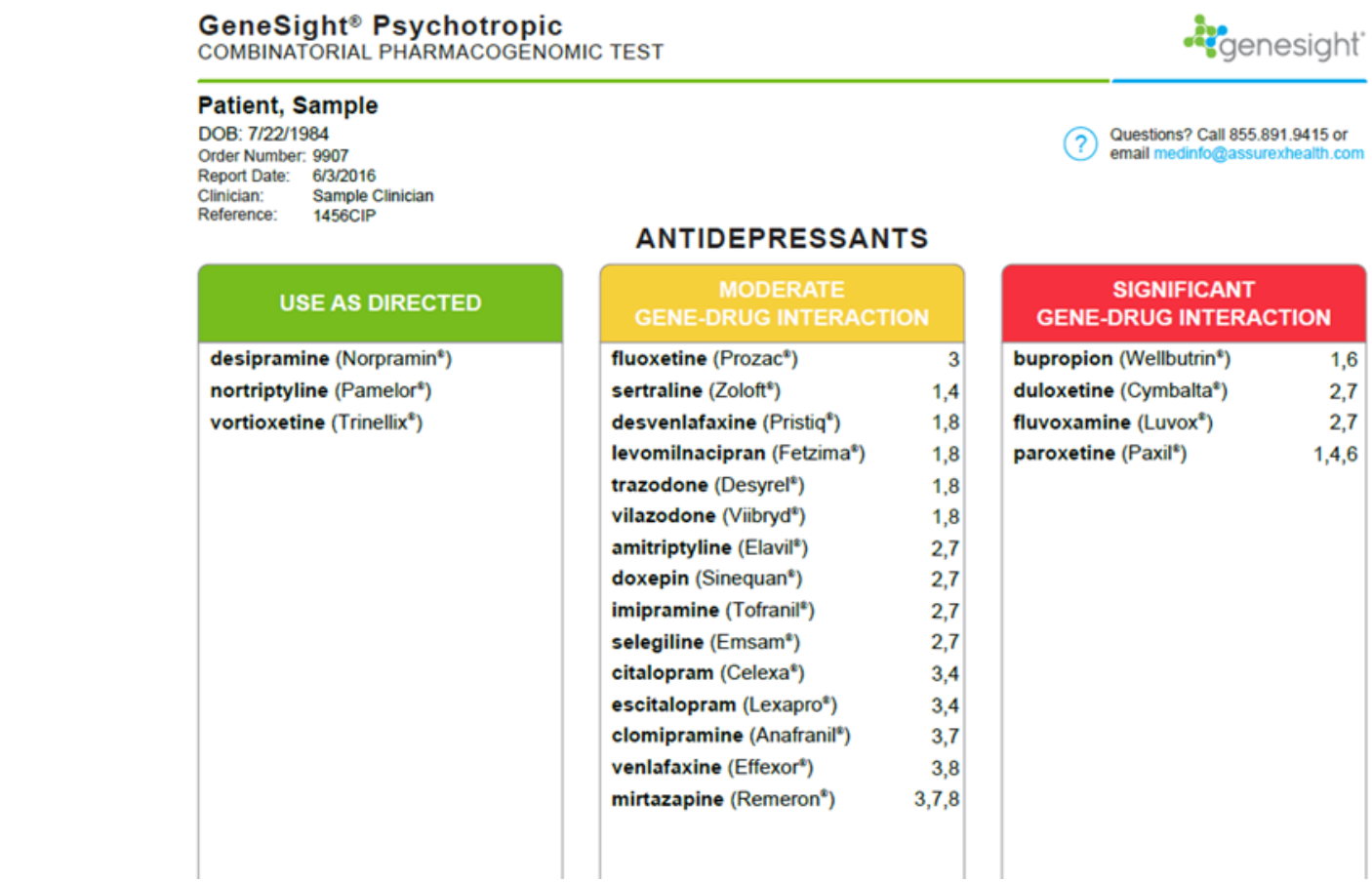
- We will also test a number of secondary outcomes related to returning genetic results, alternate outcomes, discovery, and implementation

Patient Criteria

Need to be:

- Symptomatic MDD (Single or Recurrent)
- Starting an antidepressant
- On monotherapy
- Cannot have schizophrenia, bipolar disorder
- Cannot have serious, unstable medical condition
- Doesn't require hospitalization, detox or other urgent care services at the outset of treatment

GeneSight Report



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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19 VA Study Sites Recruiting

- Albuquerque, NM
- Ann Arbor, MI
- Baltimore, MD
- Boston, MA
- Cincinnati, OH
- Cleveland, OH
- West Haven, CT
- Denver, CO
- Little Rock, AR
- Miami, FL
- Minneapolis, MN
- Palo Alto, CA
- Philadelphia, PA
- Pittsburgh, PA
- Puget Sound, WA
- Richmond, VA
- Salisbury, NC
- San Francisco, CA
- West Los Angeles, CA

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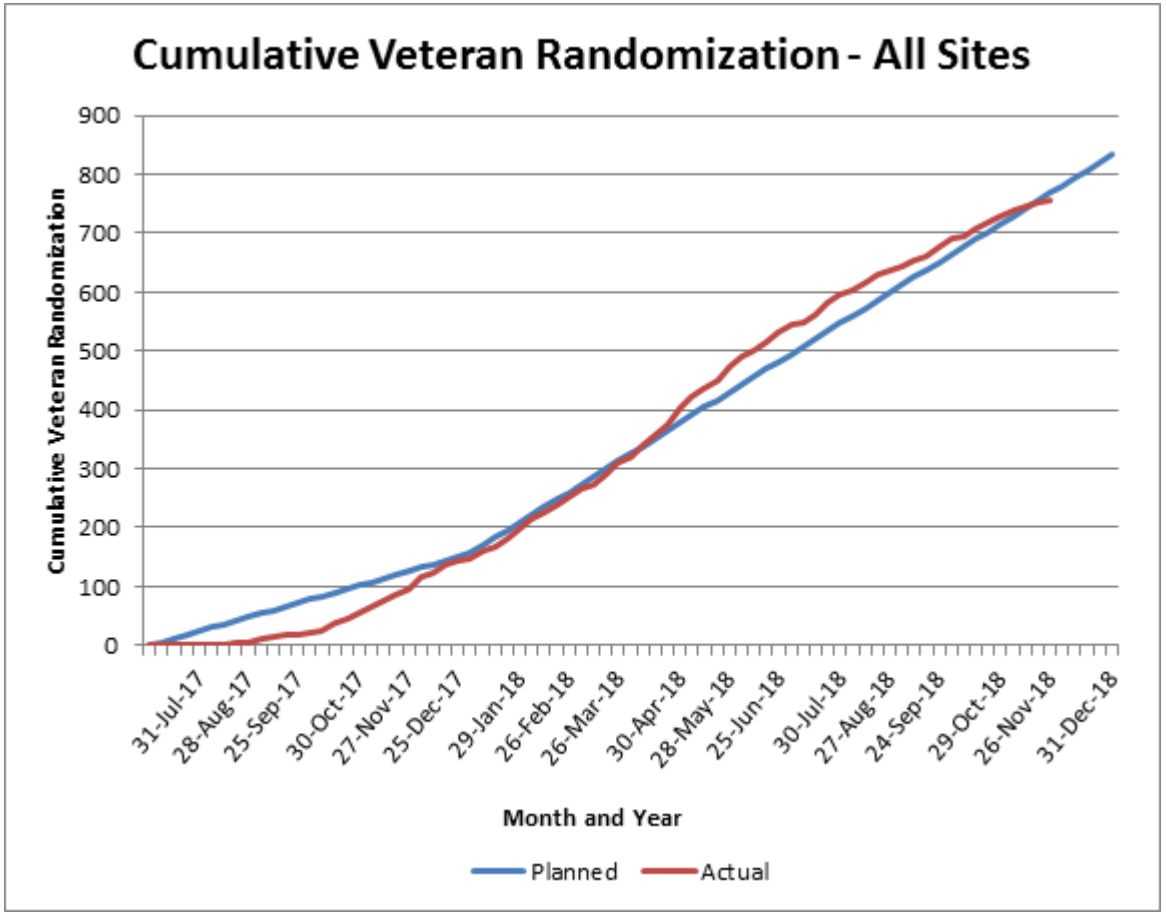
Cumulative Recruitment



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Poll #3
(Select all that apply)

- How familiar are you with Implementation Science (IS)? I am:
  - Not at all familiar
  - Experienced in implementing clinical programs/ practices
  - Learning about IS and trying to use it in my research work
  - An Implementation Scientist
  - Other

Knowledge Translation Core (KTC) Overview

KTC includes:

- Implementation Science (IS) Aims
  - Consolidated Framework for Implementation Research (CFIR)*, guides design, data collection, and analysis
  - Help to prepare for future implementation of PGx testing in VA should the RCT determine that this practice improves patient care.
- Support for the Trial
  - Production of education materials for providers and patients
  - Using formative evaluation methods to support the RCT

*Damschroder, L. J., Aron, D. C., Keith, R. E., Kirsh, S. R., Alexander, J. A., & Lowery, J. C. (2009). Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation science, 4(1),* 50.

PRIME Care Knowledge Translation Core

IMPLEMENTATION SCIENCE AIMS

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KTC Aim 1 Implementation Science

Aim 1 Goal: Understand current state of providers' knowledge and perceptions of PGx testing for depression

- CFIR "Intervention Characteristics" Domain

Aim 1 Design:

- LSIs and Advisory Board helped focus on important characteristics from the domain
- Focus groups with PC and MH providers at beginning of study participation (early in their use of PGx)
- Questions focused on perceptions of the evidence, relative advantage, and potential use of PGx testing

KTC Aim 1: Focus Groups

- 10 focus groups completed
  - 5 Primary Care
  - 5 Mental/Behavioral Health
- 31 providers total
  - 16 Primary Care
  - 15 Mental/Behavioral Health
- Data transcribed and analyzed using a rapid qualitative analysis method

KTC Aim 1: Focus Group Results

Provider Knowledge and Attitudes

- Most providers unfamiliar with current PGx evidence
  - Would like to know more
- Most have not used PGx prior to the study (for any condition)
  - Locality based variations noteworthy across the participating sites
- View PGx as potentially useful, but are curious to see whether clinically effective
  - Appreciate additional piece of information in decision-making (MHPs)
  - Interest in finding ways to improve depression treatment outcomes
- Want to be cautious in implementing
- PGx testing seen as a tool for patient buy-in to medication
  - Could be facilitator (e.g. increased confidence in treatment)
  - Or barrier (e.g. negative placebo effect if Rx comes from Red category)

KTC Aim 1: Focus Group Results

Potential Barriers to PGx Use

- Time constraints of providers
- Patient follow up with results
- Delayed prescribing due to wait for test results
  - Especially for patients that are not engaged
- Report format not necessarily intuitive
  - Red = stop, Green = go, not look at the footnotes and modify
  - Concern over misinterpretation of report categories

KTC Aim 1: Focus Group Results

Potential Facilitators to PGx Use

- Helps to engage the patient in discussion of pharmacotherapy
- Added information to help guide the choice of medication, especially for pts:
  - Without prior antidepressant treatment
  - With prior side effects
  - Without response after several different med trials
  - With comorbidities and polypharmacy

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KTC Aim 2

Aim 2 Goal:

CFIR “Individual Characteristics Domain”

- Using qualitative methods, identify barriers + facilitators to implementation of PGx testing focused on individual characteristics (provider)

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KTC Aim 3

Aim 3 Goals:

CFIR Domains of “Inner Setting”, “Outer Setting” and “Implementation Planning”

- Using qualitative methods, examine providers’ perceptions of site (Inner Setting) and VHA system (Outer Setting), and implementation support needs anticipated to prepare for national implementation of PGx testing (Implementation Planning)

- In addition to identifying important aspects of these domains, we will specifically examine the impact of PCMHI or BHIP team implementation on the fidelity of providers to PGx testing recommendations

KTC Aims 2 & 3

Data collection for each begin toward end of providers' participation

- Aim 2 Design

  Qualitative interviews (n=45) with 3 groups of providers based on referral rates:
  - High Users (Referred multiple patients)
  - Mid-range Users
  - Low Users (Consented but referred few patients)

- Aim 3 Design

  Qualitative interviews (n=45) with 2 groups of providers:
  - PCPs
  - MHPs

PRIME Care Knowledge Translation Core

SUPPORTING THE RCT

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Educational Materials

Educational Documents

- *Patient Recruitment Brochure*
- *VA Providers: Why Should You Participate?*
- *Quick Reference Guide for Providers*
- *Explanation of Test Results for Providers*
- *Explanation of Test Results for Patients*
- *Explanation of Next Steps* (2 versions)
  - *Immediate Results*
  - *Delayed Results*
- *PRIME Care Study Introduction* (PowerPoint Slides)
- *News Brief (Quarterly)*

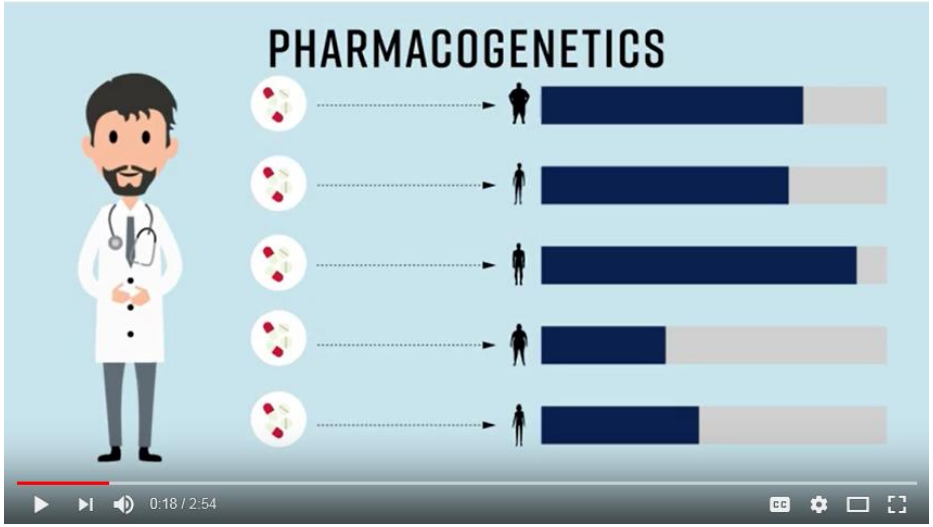
Educational Materials

Educational Videos

Patient and Provider Focused:

Introduction to Pharmacogenetics: PRIME Care Study

(whiteboard video)



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Educational Materials

Educational Videos

Provider Focused:

PRIME Care Study Introduction

Introduction to Pharmacogenetic Testing for Providers

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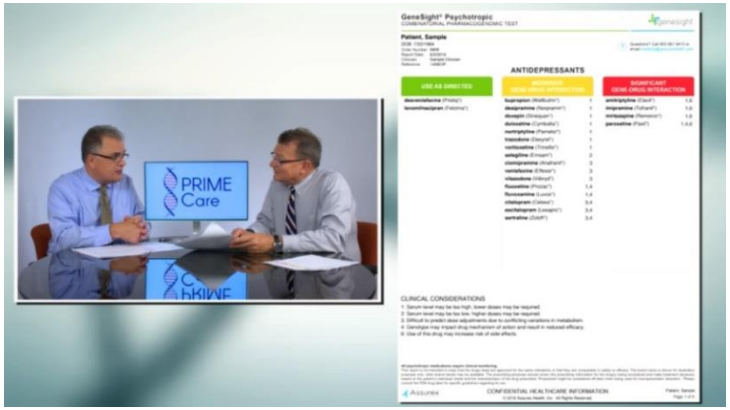
Educational Materials

Educational Videos

Provider Focused:

Using Your Patient's Test Results



Talking to Your Patients About Test Results

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Educational Materials

PRIME Care Website:

www.bit.ly/VAPRIMECare

There is a VA PRIME Care Playlist on VA YouTube that includes links to all of the educational videos along with running time.

RCT Formative Evaluation

LSI Feedback on Recruitment

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RCT Formative Evaluation: Provider Recruitment

Why Reach Out to the LSIs?

- Variability of recruitment rates across sites
- Relatively low percentage of PC providers enrolled
- First year of the project, learn from high-performance sites and share with others

LSI Feedback on Recruitment

Conversations with Site PIs

- Asked about provider and patient recruitment at their site:
  - Strategies
  - Challenges
  - Differences between primary care (PC) and mental health (MH)
  - Focused on provider and patient recruitment

LSI Feedback on Recruitment

General Observations

Sites use a variety of engagement strategies with providers:

- Presentations, staff meetings, emails, one-on-ones, casual meeting in hallways, food, study supplies (pens, notepads)
- Persistence, availability, and personal relationships key

Referral numbers differ greatly across enrolled providers

- Often most referrals originate from 1-2 active providers
- In many cases these were mid-level providers

LSI Feedback on Recruitment

General Observations

Strategies for increasing patient referrals (Facilitators):

- Case finding
  - Alerting providers regularly of eligible patients
- Engage whole team
  - Non-prescribers, office staff, etc.
- Study coordinator available and flexible
- First-hand experience of referral and results
- Patients interested
- Importance of keeping study ‘on their radar’

LSI Feedback on Recruitment Mental Health vs. Primary Care

General Observations

Sites face more challenges enrolling PCPs vs MHPs.

- Sites tend to start with recruitment in MH
- Some sites have focused less on PC recruitment
- Many sites unsure of how to better address PC recruitment or referrals
- Importance of personal connection

MHP-Specific Challenge:

- Perception at some sites that few pts in MH are eligible due to complexity

LSI Feedback on Recruitment

Barriers

- Mechanics/Logistics of study
- Identifying patients who meet inclusion/exclusion criteria
  - Improved after PTSD criterion changed for some
- Provider behavior change difficult
  - Keeping the study on their radar
  - Time pressures
- Sites that are geographically dispersed/have multiple locations
- Patient concern over sharing genetic information

LSI Feedback on Recruitment Mental Health vs. Primary Care

PCP-Specific Challenges:

- Too busy/stressed/overwhelmed
- Not doing much of the prescribing for depression (site variation)
  - Embedded MHPs at some sites
  - Everyone gets referred to MH at some sites
- Uncertainty of how to make best use of PCMHI teams
  - Implementation/configuration and workflow differs across sites
  - Some uncertainty re: who is prescribing and who is following the patient in their own system

Current KTC Activities

- RCT Support Activities:
  - Second round of LSI interviews focusing on additional patient referrals from consented providers
    - Formative evaluation, rapid feedback cycle
  - *News Brief* (quarterly)
  - Whiteboard Video 2
  - Webinar on PGx
  - Website expansion
- IS Aims Activities:
  - Finalizing preparations for Aims 2 and 3 Interviews

Resources

PRIME Care Website:

www.bit.ly/VAPRIMECare

Educational Videos:

- *Introduction to Pharmacogenetics: PRIME Care Study (whiteboard video)*
- *PRIME Care Study Introduction*
- *Introduction to Pharmacogenetic Testing for Providers*
- *Using Your Patient's Test Results*
- *Talking to Your Patients About Test Results*

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References

- Damschroder, L. J., Aron, D. C., Keith, R. E., Kirsh, S. R., Alexander, J. A., & Lowery, J. C. (2009). Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation science, 4(1),* 50.
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Questions/Discussion

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