Precision Medicine in Mental Health Care

PRIME Care

Study PI:
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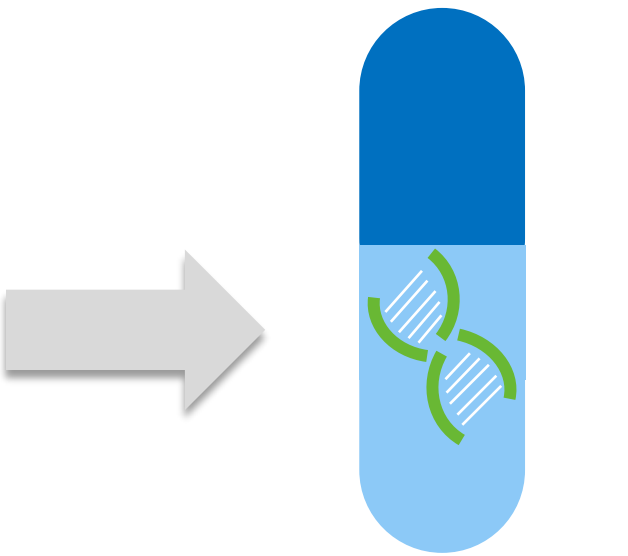
VA HEALTH CARE Defining EXCELLENCE in the 21st Century

Background: Public Health Significance

- Depression is one of the world's great public health problems
- At least 1 in 7 Veterans suffers from a depressive disorder
- 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 medication and 1/3rd will remain depressed despite multiple treatment trials
- There are no reliable clinical tools to match each patient with the AD that is the most likely to be effective

Personalized Medication Selection Factors



Personalized Medication Selection

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

PRIME Care

- 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

Primary Hypotheses

- Will providers understand and use the test results? - Provider/patient dyads in the intervention group will use fewer contraindicated medications based on established PGx criteria

- Do patients benefit? Veterans with MDD whose care is guided by the results of the PGx battery (the intervention group) will have higher rates of depression remission

- Secondary outcomes related to returning genetic results, alternate outcomes, and knowledge discovery

Clinical Trial Design

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

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

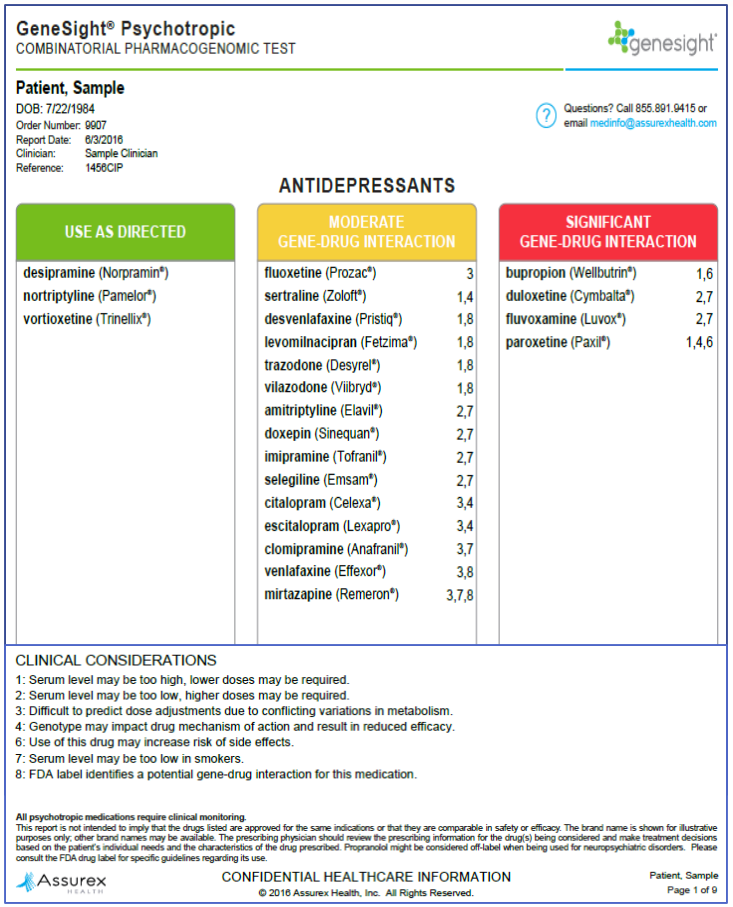
Pragmatic trial

- 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
  - PHQ9 >9
  - Age 18 - 80

THE INTERVENTION

Pharmacogenetic Test Report (1st Page)



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		

CLINICAL CONSIDERATIONS

1: Serum level may be too high, lower doses may be required.
2: Serum level may be too low, higher doses may be required.
3: Difficult to predict dose adjustments due to conflicting variations in metabolism.
4: Genotype may impact drug mechanism of action and result in reduced efficacy.
6: Use of this drug may increase risk of side effects.
7: Serum level may be too low in smokers.
8: FDA label identifies a potential gene-drug interaction for this medication.

All psychotropic medications require clinical monitoring.
This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drug(s) being considered and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed. Propranolol might be considered off-label when being used for neuropsychiatric disorders. Please consult the FDA drug label for specific guidelines regarding its use.

Assurex HEALTH

CONFIDENTIAL HEALTHCARE INFORMATION

Patient, Sample
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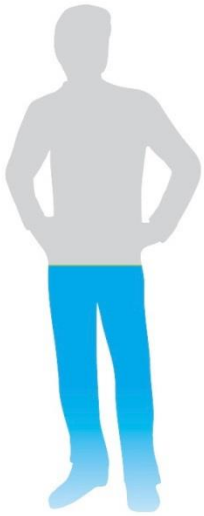
Pharmacogenomic Polymorphisms Studied in PRIME Care

Pharmacokinetic	Pharmacodynamic
CYP2D6	SLC6A4 (serotonin transporter)
CYP2C19	5HTR2A (serotonin 2A receptor)
CYP2C9	*HLA-B*1502 (Human Leukocyte Antigen)**
CYP1A2	*HLA-A*3101 (Human Leukocyte Antigen)**
CYP2B6	
CYP3A4	
*UGT1A4**	
*UGT2B15**	

**Not part of the core antidepressant battery*

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.

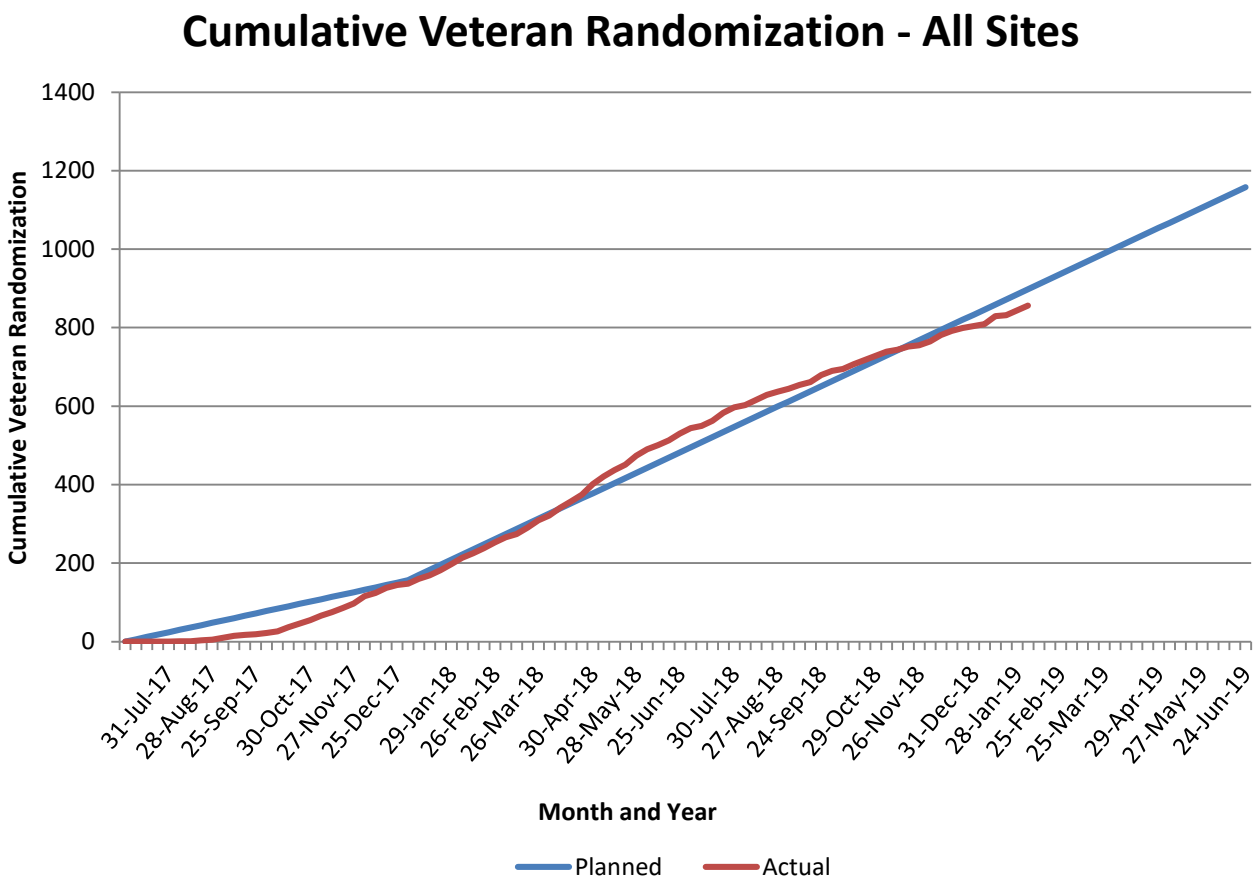
POOR METABOLIZER

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

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
- W. Los Angeles, CA
- Wilmington, DE

Cumulative recruitment



Baseline Characteristics of Randomized Sample

Sample size (n=388)	
Age	47 ± 15
Race (% Caucasian)	67 %
(% African American)	20 %
Sex (% male)	74 %
Post 2001 (%)	32 %
Financial status (% can't make ends meet)	17 %

Provider type	
MH	85 %
PCP	8 %
Other / unknown	7 %

Sample size (n=388)	
PHQ-9 score (SD)	17.2 (4.7)
PCL score (SD)	43.2 (16.7)
GAD-7 (SD)	14.0 (4.7)
Alcohol use (% at risk)	21 %
Marijuana (% recent use)	21 %
Other drugs (% recent use)	4%
Tobacco (% with any use)	32 %
Prior psychotherapy (% with)	67 %
Prior meds (% with 1 or more)	88 %
No prior treatment	6.2 %

Provider Characteristics

Characteristic	All providers (*N* = 332)	Primary care providers (*N* = 93)	Mental health providers (*N* = 239)	*P* value
Age	49.9 (12.6)	49.9 (11.2)	49.8 (13.1)	0.97
Female	182 (55%)	52 (56%)	130 (54%)	0.80
Year completed formal training				
2000 or before	149 (45%)	56 (60%)	93 (39%)	< 0.001
After 2000	183 (55%)	37 (40%)	146 (61%)	
Time spent in clinical practice				
0–49%	48 (14%)	21 (23%)	27 (11%)	0.009
50% or more	284 (86%)	72 (77%)	212 (89%)	

Provider Knowledge

Characteristic	All providers (*N* = 332)	Primary care providers (*N* = 93)	Mental health providers (*N* = 239)	*P* value
Aware that the FDA-revised drug labels to include information about PGx	87 (26%)	18 (19%)	69 (29%)	0.08
Ordered a genetic test for disease susceptibility or diagnosis in the past year	72 (22%)	40 (43%)	32 (13%)	< 0.001
Ordered a PGx test for psychotropic medications in the past year	42 (13%)	7 (8%)	35 (15%)	0.08