Precision Medicine in Mental Health Care: Can Pharmacogenomic Testing Improve Antidepressant Outcomes?
Faculty Disclosure: Past Three Years

- **Employment (spouse)**—Peloton Advantage (does business with several pharmaceuticals)
Unmet needs in depression care
Rationale for pharmacogenomics
Introduction to genomic testing
Sample test results
Examining the evidence
Reasons for skepticism
PRIME Care Primer
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 1/3 remit with the first course of medication and 1/3 will remain depressed despite multiple treatment trials
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
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
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
Current Medication Decision Factors

- Patient Experience
- Current Meds
- Adverse Effects
- Adherence
- Illness
- Cost
- Family History

Medication Selection
Personalized Medication Selection Factors

Pharmacogenomics

- Patient Experience
- Current Meds
- Adverse Effects
- Illness
- Family History
- Cost
- Adherence

Personalized Medication Selection
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.
## Selected Polymorphisms Relevant to Antidepressant Response

<table>
<thead>
<tr>
<th>Pharmacokinetic</th>
<th>Pharmacodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>SLC6A4 (serotonin transporter)</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>5HTR2A (serotonin 2A receptor)</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>HLA-B*1502 (Human Leukocyte Antigen)</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>HLA-A*3101 (Human Leukocyte Antigen)</td>
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<tr>
<td>CYP2B6</td>
<td>MTHFR (methylfolate reductase)</td>
</tr>
<tr>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>UGT1A4</td>
<td></td>
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<tr>
<td>UGT2B15</td>
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</table>
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.
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

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Guided group</th>
<th>Unguided group</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
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<tr>
<td><strong>1.1.1 GeneSight</strong></td>
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<tr>
<td>Hail–Flaviv 2012 (cohort)</td>
<td>7</td>
<td>22</td>
<td>2</td>
<td>22</td>
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<tr>
<td>Hail–Flaviv 2013 (cohort)</td>
<td>31</td>
<td>72</td>
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<tr>
<td>Winner 2013 (RCT)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td>119</td>
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<td>139</td>
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<tr>
<td>Total events</td>
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<tr>
<td><strong>1.1.2 Neuropharmagen</strong></td>
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<tr>
<td>Perez 2017 (RCT)</td>
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<td>141</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>139</td>
<td>34.6%</td>
<td>1.13 [0.86, 1.48]</td>
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<tr>
<td>Total events</td>
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<tr>
<td><strong>1.1.3 NeuroIDgenetix</strong></td>
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<tr>
<td>Bradley 2018 (RCT) (1)</td>
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<td>140</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<tr>
<td>Total (95% CI)</td>
<td>201</td>
<td>399</td>
<td>143</td>
<td>400</td>
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</tbody>
</table>

**Footnotes**

(1) Study only reported response rates for subgroup with moderate to severe depression and did not report results for entire sample

_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

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<th>Study or Subgroup</th>
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<th>Unguided group</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tr>
<td><strong>1.2.1 GeneSight</strong>&lt;br&gt;Hall-Flavin 2013 (cohort)</td>
<td>22</td>
<td>72</td>
<td>20</td>
<td>93</td>
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<td></td>
<td>5</td>
<td>25</td>
<td>2</td>
<td>24</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>97</td>
<td>117</td>
<td>50.0%</td>
<td>1.50 [0.91, 2.46]</td>
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<tr>
<td>Total events</td>
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<td>22</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 1.61 (P = 0.11)</td>
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<td><strong>1.2.2 Neuropharmagen</strong>&lt;br&gt;Perez 2017 (RCT)</td>
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<td>141</td>
<td>46</td>
<td>139</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td>139</td>
<td>27.5%</td>
<td>1.03 [0.74, 1.43]</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 0.17 (P = 0.87)</td>
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<td><strong>1.2.3 NeurolDGenetix</strong>&lt;br&gt;Bradley 2018 (RCT) (1)</td>
<td>14</td>
<td>40</td>
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<td><strong>Subtotal (95% CI)</strong></td>
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<td>53</td>
<td>16.3%</td>
<td>2.65 [1.18, 5.95]</td>
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<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 2.36 (P = 0.02)</td>
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<td><strong>1.2.4 CNSDose</strong>&lt;br&gt;Singh 2015 (RCT)</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<td>74</td>
<td>26.1%</td>
<td>2.52 [1.71, 3.73]</td>
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<td>Total events</td>
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<tr>
<td>Heterogeneity: Not applicable</td>
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<tr>
<td>Test for overall effect: Z = 4.66 (P &lt; 0.00001)</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>352</td>
<td>383</td>
<td>100.0%</td>
<td>1.74 [1.09, 2.77]</td>
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<tr>
<td>Total events</td>
<td>142</td>
<td>96</td>
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<tr>
<td>Heterogeneity: Tau² = 0.18; Chi² = 14.08, df = 4 (P = 0.007); I² = 72%</td>
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<td>Test for overall effect: Z = 2.31 (P = 0.02)</td>
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<tr>
<td>Test for subgroup differences: Chi² = 13.67, df = 3 (P = 0.003); I² = 78.1%</td>
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</tbody>
</table>

Footnotes:<br>(1) Study only reported remissions rate for subgroup with severe depression and did not report results for entire sample

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
GuDiED: 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.

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

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
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
PRIME Care

• 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!
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.