Pharmacogenomic Decision Support Tools for Major Depressive Disorder

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Emory University School of Medicine
May 30, 2020
## External Industry Relationships *

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Company Names</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers**</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>Acadia, Aptinyx, Compass Pathways, Otsuka, Sage, Takeda, NIH</td>
<td>Principal investigator/Co-investigator</td>
</tr>
<tr>
<td>Other</td>
<td>Greenwich Biosciences, Mol Dx, Myriad Neuroscience, Sophren, Otsuka</td>
<td>Consultant</td>
</tr>
</tbody>
</table>
1. **Predictor** (Non-specific)

   ![Diagram](image)

   - Characteristic X
   - Treatment A
   - Treatment B
   - Probability of Response

2. **Moderator** (Treatment Specific)

   ![Diagram](image)

   - Gene Variants
   - Treatment A
   - Treatment B
   - Probability of Response

**Other Possible Benefits**
- Optimize Dosing
- Avoid negative outcomes
  - Drop-out from treatment
  - Avoid adverse drug reactions
  - Inform medication tapering

Pharmacogenetics vs Pharmacogenomics

- **Pharmacogenetics** has historically referred to how variation in a *single* gene impacts the response to a single drug.

- **Pharmacogenomics** is a newer and broader term that encompasses how all of the genes of an organism (the genome) impact responses to a wide variety of drugs.

- Today these terms are often used interchangeably.
Pharmacokinetics vs Pharmacodynamics and the targets of PGx Testing

- **Pharmacokinetics (PK):** What the body does to the drug
  - GI, Liver, Kidney actions
- **Pharmacodynamics (PD):** What the drug does to the body
  - Receptors, Transporters

**Immune-Related Genes:**
- HLA-B*1502
- HLA-A*3101
Pharmacogenomics (PGx): A Crowded Space

Professional Guidelines

• Clinical Pharmacogenetics Implementation Consortium (CPIC)
  – [https://cpicpgx.org/](https://cpicpgx.org/)

• Dutch Pharmacogenetics Working Group (DPWG)

• Canadian Pharmacogenomics Network for Drug Safety (CPNDS)
  – [http://cpnds.ubc.ca/](http://cpnds.ubc.ca/)

Regulatory

• US Food and Drug Administration (FDA)

Industry

• PGx Decision Support Tool (DST) manufacturers
<table>
<thead>
<tr>
<th>Gene</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>amitriptyline, citalopram, clomipramine, doxepin, escitalopram, imipramine, sertraline, trimipramine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>phenytoin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>amitriptyline, aripiprazole, atomoxetine, clomipramine, desipramine, doxepin, fluvoxamine, haloperidol, imipramine, nortriptyline, paroxetine, pimozide, trimipramine, venlafaxine</td>
</tr>
<tr>
<td>HLA-A</td>
<td>carbamazepine</td>
</tr>
<tr>
<td>HLA-B</td>
<td>carbamazepine, oxcarbazepine, phenytoin</td>
</tr>
</tbody>
</table>

Guidelines published as of 10 September, 2019 from CPIC, DPWG, or CPNDS

Bousman, Forbes & Dunlop, *Precision Psychiatry*, 2020, in press
From PK Gene to Metabolizer Phenotype


**From SNPs to Activity Value**

- **SNPs**
  - 1847G>A + 100C>T

  **STAR ALLELE**
  - CYP2D6*4

  **ALLELE GROUP**
  - no function

  **ACTIVITY VALUE**
  - 0

**From Diplo type to Phenotype**

- **DIPLOTYPE**
  - CYP2D6 *1/*4

  **ACTIVITY VALUES**
  - CYP2D6*1 = 1
  - CYP2D6*4 = 0

  **ACTIVITY SCORE**
  - 1 + 0 = 1

  **PHENOTYPE**
  - CYP2D6 intermediate metabolizer

**Translation of AS into phenotype groups**

- **PM**
  - no function

- **IM**
  - decreased function

- **NM**
  - normal function

- **UM**
  - increased function

**Activity Score (AS)**

- 0
- 0.25
- 0.5
- 0.75
- 1
- 1.25
- 1.5
- 1.75
- 2
- 2.25
- >2.25

**Continuum of CYP2D6 activity due to genetic variation**
Impact of CYP2C19 on Escitalopram Exposure (Norway)

Variability in Escitalopram Concentration by CYP2C19 Genotype

### Selected psychiatric drugs with gene-drug warnings on FDA label

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Adverse drug reactions</th>
<th>Gene-Drug interaction management in PMs</th>
<th>Drug-drug interaction management*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>2D6</td>
<td>Stroke, TIA, TD, agranulocytosis, hyperglycemia</td>
<td>Reduce dose by half</td>
<td>Reduce dose by half</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>2D6</td>
<td>↑HR, BP, liver injury</td>
<td>Start at 0.5 mg/kg/day. Titrate at 4wk intervals</td>
<td>Start at 0.5 mg/kg/day. Titrate at 4wk intervals</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>2D6</td>
<td>Stroke, TIA, TD, agranulocytosis, hyperglycemia</td>
<td>Start at half usual dose</td>
<td>Start at half usual dose for 2D6 &amp; 3A4 inhibitors</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B</td>
<td>Stevens Johnson Syndrome/TEN</td>
<td>Genotype if Asian origin: HLA-B*1502: avoid using</td>
<td>None</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2C19</td>
<td>QT prolongation</td>
<td>Max dose 20 mg/day</td>
<td>Max dose 20 mg/day</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>2D6</td>
<td>QT prolongation, tachycardia, hyperglycemia, agranulocytosis</td>
<td>Reduce dose by half</td>
<td>Reduce dose by half</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2D6</td>
<td>QT prolongation, TD, torsades de pointes, cardiac arrest</td>
<td>Genotype if use &gt;4 mg/day. Titrate at 2 week intervals</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>2D6</td>
<td>QT prolongation, TD, torsades de pointes, cardiac arrest</td>
<td>Contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>2D6</td>
<td>Serotonin syndrome, bleeding</td>
<td>Max dose 10 mg/day</td>
<td>Reduce dose by half</td>
</tr>
</tbody>
</table>

*If on strong CYP inhibitor

Conrado et al., Pharmacogenomics 2013; 14:215-23
Regulatory Environment of PGx Tests is Changing

FDA is increasingly concerned that unregulated laboratory developed tests (LDTs) for genomic testing may pose a public health threat

Oct. 31, 2018

The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication


Nov. 1, 2018

Jeffrey Shuren, M.D., J.D., director of the FDA’s Center for Devices and Radiological Health and Janet Woodcock, M.D., director of the FDA’s Center for Drug Evaluation and Research on agency’s warning to consumers about genetic tests that claim to predict patients’ responses to specific medications


April 4, 2019

FDA Warns Against Use of Inova Genomics Laboratory


Feb. 20, 2020

FDA Announces Collaborative Review of Scientific Evidence to Support Associations Between Genetic Information and Specific Medications

The accrual and analysis of genomic sequencing data have identified specific genetic variants that are associated with major depressive disorder. Moreover, substantial investigations have been devoted to identifying gene-drug interactions that affect the response to antidepressant medications by modulating their pharmacokinetic or pharmacodynamic properties. Despite these advances, individual responses to antidepressants, as well as the unpredictability of adverse side effects, leave clinicians with an imprecise prescribing strategy that often relies on trial and error. These limitations have spawned several combinatorial pharmacogenetic testing products that are marketed to physicians. Typically, combinatorial pharmacogenetic decision support tools use algorithms to integrate multiple genetic variants and assemble the results into an easily interpretable report to guide prescribing of antidepressants and other psychotropic medications. The authors review the evidence base for several combinatorial pharmacogenetic decision support tools whose potential utility has been evaluated in clinical settings. They find that, at present, there are insufficient data to support the widespread use of combinatorial pharmacogenetic testing in clinical practice, although there are clinical situations in which the technology may be informative, particularly in predicting side effects.
Commercially Available PGx Decision-Support Tools
Overview of PGx Report Generation

Genetic Analysis Platform

Genotype data

PGx Clinical guidelines

Drug labeling

Other PGx info

*e.g. Published studies not incorporated into guidelines or drug labels

Database

1. Gene-drug interactions
2. Drug-drug interactions
3. Clinical condition-drug interactions

Algorithm

Drug-specific recommendations

PGx Report

Perez et al., BMC Psychiatry, 2017; 17:250
Genes Analyzed across PGx Tests Vary Substantially

Bousman & Hopwood, Lancet Psychiatry, 2016; 3:585-90
Even if including same genes, DSTs may differ in the specific allele variants tested

CYP2D6 and 2C19 Star Alleles across PGx Tests

<table>
<thead>
<tr>
<th>PGx Test Name</th>
<th>Manufacturer</th>
<th>Number of MDD RCTs</th>
<th>Incorporates Drug-Drug-Gene Interactions?</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Amplis                  | Luminus (CNS Dose)       | 1                  | No                                       | 1. Lower dose  
                               |                                         | 2. Average dose  
                               |                                         | 3. Higher dose  |
| Genecept Assay          | Genomind                 | 1                  | Yes                                      | 1. Use as Directed/Therapeutic Options  
                               |                                         | 2. Use with Caution                      |
| GeneSight Psychotropic  | Myriad Neuroscience       | 2                  | No                                       | 1. Use as Directed  
                               |                                         | 2. Use with Caution  
                               |                                         | 3. Use with Caution and ↑ Monitoring     |
| NeuroIDgenetix          | AltheaDx                 | 1                  | Yes                                      | 1. Use as Directed  
                               |                                         | 2. Use with Caution or ↑ Monitoring       |
| Neuropharmagen          | AB Biotics               | 2                  | No                                       | 1. Increased response or ↓ risk of ADRs  
                               |                                         | 2. Standard response  
                               |                                         | 3. Reduced response or ↑ Monitoring      
                               |                                         | 4. ↑ Risk of adverse drug reactions (ADRs) |
## Genes Included in Specific PGx DSTs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Amplis</th>
<th>Genesight</th>
<th>NeuroIDGenetix</th>
<th>Genecept v.2.0</th>
<th>Neuropharmagen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHARMACO-KINETIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP1A2</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>CYP3A5</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABCB1</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td><strong>PHARMACO-DYNAMIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLC6A4</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HT2A</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>5HT2C</td>
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<td>x</td>
<td></td>
<td></td>
<td>X</td>
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<td>COMT</td>
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<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>BDNF</td>
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<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>MTHFR</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td>7</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>
How Interchangeable are PGx DSTs?

Medication Recommendations

Bousman & Dunlop, The Pharmacogenomics Journal, 2018; 18(5):613-622
Except for the Amplis/CNS Dose test, each company’s largest trial failed to achieve statistical significance on the pre-specified primary outcome:

- Mean symptom change (Genesight, Genecept)
- Adverse drug reaction frequency (Neuropharmagen, NeuroIDgenetix)

<table>
<thead>
<tr>
<th>PGx DST</th>
<th>Significant Continuous Outcome</th>
<th>Significant Remission and/or Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplis/CNS Dose</td>
<td>n.r.</td>
<td>Yes</td>
</tr>
<tr>
<td>Genesight</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuropharmagen</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Genecept</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NeuroIDgenetix - “Severe” subset</td>
<td>n.r./No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Remission Rates across 5 PGx DSTs

<table>
<thead>
<tr>
<th>PGx DST</th>
<th>N Analyzed</th>
<th>Mean # Drug Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Dose/Amplis</td>
<td>148</td>
<td>n.r.</td>
</tr>
<tr>
<td>Genesight</td>
<td>1,167</td>
<td>3.5</td>
</tr>
<tr>
<td>Neuropharmagen</td>
<td>316</td>
<td>2.5</td>
</tr>
<tr>
<td>Genecept</td>
<td>296</td>
<td>1.4 (est.)</td>
</tr>
<tr>
<td>NeuroIDgenetix</td>
<td>93</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

*“Severe” subset

NNG: Number needed to genotype to get one additional remission

Neuropharmagen: Perez et al., BMC Psychiatry, 2017; 17:250
Genecept: Perlis et al., Depress Anxiety, 2020, epub.
NeuroIDgenetix: Bradley et al., J Psychiatr Res, 2018; 96:100-107
Distributions of % Change in GUIDED Trial

Greden et al., *J. Psychiatr Res*, 2019, 111:59-67 (suppl)

Forester et al., *Am J Geriatr Psychiatry*, 2020, epub
## Meta-Analysis of PGx RCTs for MDD Remission

### Relative Risk for Remission with PGx Testing

**‘Patient-specific RRR’ vs ‘Pooled RRR’**

- **“Patient-specific RRR”**: Benefit of PGx-informed prescribing for an individual with an actionable genotype

- **“Pooled RRR”**: Benefit in entire cohort (dilutes patient-specific RRR)

Relationship is a function of the frequency of actionable genotypes

---

### Table: Risk Ratio for Remission with PGx Testing

<table>
<thead>
<tr>
<th>Study</th>
<th>Guided Remission Total</th>
<th>Unguided Remission Total</th>
<th>Risk ratio</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greden et al. 2018</td>
<td>93</td>
<td>607</td>
<td>1.51</td>
<td>[1.11; 2.05]</td>
<td>28.4</td>
</tr>
<tr>
<td>Winner et al. 2013</td>
<td>5</td>
<td>25</td>
<td>2.40</td>
<td>[0.51; 11.21]</td>
<td>5.1</td>
</tr>
<tr>
<td>Singh 2015</td>
<td>53</td>
<td>74</td>
<td>2.52</td>
<td>[1.71; 3.73]</td>
<td>25.5</td>
</tr>
<tr>
<td>Perez et al. 2017</td>
<td>48</td>
<td>141</td>
<td>1.03</td>
<td>[0.74; 1.43]</td>
<td>27.7</td>
</tr>
<tr>
<td>Bradley et al. 2018</td>
<td>14</td>
<td>40</td>
<td>2.65</td>
<td>[1.18; 5.95]</td>
<td>13.3</td>
</tr>
</tbody>
</table>

### Graph: Relative Risk for Remission with PGx Testing

Relationship is a function of the frequency of actionable genotypes

---

### Notes


Effect of PGx Guided Treatment in Patients with an identified Gene-Drug Interaction

Thase et al., J Clin Psychiatry, 2019;80(6). pii: 19m12910
Conclusions 1

• Determining the utility and clinical timing of conducting PGx testing to inform drug prescribing is a work in progress
  – FDA regulation of PGx LDTs is likely to increase

• Variability across PGx DST’s gene profiles and trial outcomes limits making generalizable testing recommendations.

• A critique common to all PGx RCTs is the lack of blinding of the treating clinician to treatment arms
  – Cannot rule out expectancy/placebo or therapeutic zeal effects

• The remarkable finding of non-significant mean improvement, but higher remission rates, suggest PGx DSTs have a sizeable benefit in a small proportion of all tested patients, which is insufficient to drive average overall change.
Conclusions 2

• RCTs of PGx DSTs demonstrate the challenge of developing biologically-based precision-medicine approaches to MDD

  1. Difficult to show differences in RCTs comparing two arms with active treatment (i.e., no placebo)
  2. PGx RCTs are a blend of efficacy and effectiveness trial designs, in that prescribers do not need to follow the testing recommendation. Indeed, many do not.
  3. For the majority of patients PGx test results are not informative for antidepressant selection, greatly reducing statistical power.

• Clinical Conundrum:
  • Patients who are on a genetically-incongruent medication are mostly likely to benefit from PGx-guided care
  • BUT: Can’t know if genetically incongruent until tested!