Moving Beyond Single Gene-Drug Pairs in Clinical Pharmacogenomics Testing

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Learning Objectives

• Describe the strengths and limitations of pharmacogenomic testing.
• List examples of single gene-drug associations with the strongest levels of evidence for clinical implementation.
• Discuss cautions when considering the use of multi-gene drug associations to inform drug therapy decisions.
Disclosure

• None
Outline

• Single gene-drug based pharmacogenomics (PGx) testing
  – An introduction
  – Evidence and examples
  – Considerations for developing and evaluating clinical PGx laboratory developed tests (LDTs)

• Multi-gene PGx panels
  – Evidence and examples
  – PROs and CONs for utilizing PGx panels
  – Considerations for successful PGx implementation
Single Gene-Drug Based PGx Testing

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Associate Professor (Clinical) of Pathology, University of Utah
Medications: Myths and Facts

- ~30% people take at least one medication within a 30-day period
- Most medications cause adverse drug events (ADEs)
- Some medications like antibiotics may do more harm than good
- CDC statistics:
  - ~ 200,000 ADEs-related ER visits in pediatric population (17 years or younger)
  - ~ 450,000 ADEs-related ER visits in older adults (65 years or older)
  - Medications, e.g., anticoagulant warfarin
- Many ADEs are preventable by closely supervising of dosing, blood tests (therapeutic drug monitoring, TDM), or PGx test
Pharmacogenomics or Pharmacogenetics is the study of inheritance or acquired genomic changes on drug response phenotypes.
Pharmacokinetics (PK)
“What the body does to a drug”

- Absorption
- Distribution
- Metabolism
- Excretion

Pharmacodynamics (PD)
“What a drug does to the body”

- Target organ/tissue
- Receptor, protein
- Signaling pathway
- Physiologic effects
- Mechanism of action

Plasma drug concentration
Drug Metabolism

Drug molecule → phase 1 → Reactive metabolite → phase 2 → Conjugate → Urine

Phase I enzymes include:
- CYP1A1/2
- CYP1B1
- CYP2A6
- CYP2B6
- CYP2C8
- CYP2C9
- CYP2C19
- CYP2D6
- CYP2E1
- DPD
- NQO1
- ALDH
- ADH
- Epoxy hydrolase
- Esterases
- Others

Phase II enzymes include:
- NAT1
- NAT2
- GST-M
- GST-T
- GST-P
- GST-A
- STs
- UGTs
- HMT
- COMT
- TPMT

Factors Influencing Drug Response Phenotypes

- Genotype
  - CYP2D6 genes
  - NAT genes
  - Ethnic variation

- Physiology
  - Age
  - Gender
  - Pregnancy
  - Heart health
  - Immune system
  - Liver function
  - Kidney function
  - GI function

- Environment
  - Diet
  - Supplements & herbs
  - Smoking
  - Alcohol intake
  - Exercise
  - Stress

- Lifestyle
  - Daily/seasonal rhythms
  - Occupational exposure
  - Other medications
  - Infection
  - Disease

Clinical Pharmacology & Therapeutics

OMICS
- Metagenomics
- Transcriptomics
- Metabolomics
- Microbiomics
- Proteomics

Pharmacogenomics

UHEALTH
Utilities of Clinical PGx Testing

• Patient selection
  – Identify patient at high risk for a serious ADE
  – Identify patient not likely to respond
  – Identify patient likely to be sensitive or resistant to a drug, and require non-standard dosing

• Optimize therapy
  – Optimize dosing to a specific drug for maximum efficacy and minimum toxicity
  – Avoid toxicity and drug-drug interaction
  – Reduce medical expense
Association for Molecular Pathology Position Statement:
Best Practices for Clinical Pharmacogenomic Testing – September 4, 2019

The field of pharmacogenomics is steadily growing, and the FDA has already approved the inclusion of pharmacogenomic information in the labels of hundreds of medications. As the prevalence of pharmacogenetic testing continues to increase, so will the need for laboratory professionals to translate genetic laboratory results to healthcare providers who make prescribing decisions for patient care. Pharmacogenomic tests that are offered clinically should demonstrate evidence of clinical validity before being offered to patients, the same standard as for other practices of medicine. Such evidence may be established and/or demonstrated through peer-reviewed literature, clinical practice guidelines, and/or FDA drug labels.
Single Gene-drug Based PGx Testing

• Drug-gene pairs: strongest evidence
• Many guidelines are single gene-drug pair based
  – Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy – Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) etc.
• FDA drug label information
• Evidences and examples:
  • TPMT and 6-mercaptopurine
  • CYP2C19 and clopidogrel
  • HLA-B*5701 and abacavir
  • UGT1A1 and irinotecan
  • CYP2D6 and codeine
  • CYP2D6 and tamoxifen
• Most LDTs use a targeted genotyping approach
**TPMT and Thiopurines**

Weinshilboum and Sladek, 1980
**Evidence Supporting TPMT-Thiopurines Associations**

**TABLE S1. EVIDENCE LINKING TPMT GENOTYPE WITH THIOPURINE PHENOTYPE**

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo, preclinical or clinical)</th>
<th>Major findings</th>
<th>References</th>
<th>Level of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro</td>
<td>MP's catabolism to methylmercaptopurine absent in human erythrocytes, lymphocytes, liver, and kidneys from TPMT homozygous deficient individuals</td>
<td>Weinshilboum, et al. (1980) (65)</td>
<td>High</td>
</tr>
<tr>
<td>In vitro</td>
<td>TPMT genotype correlates with TFMT activity measured by biochemical assay (variant genotypes have lower activity in general, but activity cannot be explained by genotype alone because the *1/*1 and variant (het) activities overlap)</td>
<td>Reiling, et al. (1999) (63)</td>
<td>High</td>
</tr>
<tr>
<td>In vitro</td>
<td>7G's catabolism to methylthio guanine</td>
<td>Moore, et al. (1955B) (69)</td>
<td>High</td>
</tr>
<tr>
<td>In vitro</td>
<td>TPMT variant genotype associated with increased TGN levels and/or lower MMPN levels</td>
<td>Lenardi, et al. (2013) (127)</td>
<td>High</td>
</tr>
<tr>
<td>In vitro</td>
<td>Heterologous expression of TPMT catabolizes mercaptopurine to methylmercaptopurine, thioguanine to methylthio guanine, and 6MP to methyl6MP</td>
<td>Hill, et al. (1971) (73)</td>
<td>High</td>
</tr>
</tbody>
</table>

*Note: The level of evidence is based on the strength and consistency of the evidence supporting the association.*

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**Clinical**

- TPMT genotype correlates with TFMT activity measured by biochemical assay (variant genotypes have lower activity in general, but activity cannot be explained by genotype alone because the *1/*1 and variant (het) activities overlap.)
- TPMT variant genotype associated with increased TGN levels and/or lower MMPN levels.
- TPMT variant genotype associated with incidence of gastrointestinal ADRs.
Evidence and Clinical Utility for PGx Testing: the RCT Approach
Randomized Controlled Trials

- *HLA-B*5701 - abacavir, PREDICT-1 trial, 1956 patients with HIV randomized to prospective genetic screening with avoidance of abacavir in patients with screening positive or to abacavir without screening (Mallal et al, NEJM, 2008)

- *TPMT* - thiopurines, TOPIC trial, 783 patients with inflammatory bowel disease randomized to pre-treatment screening with thiopurine dose reduction in *TPMT* carriers (one or more *TPMT* functional alleles) to usual dosing without preemptive genotyping (Coenen et al, Gastroenterology, 2015)

- *CYP3A5* - tacrolimus, 280 renal transplant recipients randomized to *CYP3A5*-guided tacrolimus dosing vs. standard dosing regimen (Thervet et al, CPT, 2010)

Evidence for Clinical Utility of PGx Testing: Other Approaches

• Evidence for supporting clinical utility is important

• **RCTs**: the gold standard
  – Expensive
  – Ethic issues, e.g., *HLA*1502 allele-related ADE, Stevens-Johnson syndrome
  – Well controlled setting with strict eligibility criteria

• **Pragmatic studies**: to gather evidence of in the context of clinical practice
  – More generalizable, selection biases/confounding factors minimized
  – Less rigorous to conduct
CYP2C19 and Clopidogrel

• Antiplatelet clopidogrel is a prodrug to prevent heart attacks and strokes in persons with heart disease or after certain procedures

• CYP2C19 enzyme is a major enzyme for its bioactivation

• Increased risk for cardiovascular adverse events in patients after percutaneous coronary intervention (PCI)

• Nonfunctional alleles are common, i.e., ~30% in Caucasian and African Americans, ~60% in Asians
CYP2C19 and Clopidogrel: Clinical Studies

- **TAILOR-PCI trial** (May 2013 – March 2020)
  - A multi-site (41 locations), open label, prospective, randomized trial, n=5300
  - Hypothesis tested: post-PCI patients using ticagrelor is superior to clopidogrel in reducing rate of major adverse cardiovascular events in CYP2C19 reduced function allele (*2 or *3) patients
  - PI: Naveen L. Pereira, Mayo Clinic

- **POPular Genetics** (June 2011 – April 2019)
  - A multi-site (10 locations, 8 in Netherland, Italy, and Belgium), randomized, parallel assignment-based intervention study, n=2488
  - To compare clinical outcomes (adverse events, safety endpoint of using alternative drugs, pharmacoeconomics) between intervention and non-intervention groups
  - The intervention group: genotyped for CYP2C19 nonfunctional allele variants within 48 hours after primary PCI. Carriers will receive either ticagrelor or prasugrel instead of clopidogrel; Non-carriers will be treated with clopidogrel
  - The control group receives either ticagrelor or prasugrel, according to local standards at the same dosage as the CYP2C19*2 or *3 carriers in the intervention group
CONCLUSIONS

In patients undergoing primary PCI, a CYP2C19 genotype–guided strategy for selection of oral P2Y$_{12}$ inhibitor therapy was noninferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events and resulted in a lower incidence of bleeding. (Funded by the Netherlands Organization for Health Research)
Factors to Consider When Developing and Evaluating a Clinical PGx LDT

- Understand the reasons for ordering PGx tests
  - Preemptive testing or reactive (post-event)
- Evaluate the test contents not only at the gene level but also at the variant level
  - Not two PGx tests are the same
  - More genes ≠ better
- Test technical performance and workflow
- Genotypes ≠ phenotypes
- Apply guidelines when appropriate
- Testing results should be interpreted by clinicians/pharmacists
- Testing results should be utilized together with patients’ other clinical information
Contents of Single-Gene PGx Tests: Variants

No two clinical PGx assays testing the same variants and/or haplotypes

Pratt VM, et al., 2016 (GeT-RM)
AMP Recommendations for Clinical PGx Laboratories: Allele/Variant Selection (*CYP2C19, CYP2C9*…)

The Journal of Molecular Diagnostics, Vol. 20, No. 3, May 2018

SPECIAL ARTICLE

Recommendations for Clinical *CYP2C19* Genotyping Allele Selection

*A Report of the Association for Molecular Pathology*

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Professional Guidelines/Regulations for Clinical PGx Practice

CPIC guideline or known clinical implementation

Level 1a, Level 1b
high

Level 2a, Level 2b
moderate

Level 3
low

Level 4
preliminary

variant in PharmGKB VIP

Evidence

CPIC
Clinical Pharmacogenetics Implementation Consortium

PharmGKB

AMP
Association for Molecular Pathology

FDA
The fraction of 1013 RIGHT subjects among groups carrying actionable PGx variants in 0 to 5 of the PGx genes (*CYP2C9, CYP2C19, CYP2D6, VKORC1*, and *SLCO1B1*)

Multi-Gene PGx Panels

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Medical Director of Toxicology and PGx, ARUP Laboratories

Professor (Clinical) of Pathology, University of Utah
FDA Drug Labels that Contain PGx
(n=362 entries in August, 2019)

18 clinical indications

Top 10:
- Oncology (n=140)
- Infectious Disease (n=35)
- Psychiatry (n=35)
- Neurology (n=25)
- Anesthesiology (n=23)
- Hematology (n=20)
- Cardiology (n=17)
- Gastroenterology (n=16)
- Pulmonary (n=9)
- Rheumatology (n=9)

77 genes

Top 10:
- CYP2D6 (n=66)
- G6PD (n=39)
- CYP2C19 (n=22)
- ESR, PGR (n=15)
- ERBB2 (n=14)
- IFNL3 (n=12)
- BCR-ABL1 (n=10)
- CYP2C9 (n=10)
- RYR1 (n=10)
- UGT1A1 (n=9)

https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
## Examples of Drugs with Multiple Germline PGx Associations

### Cardiology / Coagulation

<table>
<thead>
<tr>
<th>Drug (generic name)</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>carvedilol</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>clopidogrel</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>flecainide</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>lidocaine</td>
<td>G6PD</td>
</tr>
<tr>
<td>metoprolol</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>phenprocoumon</td>
<td>CYP4F2</td>
</tr>
<tr>
<td>propafenone</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>propranolol</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>quinidine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>timolol</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>warfarin</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>warfarin</td>
<td>CYP4F2</td>
</tr>
<tr>
<td>warfarin</td>
<td>VKORC1</td>
</tr>
</tbody>
</table>

### Behavioral Health

<table>
<thead>
<tr>
<th>Drug (generic name)</th>
<th>Gene</th>
<th>Drug (generic name)</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>amitriptyline</td>
<td>CYP2C19</td>
<td>iloperidone</td>
<td>CYP2C6</td>
</tr>
<tr>
<td>amitriptyline</td>
<td>CYP2D6</td>
<td>imipramine</td>
<td>CYP2C6</td>
</tr>
<tr>
<td>aripiprazole</td>
<td>CYP2D6</td>
<td>imipramine</td>
<td>CYP2C6</td>
</tr>
<tr>
<td>brexipiprazole</td>
<td>CYP2D6</td>
<td>methylphenidate</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>brivaracetam</td>
<td>CYP2C19</td>
<td>midazolam</td>
<td>CYP3A5</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>HLA-A*31:01</td>
<td>mirtazapine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>HLA-B*15:02</td>
<td>modafinil</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>carvedilol</td>
<td>CYP2D6</td>
<td>nortriptyline</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>celecoxib</td>
<td>CYP2D6</td>
<td>olanzapine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>citalopram</td>
<td>CYP2C19</td>
<td>oxcarbazepine</td>
<td>HLA-A</td>
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<td>clobazam</td>
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<td>oxcarbazepine</td>
<td>HLA-B*15:02</td>
</tr>
<tr>
<td>clozapine</td>
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<td>paroxetine</td>
<td>CYP2D6</td>
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<tr>
<td>clomipramine</td>
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<td>phenytoin</td>
<td>CYP2C9</td>
</tr>
<tr>
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<td>CYP2D6</td>
<td>phenytoin</td>
<td>HLA-B*15:02</td>
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<td>desipramine</td>
<td>CYP2D6</td>
<td>protriptyline</td>
<td>CYP2D6</td>
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<td>diazepam</td>
<td>CYP2C19</td>
<td>risperidone</td>
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<td>doxepin</td>
<td>CYP2C19</td>
<td>sertraline</td>
<td>CYP2C6</td>
</tr>
<tr>
<td>doxepin</td>
<td>CYP2D6</td>
<td>sertraline</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>duloxetine</td>
<td>CYP2D6</td>
<td>timolol</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>escitalopram</td>
<td>CYP2C19</td>
<td>trimipramine</td>
<td>CYP2C6</td>
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<tr>
<td>fenfluramine</td>
<td>CYP2C19</td>
<td>trimipramine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>fenfluramine</td>
<td>CYP2C9</td>
<td>tropisetron</td>
<td>CYP2D6</td>
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<td>CYP2D6</td>
<td>venlafaxine</td>
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<td>fluoxetine</td>
<td>CYP2D6</td>
<td>vorloxetine</td>
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<tr>
<td>fluvoxamine</td>
<td>CYP2D6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Warfarin PGx

- PharmGKB (August, 2019)
  - 1086 variant annotations
  - 88 clinical annotations
  - 4 clinical guidance annotations (CPIC, CPNDS, DPWG)
  - 2 drug label annotations (FDA, HCSC)

- Three genes impact independent aspects of PK and PD
- Many RCTs and dosing algorithms have been published with mixed clinical results
- Barriers to adoption in routine clinical practice?

https://www.pharmgkb.org/chemical/PA451906
Phenytoin PGx

- PharmGKB (August, 2019)
  - 257 variant annotations
  - 33 clinical annotations
  - 2 clinical guidance annotations (CPIC, DPWG)
  - 2 drug label annotations (FDA, HCSC)

- Two genes impact independent aspects of PK and PD

https://www.pharmgkb.org/chemical/PA450947
Barriers to adoption in routine clinical practice?

- **HLA-B*15:02 genotype**
  - **HLA-B*15:02 carrier**
  - **HLA-B*15:02 non-carrier**
  - **CYP2C9 genotype**
    - **CYP2C9 EM**
      - Initiate therapy with recommended maintenance dose.
    - **CYP2C9 IM**
      - Consider 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.
    - **CYP2C9 PM**
      - Consider 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response.

https://www.pharmgkb.org/guideline/PA166122806
Examples of Positive Outcomes from Multi-gene PGx testing

• Improved antidepressant efficacy
  – 2.52-fold greater rate of remission of major depressive disorder with testing (Singh, Clin Psychopharmacology Neuroscience, 2015)

• Reduced pharmacy costs
  – $1035.60 savings over 1 yr in total medication costs with testing in cohort of psychiatric patients (Winner et al, Current Medical Research & Opinion, 2015)

• Reduced rates of hospitalization
  – 9.8% with testing versus 16.1% without testing in cohort of patients ≥65 yrs (Brixner et al, J Medical Economics, 2015)

• Improved adherence with therapy
Are more genes better?

• In a review of 22 proprietary algorithms for clinical validity, there were 46 genes represented (Bousman, Lancet Psychiatry, 2016)
  – 25 (53%) were associated with supporting evidence graded by the PharmGKB databased as preliminary or low
  – 9 (20%) were associated with high levels of evidence: CYP2D6, CYP2C19, and HLA-B
  – All algorithms include CYP2D6 and CYP2C19; most also include CYP2C9 and CYP3A4/5

• 39.1% of patients ≥65 receive at least one drug metabolized by CYP2D6, CYP2C19 and/or CYP2C9 (Kuch et al, Health Informatics, 2016)
Evidence based panel includes 16 variant alleles within five genes:
- CYP2C9, CYP2C19, CYP2D6
- HLA-A, HLA-B

Relevant to antidepressants, antipsychotics, mood stabilizers

Consistent with published CPIC guidelines:
- Tricyclics (n=7)
- Selective Serotonin Reuptake Inhibitors (n=5)
- Atomoxetine
- Anticonvulsants (n=3)


https://cpicpgx.org/guidelines/
### TABLE 1. Antidepressant Drug-by-Gene Associations With Moderate to High Levels of Evidence or Included in One of the Combinatorial Pharmacogenetic Tests Evaluated Here

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmacodynamic</th>
<th>Pharmacokinetic</th>
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<tbody>
<tr>
<td></td>
<td>ADRA2A</td>
<td>BDNF</td>
</tr>
<tr>
<td>Amitriptyline&lt;br&gt;b</td>
<td>3</td>
<td>2B</td>
</tr>
<tr>
<td>Bupropion</td>
<td>3</td>
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<td>Desipramine</td>
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<td>Doxepin&lt;br&gt;b</td>
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<td>Duloxetine&lt;br&gt;b</td>
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<tr>
<td>Fluvoxamine&lt;br&gt;b</td>
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<td>Imipramine&lt;br&gt;b</td>
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<td>Maprotiline</td>
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<tr>
<td>Mirtazapine</td>
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<tr>
<td>Nefazodone&lt;br&gt;b</td>
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<td>Venlafaxine&lt;br&gt;b</td>
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<tr>
<td>Interaction type&lt;br&gt;c</td>
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<td>E, T</td>
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</table>

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This is not a comprehensive representation of antidepressant drug-by-gene associations; it is limited to the PharmGKB search terms “depressive disorder, major; depressive disorder, depression; [antidepressant name]”; it excludes drug-gene interactions related to “bipolar disorder; anxiety disorder”; it excludes anti-psychotic and some antidepressant drugs; and it excludes many drug-gene associations for which low/preliminary (level 3/4) evidence exists, as defined by PharmGKB. The PharmGKB knowledge base, which was used to generate this table, is not the sole source of relevant pharmacogenetic information. BDNF=brain-derived neurotrophic factor; COMT=catechol O-methyltransferase; SSRI=selective serotonin reuptake inhibitor.

These agents have U.S. Food and Drug Administration labeling with CYP450 pharmacogenetic information.

Pharmacogenetic information relevant to drug efficacy (E), dosage (D), metabolism/pharmacokinetics (M), toxicity/adverse drug reactions (T), and other (O).

Values correspond to a high (1A, 1B), moderate (2A, 2B), or low (3) level of evidence according to the PharmGKB rating scale.

**Expanded PGx Panels for Behavioral Health**

<table>
<thead>
<tr>
<th>Possible PROs</th>
<th>Possible CONs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A broad test could provide guidance for a large number of drugs by considering multiple aspects of PK and PD</td>
<td>• Inconsistencies in content among commercially available tests</td>
</tr>
<tr>
<td>• May promote a more intensive review of medications, particularly for polypharmacy patients</td>
<td>• Weighted contribution of multiple gene variants to the drug response phenotype prediction may not have been well studied</td>
</tr>
<tr>
<td>• Many multi-gene tests can be consolidated to minimize time to result and costs</td>
<td>• Reimbursement may be poor for genes that are not represented by FDA labeling or published gene-based dosing guidelines</td>
</tr>
</tbody>
</table>
Using PGx to Manage Moderate to Severe Depression

Fig. 2. Patients’ symptom improvement, response rate, and remission rate from baseline to follow-up in the full cohort (N = 1871).

Using PGx to Manage Moderate to Severe Depression: GUIDED Trial

Fig. 1. Patient outcomes at week 8 in the pharmacogenomics guided-care arm (n = 560) compared to treatment as usual (n = 607). Outcomes were evaluated using the HAM-D17 depression rating scales.

Using PGx to Manage Moderate to Severe Depression: GUIDED Trial

Fig. 4. Patient outcomes among those who were taking incongruent medications at baseline in both study arms (n = 213). Patients were evaluated according to whether they were prescribed congruent (n = 77) or incongruent (n = 136) medications at week 8. Outcomes were evaluated using the HAM-D17 depression rating scale.

Published Cost Savings with PGx for Antidepressant Therapy

Table 4 Published per-patient savings using genetic testing to guide medication management (adjusted to 2016 dollars)

<table>
<thead>
<tr>
<th></th>
<th>Present findings 2016</th>
<th>Winner et al&lt;sup&gt;27&lt;/sup&gt;</th>
<th>Chou et al&lt;sup&gt;28&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-patient savings</td>
<td>USD$5,962</td>
<td>USD$6,193</td>
<td>USD$7,112–USD$10,667</td>
</tr>
</tbody>
</table>

Maciel et al, *Neuropsych Dis Treat* 14:225-30, 2018
Factors that Contribute to Successful Implementation of PGx

- Multi-disciplinary approach
  - Laboratory
  - Pharmacy
  - Providers
  - Administrators/Payers
  - Regulators
- Transparency about when to order which tests; single-gene or multi-gene panels
- Consensus on how results will be utilized
- Education

Priority should be on promoting safety and good patient care!
Conclusions

• PGx targets predict discrete aspects of pharmacology
• Clinical applications of PGx should align with needs, and consider the evidence behind any drug-gene association
• Non-genetic factors are also critical components of medication management
• No PGx test can replace the need for clinical and therapeutic monitoring
• Successful implementation requires an multi-disciplinary approach
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