**Pharmacogenomics and Behavioral Health**
Kimberly Erlich, MSN, RN, MPH, CPNP, PMHS

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**Speaker Introduction**

- Kimberly Erlich is a pediatric nurse practitioner specializing in behavioral health and practicing in a variety of outpatient psychiatric specialty settings, including intensive outpatient and partial hospitalization programs for youth with depression, anxiety and eating disorders. She is also a faculty member in the PNP program at Duke University School Nursing. Prior to her current practice, she coordinated a primary care-behavioral health integration project to expand access to behavioral health for adolescents in Northern California. She also previously worked in child neurology at an academic medical center, where she cared for patients with diverse neurologic disorders, including neurodevelopmental, genetic, learning, demyelinating and headache disorders. Prior to entering specialty practice, the bulk of her experience was in pediatric and adolescent primary care. She received her MSN from Yale University, and holds a MPH in maternal and child health from Tulane University.

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**Disclosures**

- The author has no disclosures, no conflicts of interest, monetary or otherwise, and this talk does not specifically discuss the use of either FDA or non-FDA-approved medications, although such treatment may be mentioned.
- However, the use of pharmacogenomic testing in clinical practice is, as yet, not considered standard of care.

**Disclaimer**

- The information contained herein was current as of the deadline for submission of the slides. The author will make every effort to update the information in this dynamic field should there be changes.

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**Learning Objectives**

1. Describe the rationale for and the benefits of the use of pharmacogenomic testing (0.25 Rx).
2. Recognize available and emerging pharmacogenomic technologies relevant for developmental-behavioral and mental health care (0.25 Rx).
3. Describe how gene mutations impact pharmacotherapeutic management of common behavioral disorders (e.g., depression, anxiety, ADHD) in the pediatric population (0.5 PsyRx).

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**Psychopharmacology Contact Hours**

This presentation has been approved for 0.5 psychopharmacology contact hours, as it includes pharmacology content that relates to psychotropic agents. A portion of the content of this presentation focuses on opportunities related to the use of medications and other substances utilized for their effect on behavior and the mind, particularly in the context of treatment of mental disorders, and the indications, contraindications, use, dosing, monitoring and adverse effects.

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**Application to Practice**

- At least 25% of youth aged 9-17 have a diagnosable psychiatric disorder that causes impairment.
- A significant portion of these youth will take psychoactive medication during their lifetime. Antidepressants, stimulants, and antipsychotics are among those most commonly prescribed.
- Psychoactive medications interact with multiple metabolic pathways; genetic variants contribute to heterogeneity of medication response, including efficacy, tolerability, and safety.
- Understanding pharmacogenomics supports pediatric clinicians in offering the most current evidence-based interventions possible.
Pharmacogenomics

- A discipline that uses information about individual genetic makeup to choose the meds and doses most likely to work best for that individual

- Intention is to:
  - Minimize potential side effects
  - Maximize probability for med effectiveness

Genetic Polymorphisms

- Individual variations that contribute to pharmacokinetic & pharmacodynamic properties of medications
- Genetic variation occurs for drug metabolism, drug transporter proteins, drug target proteins, and disease-associated proteins
- Single-nucleotide polymorphisms (SNPs) are most common variation associated w/drug response
- May also influence efficacy or toxicity of medications

A Review of Pharmacokinetics

- A, D, M, E + bioavailability determines:
  - concentration
  - onset
  - duration
  - Intensity
- Pharmacokinetics involves transport of drug across biological membranes

A Review of Pharmacodynamics

- Medications act by binding to receptors (mechanism of action)
- Cause either activation or inhibition of biological processes to produce a response (drug action)
- Responsible for the dose-effect relationship
- Modulated by:
  - Medication receptor status
  - Genetic factors
  - Medication interactions
  - Medication tolerance

Utility of PGx Testing in Psychiatry and Behavioral Health

- Psychoactive meds interact w/multiple metabolic pathways
- Genetic variants contribute to differences in response among humans
  - Genetic variants influence metabolism and may require dose modification
  - Genetic variants predict poor response, tolerability, or safety issues
- Testing assesses potential for gene-drug interactions, such as enzyme activity and metabolism
- Labels on >40 FDA-approved neuropsychiatric meds currently list gene-drug interactions

Another Way to Think About Pharmacogenomics

The study of how genetics influences drug pharmacokinetics and pharmacodynamics to impact treatment outcomes.
Sample List of Common Genes Relevant to Behavioral Health

Pharmacokinetic Genes:
- CYP2D6
- CYP2C19
- CYP3A4
- CYP3A5

Pharmacodynamic Genes:
- MTHFR
- BDNF
- COMT
- SLC6A4
- CACNA1C
- ABCB1
- HLA genes

Dubovsky, 2015

Relevance of PGx Testing for Behavioral Disorders

- Most commercially available tests use a combination of pharmacokinetic (PK) & pharmacodynamic (PD) gene panels
  - Panels typically grouped by condition (e.g., ADHD, depression)
- Each company’s algorithm for relative contribution of each gene is proprietary
- Most psychoactive meds metabolized by ≥1 CYP enzymes (PK)
- Drug labeling often recommends dose adjustments based on CYP status (PK)
- Ex: For SSRIs metabolized by CYP pathway, testing can show metabolizer phenotype which helps prescriber target dosing (PK)
  - There are five different phenotypes: poor, intermediate, normal, rapid, ultrarapid

Metabolizer Phenotypes

<table>
<thead>
<tr>
<th>Metabolizer Phenotype</th>
<th>Combination of Alleles</th>
<th>Level of Enzymatic Activity/Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>Alleles with no or decreased function</td>
<td>Little to no enzyme activity, with increased risk of AEs and drug failure</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Alleles with normal, reduced, and/or no function</td>
<td>Between normal and poor</td>
</tr>
<tr>
<td>Normal</td>
<td>Alleles with normal and/or decreased function</td>
<td>Fully functional</td>
</tr>
<tr>
<td>Rapid</td>
<td>Alleles with normal and increased function</td>
<td>More than normal but less than ultrarapid</td>
</tr>
<tr>
<td>Ultrarapid</td>
<td>2 increased function or &gt;2 normal function alleles</td>
<td>Greatest enzymatic activity, with increased risk of AEs and reduced efficacy</td>
</tr>
</tbody>
</table>


How Metabolizer Phenotypes May Guide Prescribing*

*This illustration is an example ONLY to facilitate understanding; please refer to guidelines and labeling re: gene-drug interactions

Using PGx Testing to Support Prescribing Practices

- Before Prescribing:
  - Helps match patients to medications that are more likely to be effective for them and less likely to cause side effects
- After Prescribing:
  - Used to evaluate unanticipated drug reactions/sensitivities and treatment resistance

Bousman, et al, 2017

Examples of Pharmacogenomic Decision Support Tools in Psychiatry

Bousman, et al, 2017
Case-Based Approach: MDD + GAD

• 15 yr-old adolescent Caucasian female with MDD + GAD X 4 yrs, chronic migraine
• Current Meds: Fluoxetine at 40 mg daily dose (helped DEP somewhat but not ANX, pt feels has caused ↑ restlessness, possibly worse ANX); Topiramate for migraine prophylaxis
• Med Hx:
  o Sertraline to 100 mg (subjective worsening of mood swings)
  o Escitalopram to 20 mg, did not help after 2.5 mos
• Patient a candidate for PGx testing d/t unanticipated response to appropriate trials of 3 different SSRIs

Case Study, MDD + GAD, cont’d.

Selected Results:

- Pharamacogenomic testing brings up these considerations:
  o Results may help explain why pt has not had anticipated response to SSRI antidepressants (r/t altered BDNF secretion)
  o May want to consider SSRI + l-methylfolate supplementation
  o May want to consider SSRI + intentional exercise regimen
  o May want to consider switching to SNRI based on val/met BDNF status (e.g., duloxetine)

- Therapeutic options:
  - Increased level of physical activity/exercise clinically indicated
  - l-methylfolate may be used if clinically indicated

Case Study, MDD + GAD, cont’d.

• 7 yr-old Caucasian male with ADHD, combined type. Not on meds.
• Trx Hx:
  o Behavioral therapy X 5 mos, as parents initially preferred no-medication approach; somewhat helpful for in-classroom impulsive behaviors but less helpful for inattention and behaviors occurring in the home.
  o Parents now willing to consider stimulant medication based on guidance from pediatric clinician; considering methylphenidate (Ritalin)
  o Mother works in biotech, heard about testing, and requests it for her child.
• What genes are of interest?
  - **ADRA2A**
  - **COMT**
  - **CYP2D6**
  - **SLC6A 3,5 and DRD 4,2**

  - **Rationale for testing:**
    - Adrenergic neurotransmission hypothesized to play role in attentional processes
    - Initial studies showed positive association between ADRA2A polymorphisms and MPH response

- **COMT**
  - Data suggest an association between Val/Val homozygosity and positive MPH response and also that COMT polymorphisms are associated with less irritability and somatic side effects with MPH tr

- **How about CYP2D6 testing and consideration of atomoxetine?**
  - Testing to determine metabolizer phenotype
  - Patient found to be a **CYP2D6 poor metabolizer** (*4/*4 genotype, connoting no functional alleles); ↓metabolism of atomoxetine could result in ↑concentrations of drug for pt. How would this impact dosing considerations for atomoxetine?
  - Pt at risk for side effects, but also may have greater improvement of ADHD sx. Poor metabolizer status is associated with lower final dose requirements as compared to non-poor metabolizers.

- **How would this information would be represented on PGx testing?**
  - Actual patient results (blinded) from Genomind

- **Many difficulties with study replication and many instances of reasonable-quality studies showing opposite responses**
- **Current recommendation:**
  - PGx not ready for prime-time for use in guiding ADHD pharmacotherapy in pediatrics, though guidelines for dosing recommendations based on testing do exist
“At the moment, additional studies are required to allow for a shift from a trial-and-error approach to a more rational pharmacologic regimen that takes into account the likelihood of treatment effectiveness at the individual level.”
-Kieling, et al, 2010

Potential Benefits of PGx Testing
- Decreased morbidity
- Improved treatment response
- Decreased treatment-related side effects
- Decreased cost of care for patient/family

Does the Research Support PGx Testing?
- Data suggest pharmacokinetic genes responsible for metabolism/tolerance vulnerabilities
- Data suggest pharmacodynamic genes responsible for response potential
- Pediatric studies to date have focused on individual gene variants & association with either treatment outcome or medication tolerance; however, these studies suggest that future research should focus on which genes are relevant to which medications in determining either tolerance or outcome
- Need more Peds studies!

Impact of Pharmacogenomics on Clinical Outcomes in MDD in the GUIDED trial: A Large, Patient and Rater-blinded, Randomized, Controlled Study
- N=1398 adults w/MDD treated for 24 weeks; previously failed one medication trial
- Randomized to: PGx guided (N=681) or unguided (TAU) (N=717)
- At week 8 symptom improvement was not significantly different
- Response rate (HAM-D) PGx: 26%; TAU:19.9%
- Remission: PGx: 15.3%; TAU: 10.1%
- Genes studied: multiple PK, PD
- Industry-supported

Efficacy of Prospective Pharmacogenetic Testing in Treatment of MDD: Results of a Randomized, Double-blind Clinical Trial
- N=280 Spanish adults
- Randomized to PGx guided (N=136) or unguided (N=144)
- Response rate (HAM-D): PGx=51%; TAU=36%
  - Lower side effects
  - Genes studied: 30 PK and PD genes
- Industry-supported

Pharmacogenetic Tests and Depressive Symptom Remission: A Meta-analysis of Randomized Controlled Trials
- Meta-analysis of 5 RCTs included 1737 eligible subjects
- Patients receiving pharmacogenetic-guided therapy (N=887) were 1.71 times more likely to achieve symptom remission compared with individuals who received TAU (N=850)
- PGx-guided prescribing has a positive effect on the likelihood of achieving symptom remission in MDD in adults

Impact of Pharmacogenomics on Clinical Outcomes in MDD in the GUIDED trial: A Large, Patient and Rater-blinded, Randomized, Controlled Study

Efficacy of Prospective Pharmacogenetic Testing in Treatment of MDD: Results of a Randomized, Double-blind Clinical Trial
Pharmacogenetics of Sertraline Tolerability & Response in Pediatric Anxiety & Depressive D/O

- Retrospective study of EMR of >4,000 inpatients with pharmacokinetic testing
- N=369 of <19 years with anxiety and/or depression treated with sertraline
  o Tolerability group n=352; tracked 10 side effects
  o Response group n=199: CGI-I
- Outcome measure: CGI-I
- CYP450 2C19 genotyping; pharmacodynamic tests= HTR2A, GRIK4, SLC6A4
- Results:
  o Response: Pts w/low level of expression of SLC6A4 treated longer
  o Tolerability: Varied by maximum dose, number of concomitant meds, tx duration

Clinical Guidelines

- Clinical Pharmacogenetics Implementation Consortium (CPIC)
  o Multidisciplinary, international, rigorously, NIH-supported effort to assess clinical relevance of drug-gene pairs applicable to various clinical fields
  o Published data re: role of pharmacokinetic genes
  o Evidence strong enough to result in a clinical recommendation for use of testing
  o Outcome was best evidence & consensus-based resource for how existing genetic information should be used
  o Guidelines were initially relevant only to adult population, though recent updates have changed that, but:
    - Still not helpful in helping us know whether we should order tests in Peds

Position Statements

- AACAP 2019 Policy Statement on PGx Testing
  o Current evidence does not support the routine use of testing to guide selection of psychotropic medications in children/adolescents
  o CYP450 pharmacogenetic genotyping not supported as a first-line approach, but may have some utility for children and adolescents who experience inadequate response or adverse reaction to previous medication trials with relevant drugs
  o Inclusion of genetic pharmacodynamic variants with insufficient relevance to drug effectiveness limits utility of many available tests
  o Future high-quality prospective studies assessing clinical significance of pharmacodynamic & combinatorial pharmacogenomic testing in children/adolescents recommended

Position Statements, cont’d.

- Taskforce Statements
  o APA Taskforce for Biomarkers and Novel Treatments
    - Assesses evidence and provides recommendations for emerging technologies
    - Pharmacogenomics testing not ready for widespread use in clinical practice
    - CYP450 may be informative for side effects
    - Lack of clarity regarding evidence supporting pharmacodynamic genes
- Organizational Statements & Consensus Guidelines ... any?

FDA

- Concerned about unsubstantiated therapeutic claims and patient/clinician misinterpretation of some types of test reports
- Regulates test reports but historically unclear whether tests themselves require approval
  - Increasing regulatory oversight on pharmacogenomic testing to reduce misleading language in reports
- FDA drug labeling requirements already stipulate that pharmacogenomic information is to be included. In fact, there are:
  - >250 drug labels mentioning human genomic biomarkers
  - >100 drug labels have pharmacogenomic information included in warnings, and/or info about dose/administration, drug interactions, precautions
  - 1/3 of these are psych/neuro meds

FDA, cont’d.

- “Health care providers are using genetic testing to help inform decisions about their patients’ health, health risks and more...we are seeing significant activity in the field of pharmacogenetics...The use of some drugs can be aided by pharmacogenetic testing; there is sufficient scientific evidence demonstrating a relationship between certain drugs and genetic variants.”
- “We are warning the public about the FDA’s concerns with pharmacogenetic tests whose claims have not been reviewed by the FDA. Specifically, we are warning consumers about many such genetic tests being marketed directly to consumers or offered through health care providers that claim to predict how a patient will respond to specific medications. Tests that make such claims that have not been evaluated by the FDA and are not included in the drug label may not be accurate, based on scientific and clinical evidence, and may not be accurate.”
Limitations

• Research Limitations:
  o Small studies, often retrospective-only, lack of rigor in statistics, mostly funded by industry
  o Many genetic variants have not been found to have independent association w/trx response or outcomes

• Other Limitations:
  o Many tests not FDA-approved or cleared for specific indications

Limitations, cont’d.

• Limitations Impacting Results:
  o Most evidence currently available comes from detection of gene-drug interactions included in drug labeling
  o Results/recommendations may differ across commercial labs
  o Results can be confusing for clinicians…must understand how to interpret results (w/caution) before ordering and discussing results
  o Vulnerabilities based on individual genetics are not certain predictions
  o Race/ethnicity-based information in some results could pose risk of clinicians deviating from evidence-based medicine
  o Testing does not capture all relevant PK or PD genes or non-genetic factors that influence drug response
    ➢ Newer testing platforms recently released that include information based on race/ethnicity, smoking & caffeine consumption status

Therefore...

Evidence-based medication prescribing practices remain gold standard;
pharmacogenomic testing should not cause clinicians to deviate from evidence-based medicine

Cost-Effectiveness

• Proponents of PGx testing say evidence to date shows it may lead to:
  ➢ less trial-and-error
  ➢ less morbidity
  ➢ and possibly, faster remission rates

Cost-effectiveness linked to all of these!

Ethical Considerations

• Testing of children/adoles requires parental consent
• Patient assent ethically recommended but not explicitly required by most commercial companies (e.g., nowhere for pt to sign)

My Thoughts

• Even though not yet standard of practice, there are many examples of testing being helpful to patients/families in my own practice and that of others
• I like the idea of personalized medicine based on a patient-specific decision made using patient-level data rather than population-level data
• For now, PGx testing helpful as an adjunct, esp. in cases where pts have not had anticipated response to 1, 2 or 3 med trials
So...What to Do?

Use pharmacogenomic testing as a "decision-support tool... enhancing rather than offering an alternative to standard protocols."

Also:

"...when pharmacogenetic testing results are already available... integrate this information into medication selection and dosing decisions. Genetic information for CYP2C19 and CYP2D6 would likely be most beneficial..."

About PGx Testing Companies

• Different companies offer different tests (different tests mean different panels of genes may be analyzed)
• Most information on reliability is available through company itself (and paid for by company resources); look for independent validation and seek it out (e.g., use in non-pharma supported studies, citation of testing platform in papers about something else)
• Research a few companies that offer the type of testing likely to be most useful for you in your practice; make friends w/reps; attend their educational events; ask questions
• If possible, use a few and then decide on which company seems to offer what you find useful

Clear as Mud?

• Where To Get Further Information:
  o Existing guidelines, e.g., CPIC
  o The FDA (complicated, confusing)
  o Research (complicated, confusing)
  o Drug reps (biased based on economics but often gatekeepers of direct access to clinician-researchers who can explain studies well)
  o Trusted colleagues/other clinicians (biased based on experience)
  o Other Resources:
    • https://www.pharmgkb.org/
    • http://www.pgrn.org/

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Thank You for Your Attention!

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