Speaker Profiles

Rif El-Mallakh, MD

Position: Dr. El-Mallakh is Professor and Director of the Mood Disorders Research Program in the Department of Psychiatry and Behavioral Sciences at the University of Louisville School of Medicine in Louisville, Kentucky. For the past 25 years, Dr. El-Mallakh has focused his research on the pathophysiology of bipolar illness. Dr. El-Mallakh has authored or coauthored over 250 peer-reviewed articles and 2 books.

Education: Dr. El-Mallakh received his MD degree from the University of Illinois. He completed a medical internship and an adult psychiatry residency at the University of Connecticut. He spent 3 years as a clinical research fellow at the National Institute of Mental Health (NIMH) and joined the faculty of the Department of Psychiatry at the University of Louisville in 1992.

Henry A. Nasrallah, MD

Position: Dr. Nasrallah is the Sydney W. Souers Professor and Chair of the Department of Psychiatry and Behavioral Neuroscience at Saint Louis University (St. Louis, MO), and he is the Editor-in-Chief of Schizophrenia Research and Current Psychiatry.

Education: Dr. Nasrallah earned his MD degree from the American University of Beirut, School of Medicine (Beirut, Lebanon). He completed a psychiatry residency at the University of Rochester Medical Center (Rochester, NY) and a neuroscience research fellowship at the National Institutes of Health (National Institute of Mental Health) Laboratory of Clinical Psychopharmacology (Washington, DC).
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Objectives

• Define precision medicine and its potential benefits in patient care
• Review the history and basics of pharmacogenetics and pharmacogenomics
• Discuss the role of biomarkers in precision medicine
• Explore current developments in the use of pharmacogenomics and precision medicine in the psychiatric clinic
• Address gaps in understanding and barriers to the successful implementation of precision medicine
Pharmacogenomics in Precision Medicine
**Precision Medicine in Psychiatry**

**Precision Medicine:** proposes tailoring health care to the individual by integrating data from their genetic makeup, epigenetic modifications, other biomarkers, clinical symptoms, and environmental exposures.

- **Goal:** combine *early diagnosis*, *targeted therapies*, and more accurate prediction of *disease susceptibility* to reduce morbidity and mortality of psychiatric conditions.

- Two important tools of precision medicine are *pharmacogenomics* and *biomarkers*.
Pharmacogenetics and Pharmacogenomics

- According to the Pharmacogenomics Knowledge Base (PharmGKB.org)¹:
  - **Pharmacogenetics**: how variation in a single gene influences an individual’s response to a single drug
  - **Pharmacogenomics**: how all genes influence an individual’s response to drugs

- Both have the potential to identify patients genetically predisposed to not respond to therapy or to develop unacceptable toxicity²

- Much of the early work in pharmacogenetics has focused on the contribution of genetic variability to variations in drug metabolism³

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The Cytochrome P450 (CYP450) Family of Enzymes

CYP450s are an important class of enzymes that catalyze a wide variety of reactions

CYP450s are responsible for:

- Production and metabolism of endogenous compounds
  - Example: Metabolism of estrogens by CYP3A4

- Detoxification of food
  - Example: CYP2D6 metabolizes plant alkaloids to less toxic compounds

- Metabolism of foreign chemicals
  - Example: Drug metabolizing enzymes contribute to a series of chemical reactions that increase the water solubility of drugs, allowing for excretion

Genetic variability in CYP450 enzymes (polymorphisms) influence a patient’s response to a particular drug

CYP450s and Drug Metabolism

- CYP450s are responsible for 96% of reactions involved in the metabolism of drugs (marketed and under development):
  - 75% of those reactions are carried out by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5

Enzymes responsible for drug metabolizing reactions

P450 subtype contribution to drug metabolizing reactions

AKR, aldo-keto reductase; CYP, cytochrome P450; FMO, flavin-containing monooxygenase; MAO, monoamine oxidase.

Drug Metabolism Phenotypes: Cytochrome P450s

- **Poor Metabolizers**
  - Nonfunctional genes
  - Greater risk of adverse effects

- **Intermediate Metabolizers**
  - 1 Functional and 1 nonfunctional gene
  - Increased risk of adverse effects

- **Extensive Metabolizers**
  - 2 Functional wild-type genes
  - Most common phenotype

- **Ultra-rapid Metabolizers**
  - Extra gene copies
  - Low response to drug
  - Potential risk of high levels of metabolites

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2. Ingelman-Sundberg M and Sim SC. *Biochem Biophys Res Commun.* 2010;396:90-94.
Genetic Variability of Cytochrome P450 Drug Metabolism

Certain polymorphisms of CYP450 can influence a patient’s response to a particular drug:

- There is large variation in the representation of different alleles in different ethnic populations, which can be viewed as a reflection of foods available for those populations:
  - The CYP2D6*17 allele, which shows altered substrate affinity, is the most common allele in black Africans, but is absent in Caucasian and Asian populations.
  - The CYP2D6 intermediate metabolizer phenotype is nearly twice as prevalent in African Americans (~13%) than in Caucasians (7%)4.
  - Ethiopians have a higher frequency of gene duplication (resulting in ultra-rapid metabolism) of CYP2D6 (up to 29%) than the general population5.
  - 51% of Asians have the CYP2D6*10 allele, which generates an unstable enzyme and contributes to an intermediate metabolizer phenotype, while only 1-2% of Caucasians have this allele3.
  - African Americans are 1.5- to 2.1-fold more likely to have only 1 functional copy of CYP2D6 (poor / intermediate metabolizer) and 1.4- to 3.4-fold higher to have 3 or more copies of CYP2D6 (ultra-rapid metabolizer) compared with other ethnicities6.

CYP, cytochrome P450.

Drug Target and Pharmacogenomics

- Genetic variations related to disease susceptibility tend to be a much more powerful predictor of response compared with the CYP450 genotype

- Examples
  - Serotonin transporter
    - Variants associated with poorer response to antidepressants in MDD
  - BDNF
    - Polymorphism associated with more severe depressive illness
  - Catechol-O-methyltransferase
    - Variant associated with poor response to antidepressants
  - Dopamine receptors
    - Variants associated with schizophrenia and antipsychotic response

BDNF, brain-derived neurotropic factor; CYP450, cytochrome 450; MDD, major depressive disorder.
SERT: “short” vs “long form”

- A 44-base-pair deletion in the promoter region leads to decreased expression of SERT

SERT, serotonin transporter.
The “Short-form” SERT Allele

- Patients heterozygous or homozygous for the “short-form” SERT gene may have:
  - An increased chance of developing depression following significant life adversity*1
  - A decreased response to SSRI treatment1
  - A slower response to SSRI treatment2:
    - In a double-blind, placebo-controlled study in depressed patients aged ≥ 60 years (n = 176):
      - Patients with 1 or 2 copies of the “short-form” allele had a significantly decreased response† to an SSRI at week 1 (1.6% vs 16.7%) and week 2 (9.1% vs 34.6%)‡
      - There was no difference in response between genotypes by week 8
    - Patients with bipolar disease who were homozygous for the “short-form” SERT were more likely to have a history of rapid cycling1:
      - “Short-form” allele was associated with an increased risk of antidepressant-induced mania in patients with bipolar disease1
  - Some evidence suggests that identifying the “short-form” allele in patients can be used to guide treatment decisions1

*Demonstrated in multiple longitudinal studies.
†Response measured as Clinical Global Impression Scale - Improvement score of ≤ 2.
‡Compared with patients homozygous for the long-form allele.

SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor.
Current Progress and Advances in Precision Psychiatry
Polling Question

How often do you use pharmacogenomic testing to guide treatment decisions in your practice?

A. Never  
B. Rarely  
C. Sometimes  
D. All the time
The Potential Impact of Pharmacogenetic Testing

• In a study that examined whether variations in metabolic capacity translate into clinically important parameters (predisposition to AEs or to be a nonresponder):
  – Genotype was determined in patients at clinical extremes (ie, those with AEs or nonresponders):
    • The poor metabolizer frequency in patients with AEs (n = 28) was 4-fold that of the country’s population
    • The ultra-rapid metabolizer frequency in nonresponders (n = 16) was ~5-fold that of the country’s population

• Other studies have demonstrated an increased hospitalization rate in poor metabolizers treated with antidepressants and antipsychotics and an increase in the development of AEs*

*Compared with extensive metabolizers.

AE, adverse effect.
The Potential Impact of Pharmacogenomic Testing

• Gene-by-gene testing has shown limited clinical utility\(^1\)
• In an analysis of 3 studies\(^*\) utilizing combinatorial pharmacogenomic test results to inform medication changes for patients with treatment-resistant depression (N = 258), compared to unguided treatment, pharmacogenomic-guided treatment resulted in\(^2\):
  • A 2.3-fold increase in the odds of clinical response (\(P = 0.004\))
  • A 53% greater improvement in depressive symptoms (\(P = 0.0002\))
  • A 1.7-fold relative improvement in response (\(P = 0.01\))
  • A NNT for 1 clinical response above that seen in the unguided group of 6.07
  • Phenotypes ascribed to any of the single genes failed to predict clinical outcomes
• Clinical utility analysis: medication decision congruent with testing guidance were reported to save significantly in medication costs\(^3\)
  • Proved especially effective at reducing costs in the primary care setting

\(^*\)8-10 weeks in duration.

CYP, cytochrome P450; HRT2A, serotonin receptor 2A; NNT, number needed to treat; SLC6A4, serotonin transporter.

Biomarkers in Precision Medicine

**Biomarker:** a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how a patient feels, functions, or survives.

- While other medical fields utilize clinical examination in combination with biological tests and quantitative measurements, psychiatric diagnosis often relies solely on clinical examination.
- The FDA-NIH Biomarker Working Group divides biomarkers by clinical use into 7 classes:
  - Diagnostic
  - Monitoring
  - Pharmacodynamic / response
  - Predictive
  - Prognostic
  - Safety
  - Susceptibility / risk

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FDA, Food and Drug Administration; NIH, National Institutes of Health.
# Biomarkers in Psychiatry: Current Developments

- Beyond pharmacogenetics, there are no biomarkers qualified by the FDA for use in psychiatry\(^1,2\)

## Examples of Biomarkers Under Investigation or In Use in the Psychiatric Clinic

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<th>Class</th>
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| **Diagnostic**             | • Increased blood levels of inflammatory markers (ie, CRP, IL-6, and TNF\(\alpha\)) were significantly associated with atypical depression as compared to typical/melancholic depression\(^3\)  
  • Measurement of cellular membrane potential may help diagnose ADHD\(^4\) and bipolar disorder\(^5\)                                                                 |
| **Monitoring**             | • Blood concentrations of an addictive drug can be used to monitor abstinence and compliance in patients prone to substance abuse\(^6\)                                                                                                         |
| **Pharmacodynamic**        | • Serum BDNF levels are decreased in untreated MDD patients and treatment with antidepressant medications can restore these levels\(^7\)                                                                                     |
| **Predictive**             | • REM latency was reported to predict response to treatment with certain antidepressants\(^7\)  
  • Patients with MDD and high blood CRP levels corresponded to a better response to a TCA than an SSRI\(^8\)                                                                                       |
| **Prognostic**             | • Individuals with a copy of the short-form of the SERT promoter polymorphism exhibited more depression and suicidality in relation to stressful life events than did individuals homozygous for the long allele\(^7\)  
  • In older patients (≥60 years) with MDD, lower evening cortisol levels predicted poorer course at 2 year follow-up\(^9\)                                                                               |
| **Safety**                 | • **Currently in use:** CYP2D6 poor metabolizers have higher than expected plasma concentrations of TCAs when given usual doses\(^2\)                                                                                                 |
| **Susceptibility / risk**  | • Polymorphisms and variable number tandem repeat regions in the serotonin transporter gene were associated with development of MDD\(^7\)                                                                                      |

BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; CYP, cytochrome p450; IL-6, interleukin 6; FDA, Food and Drug Administration; MDD, major depressive disorder; REM, rapid eye movements; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TNF\(\alpha\), tumor necrosis factor \(\alpha\).

Clinical Tools in Psychiatry

• Current clinical assessment of psychiatric disorders is predominantly restricted to evaluating mental and behavioral signs and symptoms

Physical Assessments Which Can Be Useful in Diagnosis of Psychiatric Conditions

Presence of Cognitive Impairment
- Severe cognitive deficits across multiple domains are present in schizophrenia, bipolar disorder, and major depression
- Test Batteries for memory, attention, visuospatial skills, and executive function can aid in diagnosis
- Monitoring of cognitive impairment can be clinically useful, ie, in diagnosis, assessment of illness severity, and to monitor response to treatment

Presence of Neurological “Soft Signs” (NSS):
- One meta-analysis found that NSS scores decreased with remission of psychopathological symptoms of schizophrenia
- This decrease is less pronounced in patients with non-remitting schizophrenia

Presence of Comorbidities:
- Physical illnesses can be markers for subsequent psychological disturbances
- Mental health problems can be markers of later physical pathologies

References:
DISCUSSION
Polling Question

For those who answered “never” or “rarely”: What prevents you from implementing pharmacogenomic or biomarker testing?

A. Reimbursement considerations
B. Lack of sufficient knowledge
C. Need for more clinical trial evidence
D. Lack of standardization
E. I currently use such testing in my practice
Barriers to Successful Implementation of Precision Medicine
Gaps in Understanding

• Difficulty interpreting how multiple genetic risk factors coalesce to affect disease risk\(^1\)

• Heterogenous nature of most psychiatric disease\(^2\):
  – Use of sophisticated clinical approaches to subdivide psychiatric syndromes into groups that exhibit a more homogenous response may aid in identification of pharmacogenomic targets for investigation\(^2\)

• According to a survey of psychiatrists, \(\frac{3}{4}\) of respondents agreed that genotyping results should be accompanied by psychoeducation such as genetic counseling\(^3\):
  – There is a need for physician training on how to interpret and convey complex genetic results\(^4\)

• Most tools have been developed based on Caucasian populations\(^5\):
  – Design of tests can lead to “false phenotyping” in minority populations\(^5\)

• Sparsity of data concerning clinical effectiveness:
  – Few randomized controlled trials\(^6\)
  – Limited analysis of utility and cost effectiveness\(^5\)

Barriers to Implementation

• Lack of infrastructure and standardization¹
• Clinician inexperience¹
• Scarcity of clear and consistent recommendations for testing:
  – As of mid-2017, the CPIC had published pharmacogenetic guidelines for 33 drugs, the majority of which relate to metabolism²:
    • 12 guidelines have been released for drugs with psychiatric indications, 6 of which relate to metabolism of tricyclic antidepressants
• Lack of prospective randomized clinical trials for approach validation¹
• Cost and reimbursement considerations¹:
  – Coverage is variable and reimbursement policies may change over time

CPIC, Clinical Pharmacogenetics Implementation Consortium.
## Upcoming Virtual Fora*

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| **HEDIS® Behavioral Health Measures: An Update From NCQA®** | • Junqing Liu, PhD, MSW  
• Emily Morden, MSW  
• Lauren Niles, MPH | Tuesday, August 15, 2017 | 12:00 pm – 1:00 pm EST |
| **Suicide Affects Everyone: The Role of the Health Care Professional in Suicide Prevention** | • Christine Moutier, MD | Thursday, September 14, 2017 | 12:00 pm – 1:00 pm EST |
| **Innovations in The Criminal Justice System for Individuals with Mental Illness** | • Lawrence G. Brown, JD  
• Dean Barker | Thursday, September 28, 2017 | 12:00 pm – 12:30 pm EST |

*Register for these programs at [https://www.psychu.org/events/](https://www.psychu.org/events/)*
Pharmacogenomics & Personalized Medicine: Where Are We Now & Where Are We Going?

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