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COLUMBIA UNIVERSITY
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Potential Utility of Pharmacogenomics in Older Adults with Poorly Controlled Depression

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BACKGROUND

- Considerable inter-individual variability in therapeutic response to psychotropic medications has been widely described (Al-Harbi, 2012).
- Initial treatment with antidepressant medications results in complete remission of only 35-45% of depressed patients (Kemp, 2008).
- As patients continue to demonstrate course of treatment resistant depression, the likelihood of responding to a subsequent antidepressant drugs falls to 18% (Warden, 2007).
- It takes at least 4-6 weeks of observation to establish lack of efficacy of any individual dosing of a particular antidepressant (Suehs, 2008).
- It takes on average 5 drug trials to establish antidepressant regimen resulting in remission in patients who initially failed antidepressant treatment (Dunner, 2006).

STUDY OBJECTIVE

- Pharmacogenomic testing is increasingly being used as a promising tool in optimizing medication regimens by identifying genetic biomarkers of personal response to particular drugs (McLeod , 2001).
- To a large extent, variability in antidepressant efficacy can be explained by genetic variations that affect medication-metabolizing enzymes, drug transporters, and medication targets (Evans, 2003; Fabbri, 2015).
- Recent reviews demonstrated significant potential of pharmacogenomic testing in improving treatment of major depressive disorder (Malhotra, 2012; Panza, 2016).
- One of the major barriers towards successful implementation of pharmacogenomic testing for patients with major depressive disorder is lack of systematic evaluation of impact of this approach in routine clinical care settings.
- **The major objective** of this study is to systematically evaluate impact of comprehensive pharmacogenomic testing on the treatment of major depressive disorder in ambulatory setting.

AIMS AND HYPOTHESES

Specific Aims:

1. Conduct a prospective randomized double-blind study to evaluate the clinical impact of comprehensive pharmacogenomic testing on the treatment of major depressive disorder.

- *Primary Hypothesis:* The pharmacogenomic-guided treatment group will demonstrate significantly higher percent improvement in depression score compared to treatment-as-usual group.

2. Assess impact of pharmacogenomic-guided care on depression symptomatology measured by major depression scales (HAMD-17, QIDS-SR, PHQ-9), side effects (FIBSERS), patient satisfaction with care and medication regimen, medication adherence, quality of life, care utilization and provider attitudes towards pharmacogenomic-driven care.

- *Secondary Hypothesis:* Pharmacogenomic-guided care will be associated with reduction depressive symptomatology and medication side effects, and improvements in medication adherence, quality of life, and patient and provider attitudes.

3. Identify potential cost savings and conduct cost-effectiveness analysis of pharmacogenomic testing.

- *Secondary Hypothesis:* Pharmacogenomic testing will result in potential cost savings from societal prospective.

METHODS

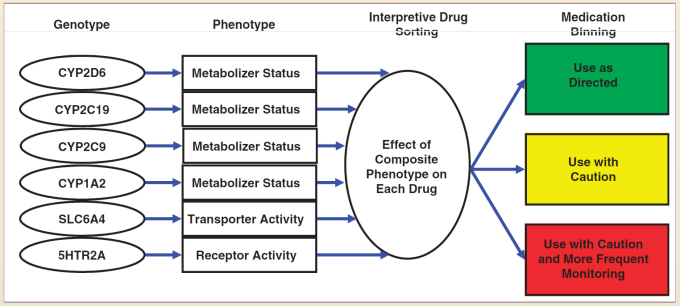
- Two-arm double-blind prospective randomized controlled trial (RCT) is conducted by personnel at Columbia University Medical Center.
- Participants are randomly assigned to two groups: pharmacogenomic-guided therapy group (guided group) and treatment as usual group (TAU group).
- Buccal swab is collected at baseline from subjects in both groups to perform pharmacogenomic testing using PGxOne™ Plus.
- In the guided group, the patient's treatment provider begins antidepressant adjustments based on pharmacogenomic testing report within a week of the baseline visit. In the TAU group, antidepressant adjustments are carried out with 3-mn delay.

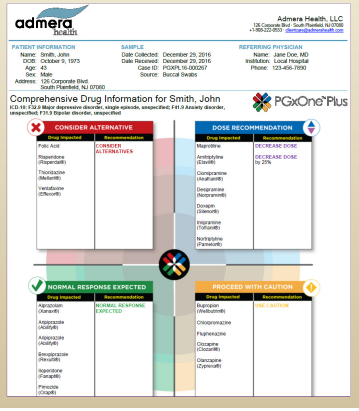
INCLUSION/EXCLUSION CRITERIA

Adult patients seen in outpatient clinics are eligible to participate in the study if they meet the following inclusion criteria:
1) a clinical diagnosis of major depressive disorder (MDD)
2) prescription of index antidepressant medications (see attachment)
3) a minimum score of 14 on the 17-item Hamilton Rating Scale for Depression (HAMD-17)

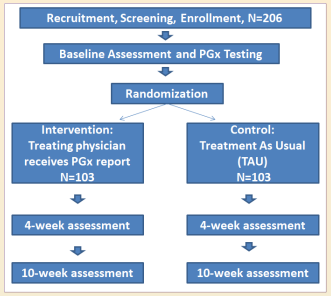
Potential subjects are excluded from the study if they meet at least one of the following exclusion criteria:
1) a diagnosis of bipolar disorder (any type), schizophrenia, or schizoaffective disorders
2) an active diagnosis of substance abuse or dependence.

PGx Testing with PGxOne Plus from Admera Health





STUDY WORKFLOW



STUDY POPULATION

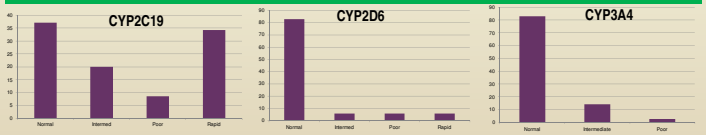
- *Current sample size:39*
- *Age:* 62±12;
- *Gender:* women - 94%; men – 6%;
- *Race:* 12% Blacks; 75% Whites; 3% Asians; 10% Others;
- *Ethnicity:* 44% Hispanics;
- *Marital Status:* 31% Single;
- *Education:* 14±3 years in school
- *U.S. born:* 75%;
- *Employment:* 16%
- *Knowledge about depression:* none or limited – 28%
- *Any Knowledge about Pharmacogenomics*: 19%

COMPARISON OF STUDY OUTCOMES (§) AT BASELINE (BL) AND FOUR WEEKS (4wk) IN INTERVENTION (INT) AND CONTROL (CTRL) GROUPS

Outcomes	INT BL	INT 4wk	CTRL BL	CTRL 4wk
HAMD	17.6±4.3	10.9±3.8 (*)	17.5±5.5	16.4±5.3
PHQ-9	15.5±4.0	5.7±4.6 (*)	17.8±6.7	14.3±6.6
TSQM-E	65.5±12.2	73.3±21.1 (*)	59.3±23.7	60.2±24.2
TSQM-SE	82.1±22.8	95.8±28.1 (*)	64.6±25.5	83.3±18.2
TSQM-C	59.5±25.2	83.9±17.7 (*)	71.5±21.7	71.6±12.3
TSQM-GS	61.9±22.3	77.5±18.9 (*)	64.6±27.7	65.7±29.0
QIDS-SR16	10.3±4.3	7.7±4.1 (*)	14.7±5.8	14.9±4.4
EQ-5D	68.7±14.8	79.5±14.4 (*)	67.5±13.5	59.4±23.2

(§) HAMD-17: Hamilton Rating Scale for Depression ; PHQ-9: 9-item Patient Health Questionnaire; TSQM: Treatment Satisfaction Questionnaire for Medication (E – Efficacy; SE – Side Effects; C – Convenience; GS – Global Satisfaction); QIDS-SR16: subject-rated 16-item Quick Inventory of Depression Symptomatology Scales; EQ-5D – Quality of Life.
(*) Statistically significant difference between BL and 4wk based on paired T-test (p<0.05)

CYTOCHROME POLYMORPHISM FREQUENCY IN THE STUDY SAMPLE



CONCLUSION

- Actionable variants were detected in 88% of patients
- Polypharmacy was observed in 94% of patients
- Significant drug-drug interactions were documented in 70% of patients
- Following pharmacodenomic testing in the intervention group, antidepressant medications were changed in 40% of patients and dosage was changed in 32% of patients
- Pharmacogenomic-driven medication optimization resulted in a significant improvement of study outcomes in the intervention group as compared to the control group
- Pharmacogenomic-driven medication optimization has significant potential in treatment of major depressive disorder