Original article
Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation

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Abstract

Objectives:
The objective of this project was to determine pharmacy cost savings and improvement in adherence based on a combinatorial pharmacogenomic test (CPGx*) in patients who had switched or added a new psychiatric medication after having failed monotherapy for their psychiatric disorder.

Research design and methods:
The prospective project compared 1 year pharmacy claims between a GeneSight CPGx guided cohort and a propensity-matched control group. Patients were project eligible if they augmented or switched to a different antidepressant or antipsychotic medication within the previous 90 days. Following the medication switch or augmentation, pharmacogenomic (PGx) testing was offered to each patient’s treating clinician. Pharmacy claims were extracted from the Medco pharmacy claims database for each patient (n = 2168) for 1 year following testing and compared to a 5-to-1 propensity-matched treatment as usual (TAU), standard of care control group (n = 10,880).

Main outcome measures:
Total pharmacy spend per member per year; adherence.

Results:
Patients who received PGx testing saved $1035.60 in total medication costs (both CNS and non-CNS medications) over 1 year compared to the non-tested standard of care cohort (p = 0.007). PGx testing improved adherence compared to standard of care (ΔPDCPGx = 0.11 vs ΔPDCTAU = 0.01; p < 0.0001). Pharmacy cost savings averaged $2774.53 for patients who were changed to a CPGx congruent medication regimen, compared to those who were not (p < 0.0001).

Conclusions:
PGx testing provides significant ‘real world’ cost savings, while simultaneously improving adherence in a difficult to treat psychiatric population. Limitations of this study include the lack of therapeutic efficacy follow-up data and possible confounding due to matching only on demographic and psychiatric variables.

Introduction

Direct treatment costs for mental illness far exceed those for diabetes and hypertension and lag only behind cardiovascular disease, traumatic injury, *CPGx is a trade name of Assurex Health Inc.
and cancer. Indirect treatment costs for mental illness are staggering, with major depressive disorder (MDD) responsible for the highest disability costs among all major illnesses. The National Institute of Mental Health reports that annual direct and indirect costs for depression is $200 billion, of which treatment-resistant depression comprises $64 billion. Annual medication costs of $30.3 billion are spent on psychiatric medications.

One in four adults suffer from a mental illness in any given year. MDD is the most common among these illnesses with a 1 year prevalence of 6.7%. Many individuals suffering from MDD do not receive treatment because of social stigma, financial outlay, and limited access to healthcare. Of those who do pursue treatment, two-thirds do not achieve full remission. Instead, they often end up on a pharmacologic odyssey requiring multiple failed medications to ultimately find a medication with a favorable risk/benefit balance. This perpetuation of treatment-resistant depression results in greater loss of work productivity and disability, and 70% higher annual medical costs than for treatment-responsive patients. The economic and societal costs of MDD derive from the relative early age of onset, chronicity of illness, and poor treatment outcomes. Intermittent and extended periods of disability, unemployment or under-employment, and increased direct treatment costs can span the life of the individual.

Some clinicians seeking to positively alter this trajectory and improve outcomes for patients with mental illness have recently incorporated PGx guided treatment into their practice. PGx identifies individual genetic differences in pharmacokinetic (PK) genes involved in the absorption, distribution, metabolism and elimination of medications, and pharmacodynamic (PD) genes involved in the mechanism of action of medications. However, given the lack of genetic education, the multidimensional genomic variants, and their vast array of interactions with medications, it is daunting for clinicians to utilize PGx in practice. To address this implementation challenge, the GeneSight Psychotropic test was developed to provide clinicians with a suite of validated PK and PD genes yielding a composite phenotype for each patient that is applied to the known pharmacology of each psychiatric medication. This combinatorial pharmacogenomic (CPGx) approach uniquely accounts for multiple metabolic pathways and mechanisms of each medication, resulting in significantly greater predictive power for patient outcomes compared to single gene approaches.

Based on a patient’s precise composite phenotype, the GeneSight CPGx process stratifies antidepressant and antipsychotic medications into three color-coded categories: little or no gene–drug interaction (green, ‘use as directed’), moderate gene–drug interaction (yellow, ‘use with caution’), and severe gene–drug interaction (red, ‘use with increased caution and with more frequent monitoring’). Further information detailing specifics of each gene–drug interaction and dosing recommendations are provided through footnotes.

In three prospective clinical trials, GeneSight CPGx guided treatment has demonstrated clinical utility with 71% greater symptom improvement relative to treatment as usual (TAU). In a 1 year retrospective healthcare utilization study, GeneSight testing predicted a greater number of general medical visits, total healthcare visits including psychiatric visits, medical absence days, and disability claims over 1 year for patients taking red versus green and yellow category medications. To extend these findings, the current project was conducted in collaboration with a large pharmacy benefits manager (PBM) to assess whether GeneSight testing improved medication utilization and lowered costs in individuals prescribed psychiatric medications across multiple US practice settings.

Patients and methods

Project design

We compared pharmacy claims over 1 year between a prospectively generated cohort of CPGx tested subjects (n = 2168) and a 5-to-1 propensity-matched control group (n = 10,880). Patients were eligible for either group if they 1) were newly starting an antidepressant or antipsychotic medication (i.e., 180 day look back for no previous prescription [Rx] record), 2) were augmented or switched to a different antidepressant or antipsychotic (index) medication, as evidenced by a new medication Rx within a 90 day window of the last Rx for the initial medication, and 3) maintained continual pharmacy benefit eligibility from 180 days prior to the initial Rx to the date of the first Rx for the index medication.

Once the patient was prescribed an index medication, the prescribing clinician was contacted. If the treating clinician authorized GeneSight testing, patient consent was obtained and a buccal swab was provided to the patient for DNA collection. GeneSight results were made available to the patient’s clinician within three business days of sample receipt.

A TAU group was selected from a pool of approximately 65 million eligible plan members. Patients were propensity matched on gender, age, index CNS medication, primary CNS diagnosis, and date of project enrollment (Table 1).

Pharmacy claims from the PBM database were extracted for each patient for 180 days prior to the index medication initial Rx (index date) (i.e., the ‘pre-test’ period) to 365 days after the index date (i.e., the ‘post-test’ period). The first new GeneSight panel medication prescription after the index medication was operationally defined as the ‘incident’ or third medication, as this fall was
the first opportunity for the prescriber to make a CPGx informed medication decision within the GeneSight group. Antidepressants and antipsychotics eligible for inclusion were limited to the 26 medications covered by the GeneSight Psychotropic panel (panel medications) at the time of project commencement (Figure 1a).

All claims analyzed for the project spanned the time between September 2011 and December 2013. All reversals of Rx fills were identified and excluded from analyses. Medication costs and associated metrics were tabulated during the pre- and post-test periods for both groups. Total medication costs for each patient were derived via the summation of 1) the net amount billed to the payer of each patient, 2) the flat dollar amount each patient incurred for their respective co-pay, and 3) the deductible amount that each member must have satisfied before insurance coverage began for each respective medication.

**Between group comparisons**

**Drug spend and polypharmacy**

The total drug spend per member per year (PMPY) was calculated for both groups across the 365 day post-test period and annualized across the 180 day pre-test period. The within group pre-to-post changes in PMPY Rx amount and spend were calculated. Between group differences in pre-to-post change in PMPY Rx amount and spend were compared.

**Adherence and discontinuation**

Adherence, discontinuation, and time to discontinuation for index and incident medications were calculated in the post-test period for patients in both groups. Adherence was calculated using the proportion of days covered (PDC) methodology. The PDC ratio is a commonly used pharmacy-claims-based metric that gauges the number of days each patient has a medication in his or her possession during a specified period of time. Discontinuation was defined as a 45 day or greater interval in refills for the incident or index medication after the days supplied from the previous Rx had elapsed.

**Statistical analysis**

As parametric modeling assumptions were upheld for comparisons between groups with respect to pharmacy costs and number of medications (i.e., polypharmacy), independent t-tests were used to model these outcomes between groups from the pre-test to the post-test period. Parametric modeling assumptions were not upheld for statistical comparisons between tested and non-tested groups with respect to adherence, rates of discontinuation, and time to discontinuation (TTD) or for comparisons within each group with respect to pharmacy costs and number of medications. Therefore, Wilcoxon rank-sum tests were used to model adherence to index and incident medications and TTD between groups and the same tests were used to model pharmacy costs and number of medications within groups from the pre-test to the post-test period. McNemar’s tests were used to compare differential rates of adherence to and discontinuation of index and incident medications within each group. Chi-square tests were used to model rates of discontinuation between groups.

**Within GeneSight group comparisons**

**Definition of congruence**

Although the GeneSight report was made available to treating clinicians of all patients in the GeneSight group, clinicians may or may not have made medication changes that were congruent with their patient’s CPGx results. Prior studies have shown that individuals who remain on a genetically misappropriated ‘red category’ medication experience poorer efficacy and excess healthcare utilization. To replicate and extend these findings, further analyses were conducted within the GeneSight group as a function of congruence with the GeneSight report (Table 2). A genetically congruent decision occurred when a patient’s most severely categorized medication was yellow and/or green in the last 90 days of

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**Table 1. Propensity score matching characteristics.**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>TAUa</th>
<th>GeneSight</th>
<th>p valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.87</td>
</tr>
<tr>
<td>Female (%)</td>
<td>69.2</td>
<td>69.4</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>30.8</td>
<td>30.6</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Mean (years ± SD)</td>
<td>51 (15)</td>
<td>51 (17)</td>
<td></td>
</tr>
<tr>
<td>Index Neuropsychiatric Medicationd</td>
<td></td>
<td></td>
<td>0.997</td>
</tr>
<tr>
<td>Antidepressics (%)</td>
<td>15.7</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>SNRIs (%)</td>
<td>16.7</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>SSRIs (%)</td>
<td>33.4</td>
<td>33.8</td>
<td></td>
</tr>
<tr>
<td>Tricyclics (%)</td>
<td>4.9</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD-9 Primary Diagnosis</td>
<td>29.3</td>
<td>29.3</td>
<td>0.98</td>
</tr>
<tr>
<td>Anxiety Disorder (%)</td>
<td>21.1</td>
<td>21.0</td>
<td></td>
</tr>
<tr>
<td>Bipolar Disorder (%)</td>
<td>5.0</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia (%)</td>
<td>0.9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Depression (%)</td>
<td>13.5</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>Other Depressive (%)</td>
<td>3.9</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Conduct Disorder (%)</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Personality Disorder (%)</td>
<td>13.1</td>
<td>13.2</td>
<td></td>
</tr>
</tbody>
</table>

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**Notes:**

aTreatment as usual.

b_p values were calculated using logistic regression models.

cStandard deviation.

dIndex medication refers to the first GeneSight panel antidepressant or antipsychotic medication that served as a replacement for or an addition to a medication in a patient’s regimen.

eSerotonin–norepinephrine reuptake inhibitor.

fSelective serotonin reuptake inhibitor.

gTricyclic class of antidepressants.
the post-test period. A genetically incongruent decision was defined as the subject taking a prescribed red category medication in the last 90 days.

**Total drug spend by congruence**

Differences in total drug spend during the 365 day post-test period were calculated for the GeneSight congruent and incongruent subgroups and were then further stratified by medication therapeutic chapter, patient diagnosis, and prescribing physician specialty. Medications were stratified according to therapeutic application (i.e., therapeutic chapter index) within the formulary reference guide available from the PBM at the time of project commencement. For diagnosis stratification, patients were grouped

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>USE AS DIRECTED</th>
<th>USE WITH CAUTION</th>
<th>USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>citalopram (Celexa)</td>
<td>desvenlafaxine (Pristiq)</td>
<td>escitalopram (Lexapro)</td>
<td>fluvoxamine (Luvox)</td>
</tr>
<tr>
<td>selegiline (Emsam)</td>
<td>sertraline (Zoloft)</td>
<td>duloxetine (Cymbalta) [1]</td>
<td>mirtazapine (Remeron) [1]</td>
</tr>
<tr>
<td>trazodone (Desyrel) [1]</td>
<td></td>
<td>fluoxetine (Prozac) [6]</td>
<td>desipramine (norpramin) [6]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>USE AS DIRECTED</th>
<th>USE WITH CAUTION</th>
<th>USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td>quetiapine (Seroquel)</td>
<td>ziprasidone (Geodon)</td>
<td>clozapine (Clozaril) [1]</td>
<td>aripiprazole (Abilify) [6]</td>
</tr>
</tbody>
</table>

[1]: Serum level may be too high, lower doses may be required.
[6]: Use of this drug is associated with an increased risk of side effects.

![Figure 1](a) Sample GeneSight Psychotropic combinatorial report for an individual patient at the time of testing. Medications characterized in the yellow and red categories are footnoted to describe the nature of the pharmacokinetic and/or pharmacodynamic gene–drug interaction(s) (e.g., ‘serum levels may be too low, higher doses may be required,’ or ‘serum level may be too high, lower doses may be required’). (b) Distribution of patients defined by their most severely categorized medication during the pre-test and last 90 days of post-test period. Numbers in columns indicate sample size.

The post-test period. A genetically incongruent decision was defined as the subject taking a prescribed red category medication in the last 90 days.

Total drug spend by congruence

Differences in total drug spend during the 365 day post-test period were calculated for the GeneSight congruent and incongruent subgroups and were then further stratified by medication therapeutic chapter, patient diagnosis, and prescribing physician specialty. Medications were stratified according to therapeutic application (i.e., therapeutic chapter index) within the formulary reference guide available from the PBM at the time of project commencement. For diagnosis stratification, patients were grouped

![Figure 1](b) Percentage of patients

<table>
<thead>
<tr>
<th></th>
<th>Pre-test</th>
<th>Last 90 days</th>
<th>Pre-test</th>
<th>Last 90 days</th>
<th>Pre-test</th>
<th>Last 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>337</td>
<td>558</td>
<td>823</td>
<td>743</td>
<td>502</td>
<td>361</td>
</tr>
</tbody>
</table>
by primary or co-primary ICD-9 diagnosis: anxiety disorders, depressive disorders, bipolar disorders, psychotic disorders, and other ICD-9 diagnosis (Table 3). Patients were stratified according to the specialty of the treating clinician20 who prescribed the index medication and ordered GeneSight (i.e., psychiatrist, non-psychiatrist). One-way independent ANOVAs were used to model pharmacy costs as a function of each of the above defined independent variables, as parametric modeling assumptions were upheld. The Sidak correction was employed using the formula $1 - (1 - \alpha)^{1/n}$ where $n$ is the number of independent tests and $\alpha$ is the nominal level of statistical significance (i.e., 0.05) and all reported $p$ values have been adjusted for multiple testing. All data management and statistical analyses were conducted using SAS version 9.321.

### Results

Subject attrition is described in Figure 2. Of the initial 2168 PGx tested subjects, two did not have complete pre-test claims data, and 34 did not complete post-test claims data. Of the 2132 patients entering the post-test period, 80 were no longer on a GeneSight panel medication, 330 lost PBM eligibility, and 60 were no longer on a GeneSight panel medication during the last 90 days, leaving 1662 for analyses.

### Case–control analyses

Average medication costs PMPY increased by $1725.24 from the pre-test period to the study end in the TAU group ($p < 0.0001$), which exceeded the mean increase of

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**Table 2. Method of determining congruence with GeneSight test results.**

<table>
<thead>
<tr>
<th>Most severe med prior to index date</th>
<th>Most severe med during last 90 days of follow-up</th>
<th>Category</th>
<th>Congruence with GeneSight test (dichotomous)</th>
<th>Congruence with GeneSight test (ordinal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red</td>
<td>Green</td>
<td>1</td>
<td>Congruent</td>
<td>Most Congruent</td>
</tr>
<tr>
<td>Red</td>
<td>Yellow</td>
<td>1</td>
<td>Congruent</td>
<td>Most Congruent</td>
</tr>
<tr>
<td>Yellow</td>
<td>Green</td>
<td>2</td>
<td>Congruent</td>
<td>Congruent</td>
</tr>
<tr>
<td>Yellow</td>
<td>Yellow</td>
<td>2</td>
<td>Congruent</td>
<td>Congruent</td>
</tr>
<tr>
<td>Yellow</td>
<td>Red</td>
<td>3</td>
<td>Incongruent</td>
<td>Incongruent</td>
</tr>
<tr>
<td>Yellow</td>
<td>Red</td>
<td>4</td>
<td>Incongruent</td>
<td>Most incongruent</td>
</tr>
<tr>
<td>Green</td>
<td>Red</td>
<td>4</td>
<td>Incongruent</td>
<td>Most incongruent</td>
</tr>
</tbody>
</table>

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**Table 3. ICD-9 codes utilized to develop each diagnostic category.**

<table>
<thead>
<tr>
<th>Anxiety Disorders</th>
<th>Depressive Disorders</th>
<th>Bipolar Disorders</th>
<th>Psychotic Disorders</th>
</tr>
</thead>
</table>
$689.64 PMPY in the GeneSight group \((p<0.0001)\). Thus, patients who received GeneSight testing saved $1035.60 in total annual medication costs compared to TAU patients \((p=0.0007)\) (Figure 3a). Total annual medication savings were $714.24 (69%) for non-CNS medications and $321.36 (31%) for CNS medications.

An annual decrease of 0.186 medications was observed for the GeneSight group compared to TAU \((p<0.0001)\), due to a mean increase of 1.07 medications PMPY in the TAU group from the pre-test to the post-test period \((p<0.0001)\), compared to a mean increase of 0.88 medications PMPY in the GeneSight group \((p<0.0001)\).

Within the GeneSight group, the PDC ratio for the index medication was 0.63, which increased to 0.74 for the incident medication \((p<0.0001)\), resulting in an increased adherence rate of 0.111. This increase of 0.111 exceeded the 0.01 decrease in PDC ratio within the TAU group \((0.80 \text{ to } 0.79, p=0.09)\), resulting in a net improvement of 0.123 for the GeneSight group compared to TAU \((p<0.0001)\).

Within the GeneSight group, 60.9% of patients discontinued their index medication, while 53.3% discontinued their incident medication (7.6% decrease, \(p<0.0001\), compared to 40.9% and 41.2% respectively within the TAU group (0.3% increase, \(p=0.69\)). The differential discontinuation rates from index to incident medications in the GeneSight group was 7.9% less than in the TAU group \((p<0.0001)\). The mean TTD of the index medication in the GeneSight group was 103 days, while the mean TTD of the index medication in the TAU group was 134 days \((p<0.0001)\). The mean TTD of the incident medication for patients in the GeneSight

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**Figure 2.** Subject attrition.
and TAU groups was 150 and 152 days, respectively ($p = 0.98$).

**Congruence with the GeneSight report**

Among the 1662 PGx tested patients, the percentage of those whose most severe category medication during the pre-test period was red or yellow decreased from 30.2% to 21.7% and from 49.5% to 44.7%, respectively, by the last 90 days of the post-test period (Figure 1b). The percentage of patients whose most severe category medication was green during the pre-test period increased from 20.3% to 21.7% and from 49.5% to 44.7%, respectively, by the last 90 days (Figure 1b).

The clinicians for 1301 GeneSight guided patients made congruent medication selections, as shown in Table 2, while 361 patients experienced incongruent selections, from the pre-test period compared to the last 90 days of the study (Figure 1b). GeneSight guided patients with congruent medication regimens spent an average of $7289.96 on medications over the post-test period, while patients with incongruent medication regimens spent $10,064.49, resulting in net annual cost savings of $2774.53 for patients with PGx congruent medication selections ($p < 0.0001$, Figure 1b). When congruence was analyzed according to therapeutic chapter, CNS medications accounted for 54.5% ($1512.44$, $p = 0.0002$) of the differential in total savings. Additional savings of $641.01 for anti-neoplastics ($p = 0.02$), $286.95 for diabetes ($p = 0.007$), and $145.85 for cardiovascular medications ($p = 0.08$) were also observed.

Of the 1662 PGx tested patients, 328 (19.7%) had an anxiety disorder, 470 (28.3%) had a depressive disorder, 96 (5.7%) had bipolar disorder, 11 (<1%) had a psychotic disorder, and 1133 (68.2%) had additional comorbid (mainly non-CNS) diagnoses (Figure 4a). The difference in total drug spend between the congruent and incongruent patients (Figure 4b) showed that congruent patients with anxiety disorder saved $6874.69 ($5777.72 vs $12,652.41 $F = 19.75$, $p < 0.0001$), those with depressive disorder saved $3579.81 ($7715.17 vs $11,294.98, $F = 7.26$, $p < 0.007$), those with bipolar disorder saved $4795.23 ($10,979.47 vs $15,774.70, $F = 2.26$, $p = 0.14$), and those with additional, mainly non-CNS comorbid diagnoses saved $4056.18 ($7338.34 vs $11,394.52, $F = 25.94$, $p < 0.0001$) more than incongruent patients.

PGx tested patients whose treating clinician was a psychiatrist spent $8830.82 annually on total drug spend, while patients of non-psychiatrists spent $7514.95 ($F = 5.23$, $p = 0.02$). Non-psychiatrists and psychiatrists made a congruent medication change at similar frequencies, 79.1% and 76.3%, respectively ($\chi^2 = 1.53$, $p = 0.22$).

The resulting cost differential as a function of congruence for patients whose treating clinician was not a psychiatrist was $3360.10 (Figure 5; $p < 0.0001$). The same trend was observed for the patients of psychiatrists, but the $1308.00 cost difference as a function of congruence was not statistically significant ($p = 0.24$).

**Discussion**

The current ‘real-world’ project included only patients who failed initial therapy for their psychiatric condition who typically represent about half of all treated depression patients¹, and likely more for bipolar disorder²², anxiety disorders²³, and schizophrenia²⁴. Patients whose physicians had the benefit of GeneSight PGx testing to guide their medication selection saved $1035.60 in total drug spend over 1 year compared to unguided, propensity-matched controls. Given that the inclusion criteria were designed to capture a costly treatment refractory population it is not surprising that, while the change in total drug spend was significantly less in the GeneSight group, both groups still showed increases in their medication spend compared to the prior 180 days.
Limitations of this study include the lack of therapeutic efficacy follow-up data and possible confounding due to matching only on demographic and psychiatric variables. However, the matched cohort was created using rigorous and well established techniques, resulting in demographic attributes that were exceptionally similar to those of the CPGx group. While psychiatric prescriptions and diagnostic categories were also distributed in a near perfect match, it is impossible to say with certainty that the tested and control cohorts were identical in all other respects.

One of the drivers of the drug cost savings might be the decrease in the number of medications in the GeneSight group. Approximately one in five patients in the GeneSight group were on one less medication by the last 90 days of the post-test period compared to the TAU group ($p < 0.0001$). Thus, CPGx offers the possibility of improved efficacy and decreases in pharmacy costs while concomitantly decreasing patients' exposure to polypharmacy.

Clinicians in the GeneSight group made their medication decisions based on mitigating genetic and non-genetic factors. Their use of the GeneSight test was evidenced by 65% increases in prescriptions for green category medications and nearly a third decrease in red medications, relative to the pre-test period (Figure 1b). Furthermore, approximately 80% of physicians in the GeneSight group made a treatment decision congruent with the CPGx report, saving patients $2774.54 in annual total drug spend over those patients who experienced an incongruent decision ($p < 0.0001$, Figure 3b).

Our data demonstrate an improvement in adherence from the index to the incident medication in the GeneSight group. A similar effect was seen with the rate of, and time to, discontinuation, which for the GeneSight group improved by 2.6 fold over the TAU group. The difference in baseline adherence, with resultant improvement after GeneSight testing suggests a CPGx-driven improvement in adherence specifically in those...
individuals who tend to be less adherent and potentially less responsive to their initial medications. Impressively, this improvement in adherence exists in the context of decreased comparative pharmacy costs. Given the lack of general pharmacogenomic knowledge in primary care and psychiatry, it is possible that the combinatorial and integrative aspects of GeneSight’s combinatorial approach contribute to this synergistic effect of improved adherence and decreased cost when compared to other gene-by-gene PGx assays which have demonstrated similar improved adherence, but increased pharmacy costs.

Mental health treatment outcomes correlate with the outcomes of comorbid chronic illnesses such as heart disease, diabetes, and cancer. Our comparisons of pharmacy costs across groups show that 69% of the $1035.60 in annual pharmacy savings in the PGx tested group were for non-CNS medications. A growing body of literature shows that the appropriate treatment of mental illness improves outcomes of comorbid medical conditions and lowers cost for their treatment. Mental health treatment outcomes correlate with the outcomes of comorbid chronic illnesses such as heart disease, diabetes, and cancer. Our comparisons of pharmacy costs across groups show that 69% of the $1035.60 in annual pharmacy savings in the PGx tested group were for non-CNS medications. A growing body of literature shows that the appropriate treatment of mental illness improves outcomes of comorbid medical conditions and lowers cost for their treatment. This pattern was found here, where significant annual savings for diabetes ($286.95), oncology ($640.01), and cardiovascular ($168.17) medications were obtained in the CPGx congruent subgroup suggesting that non-CNS pharmacy spend savings might be a consequence of improvement in patients’ psychiatric conditions. Another possible reason for savings in non-CNS medications may be that the clinician evaluated Genesight tested patients' non-CNS pharmacology in light of the pharmacogenomic information and made cost efficient changes to non-CNS medications. Finally, there is the possibility of improved patient engagement in their care allowing the patient to more actively work with the physician regarding their pharmacologic treatment leading to more streamlined medication management and therefore improved non-CNS pharmacologic costs.

Our data show that non-psychiatrists who have access to GeneSight information make more CPGx driven congruent decisions and therefore save an additional $1315.87 on drug spend per patient compared to psychiatrists. Given the shortage of psychiatrists in the United States and the increasing burden of mental healthcare for non-psychiatric practitioners, it is encouraging that non-psychiatrists who categorically implemented the GeneSight test engendered this improvement.

The current project confirms and expands upon the UHS retrospective healthcare utilization study which included anxiety and depressive disorders and the comorbidity between anxiety and depression. However, 71.7% of patients in the present study did not have a primary or co-primary diagnosis of a depressive disorder. Of those who did, patients who were maintained on a congruent medication regimen showed a $3579.81 reduction in pharmacy costs compared to patients on an incongruent medication regimen, while congruent patients with a primary or co-primary diagnosis of an anxiety disorder demonstrated a $6880.69 improvement in pharmacy costs compared to incongruent patients (Figure 4b). As summarized in Figure 3b, the GeneSight cost savings effect increases as a function of congruence with the report, and is beneficial for patients with primary diagnoses of depressive disorders and/or anxiety disorders (Figure 4b).

**Conclusion**

The current study compares an integrated, combinatorial psychiatric pharmacogenomic test (CPGx) to untested
standard of care in patients who failed monotherapy for their condition. Patients who received pharmacogenomic testing (n = 2168) saved over $1000 in medication costs annually and improved the rate of medication adherence compared to the untested standard of care cohort (n = 10,880). This study is the largest psychiatric CPGx economic outcome study to date. It is also the only economic outcome study of psychiatric pharmacogenomics to show decreased direct pharmacy costs in conjunction with improved adherence and a reduction in medications for co-morbid conditions. The integrative/combinatorial aspects of GeneSight, the congruence of clinical decisions with its recommendations, and improved pharmacy costs provide direct evidence of a CPGx induced cost savings effect. Further increases in cost savings from non-psychiatrists provide evidence for the applicability of GeneSight in a broad range of clinical practice settings. When assessed together, the efficacy and economic data make a compelling argument for the use of GeneSight testing in the difficult to treat populations of treatment-resistant depression and anxiety.

Transparency

Declaration of funding
The project was fully funded by Assurex Health.

Declaration of financial/other relationships
J.G.W., J.D.A., A.G.M. and B.M.D. have disclosed that they are employees of Assurex Health and own stock in the company. J.M.C. and C.A.A. have disclosed that they are employees of Assurex Health. S.Go., G.L., K.K.P. and S.Ga. have disclosed that they are employees of Express Scripts.

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