Pharmacogenetic-Guided Psychiatric Intervention Associated With Increased Adherence and Cost Savings

Jesen Fagerness, JD; Eileen Fonseca, MS; Gregory P. Hess, MD, MBA, MSc; Rachel Scott, PharmD; Kathryn R. Gardner, MS; Michael Koffler, MBA; Maurizio Fava, MD; Roy H. Perlis, MD, MSc; Francis X. Brennan, PhD; and Jay Lombard, DO

Objectives

Pharmacogenetic testing as a means of guiding treatment decisions is beginning to see wider clinical use in psychiatry. The utility of this genetic information as it pertains to clinical decision making, treatment effectiveness, cost savings, and patient perception has not been fully characterized.

Study Design

In this retrospective study, we examined health claims data in order to assess medication adherence rates and healthcare costs for psychiatric patients.

Methods

Individuals for whom pharmacogenetic testing was ordered (cases) were contrasted with those who did not undergo such testing (controls). Cases and controls were propensity score matched in order to minimize risk of confounding in this nonrandomized study. An initial analysis of 111 cases and 222 controls examined both adherence and healthcare costs. A replication study of 116 cases and 232 controls examined adherence alone, as cost data was not available for this latter cohort.

Results

Overall, individuals with assay-guided treatment were significantly more medication adherent ($P = 1.56 \times 10^{-3}$; Cohen's d = 0.511) than patients with standard treatment and demonstrated a relative cost savings of 9.5% in outpatient costs over a 4-month follow-up period, or $562 in total savings.

Conclusions

The data show the utility of pharmacogenetic testing in everyday psychiatric clinical practice, as it can lead to improved patient adherence and decreased healthcare costs.

Am J Manag Care. 2014;20(5):e146-e156

Depression and other psychiatric illnesses have substantial costs in human and financial terms, accounting for 4 of the top 10 causes of disability worldwide.[1] In the United States, it is estimated that mental health disorders account for 6.2% of the nation's healthcare spending.[2] A major driver of depression costs is treatment-resistant depression (TRD),[3] defined as a failure to reach symptomatic remission despite at least 2 adequate treatment trials.[4] An estimated two-thirds of patients with depression will not respond to first-line treatment and more than one-third of patients will become treatment resistant.[5-7] These individuals pose an even more striking cost burden, approximately 40% higher, compared with patients without TRD.[8,9] Treatment for psychiatric disorders is further complicated by variation in medication response across populations. Known pharmacodynamic and pharmacokinetic variations exist across ethnic groups impacting response to common psychiatric medications.[10] There is abundant evidence that genetic variations influence drug disposition, metabolism, transport, and response, resulting in changes to efficacy and tolerability of psychotropics.[11-13] An estimated 40% of the interindividual differences in antidepressant response are explained by common genetic variations.[14] Genetic variations may compound already elevated costs by increasing the risk for intolerable side effects or poor efficacy, which may contribute to nonadherence.[15-19]

Identifying genetic variations involved in treatment response may facilitate more targeted evidence-based interventions in order to improve the likelihood of remission. While a theoretical basis for expecting benefit from genetic testing exists, the actual impact on outcomes—and potential cost savings in particular—has not been well established. The use of claims data to establish these benefits provides advantages through the efficiency of data collection, ability to observe effectiveness in real-world clinical practice, and the ability

to directly measure costs. While such methods pose a risk of confounding, modern analysis and matching techniques, including propensity score matching, can be used to reduce these potential sources of bias. The objective of the current study was to determine whether patient and clinician access to genetic information during psychiatric treatment selection would influence medication adherence and healthcare costs among psychiatric patients.

Take-Away Points

This research describes the clinical utility of pharmacogenetic testing in psychiatric practice through the analysis of pharmacy and private practitioner medical claims. Patients whose clinicians had access to results of a genetic test to help guide treatment decisions had improved medication adherence as well as decreased overall healthcare costs. This study was able to demonstrate that:

- Genetic testing can lead to a relative cost savings of 9.5% in outpatient costs, or $562 per patient over 4 months.
- Genetic testing can lead to improved patient medication adherence.
- Genetic testing in psychiatric populations could become a useful tool in everyday practice.

MATERIALS AND METHODS

Design

This retrospective, observational study used patients' claims data from September 2010 through September 2012. Patients were divided into 2 groups: (1) cases whose treating clinicians ordered genetic testing and (2) a matched set of controls whose treating clinicians did not have access to genetic information, treating patients as usual.

Data Source

The genetic test used in this study, the Genecept Assay, analyzed variations in 5 pharmacodynamic and 2 pharmacokinetic genes associated with treatment response, side effects, metabolism, tolerability, and overall efficacy of many psychiatric medications.[15,20-24] Pharmacokinetic genes included cytochrome P450 2D6 (*CYP2D6*) and 2C19 (*CYP2C19*). Pharmacodynamic genes included the serotonin transporter (*SLC6A4*), calcium channel subunit (*CACNA1C*), dopamine receptor subtype (*DRD2*), catechol-O-methyl transferase (*COMT*), and methylenetetrahydrofolate reductase (*MTHFR*).

The saliva-based test was administered to cases at their clinician's office. Clinicians were provided with instructions and telephone support. Samples were sent to a Clinical Laboratory Improvement Amendments (CLIA) certified lab for analysis. After genotyping via polymerase chain reaction (PCR) Taqman, a results report was provided to clinicians with a summary of clinical interpretation and implications for each variant supported by peer-reviewed published literature. An algorithm that was designed based on the functional significance of each variant and the associated effects on treatment outcomes was applied to generate a unique report for each patient. Professionals with experience in medical genetics and psychopharmacology were available to assist clinicians with interpretation of results.

Healthcare utilization and cost data were extracted from IMS Health longitudinal patient-level databases which included pharmacy claims, private practitioner medical claims, and hospital detail charge master records. Available data included all claims submitted to third-party payers including commercial insurers, Medicare and Medicaid via Centers for Medicare & Medicaid Services (CMS) 1500 forms and others (eg, Tricare) in all 50 US states, and cash claims. Prescriptions were analyzed using the National Council for Prescription Drug Programs claim forms, which included approximately 2 billion dispensed claims per year within the database. Patients were assigned a synthetic identifier, and the databases were certified as being compliant with the Health Insurance Portability and Accountability Act. This study was deemed exempt from additional consent requirements by Chesapeake IRB (Pro00008398), as data were completely deidentified.

Sample Measures and Selection Criteria

Cases were included if their practitioner received their test results between May 1, 2011, and March 31, 2012. The index date for cases was defined as the date the Genecept Assay results were available to clinicians. Additional inclusion criteria for cases required a psychotropic prescription be dispensed between 5 and 60 days postindex (**Appendix A**) as well as pharmacy activity between 5 and 8 months pre-index, as evidenced by claims data. Cases were required to have a psychiatric diagnosis listed in the claims database (**Appendix B**). Additional selection criteria were applied to create a final pool of cases utilized in propensity score matching (PSM) (**Table 1**).

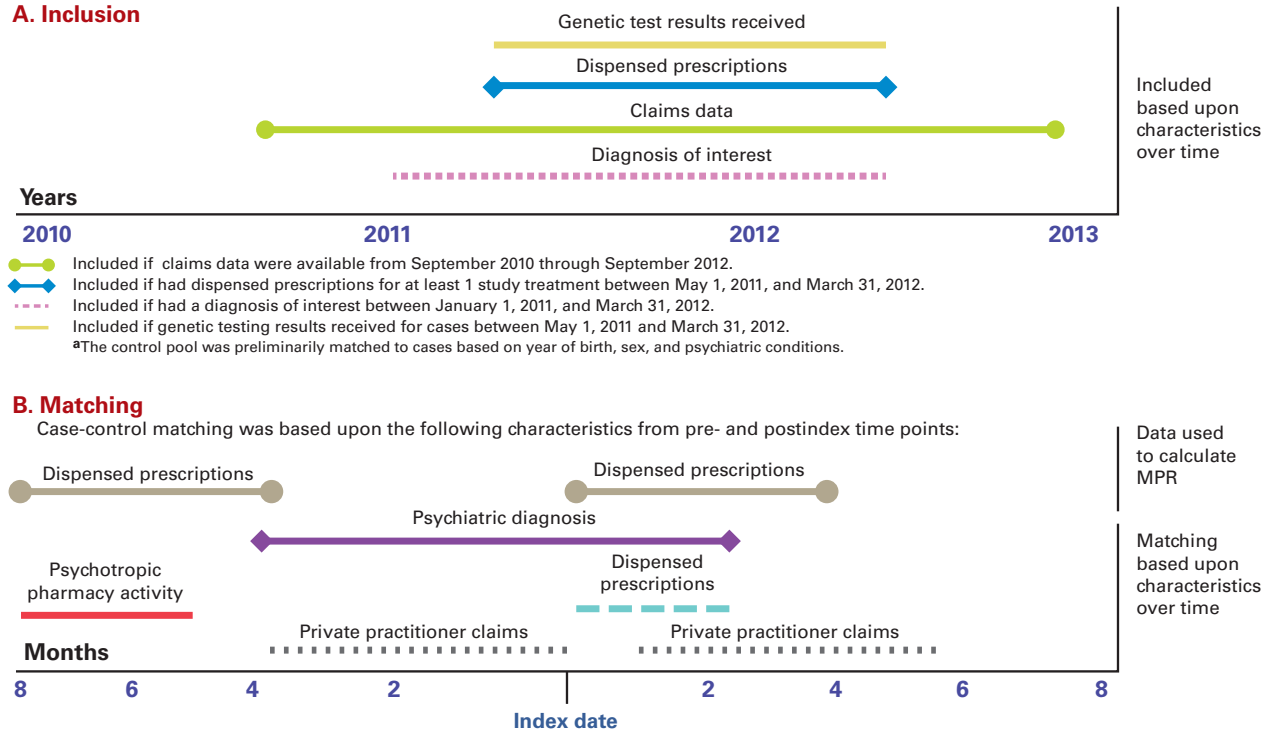
The pool of controls was created by selecting patients available in the claims database with matching year of birth, sex, and psychiatric condition to any cases. The index date for the corresponding case was assigned to all matching controls. The matching controls must have received any dispensed psychotropic agent within +/– 7 days from the date of a case's in both the pre- and postindex periods. Additional selection criteria were applied

Table 1. Attrition Table

Attrition Table—Case Selection			
Step	**Criteria**	**Cases**	**Replication Cases**
1	Unique patients with genetic test result between May 2011 and March 2012 and observed within IMS databases (the "index date")	1016	1016
2	Patients observed with a dispensed prescription for at least 1 dispensed study treatment between 5 and 60 days postindex (the earliest dispensed fill becomes the "postdrug start date")	505	505
3	Patients observed, with psych-related drug activity, in the pharmacy claims between 5 and 8 months prior to the index date	401	401
4	Patients observed, with any activity, in the pharmacy claims database 4 months or more after their postdrug start date	364	364
5	Patients have a psychiatric diagnosis of interest (eAppendix B)	305	305
6	Patients observed, with any activity, in the private practitioner claims (CMS1500) (a) 4 months or more prior to the index date and (b) 4 months or more after their postdrug start date	192	
7	Patients observed in or eligible for observation within the hospital charge detail master's data	113	
8	Patients already observed in the primary analysis		192
9	Matched final sample (1 case: 2 control)	111	116
Attrition Table—Control Selection			
Step	**Criteria**	**Controls**	**Replication Controls**
1	Patients with a dispensed prescription for at least 1 of the study treatments between May 1, 2011, and March 31, 2012 (possible index dates) and who have not had a Genecept Assay through July 2012	42,451,929	42,451,929
2	Patients observed in IMS private practitioner claims (CMS1500) database with a diagnosis of interest between January 1, 2011, and May 31, 2012	8,916,352	8,916,352
3	Patients with a dispensed prescription for at least 1 of the study treatments between May 1, 2011, and March 31, 2012 (possible index dates), was observed in private practitioner claims (CMS1500) with a psychiatric diagnosis of interest (eAppendix B), had a known age and gender, and who did not have genetic testing with the Genecept Assay	8,785,951	8,785,951
4	Patients observed in or eligible for observation within the hospital charge detail master's data	4,785,849	4,785,849
	Preliminary matching – to help focus the "search population"		
3	Possible controls that have the same year of birth and gender as at least 1 case patient (case attrition step #8)	2,570,715	2,570,715
4	Possible controls that have at least 1 psychiatric diagnosis group the same as at least 1 case patient	1,586,347	1,586,347
5	Possible controls that received a dispensed fill for a study treatment within +/– 7 days from at least 1 case's pre-index psych-related dispensed drug date (the drug identified in case attrition step #3)	540,112	540,112
6	Possible controls that received a dispensed fill for a study treatment within +/– 7 days from at least 1 case's postindex psych-related dispensed drug date (the drug identified in case attrition step #2)	253,609	253,609
	Controls were assigned the index date of each case where the control and that case pass Steps 3 through 6 above. While counts represent unique number of controls, a control could be considered for multiple case matches.		
7	Patients observed with a dispensed prescription for at least one dispensed study treatment between 5 and 60 days postindex (the earliest dispensed fill becomes the "postdrug start date")	251,112	251,112
8	Patients observed, with psych-related drug activity, in the pharmacy claims between 5 and 8 months prior to the index date	250,624	250,624
9	Patients observed, with any activity, in the pharmacy claims 4 months or more after their postdrug start date	239,125	239,125
10	Patients have a psychiatric diagnosis of interest between 4 months pre- to 60 days postindex date	155,573	155,573
11	Patients observed, with any activity, in the private practitioner claims (CMS1500) (a) 4 months or more prior to the index date and (b) 4 months or more after their postdrug start date	126,933	
12	Patients with an known US Census Region, a calculated MPR >0 (eg, excludes those patients with poor prescription fill data pre- or postindex)	126,649	
13	Patients already observed in the primary analysis		28,924
14	Matched final sample (1 case: 2 control)	222	232

CMS indicates Centers for Medicare & Medicaid Services; MPR, medication possession ratio.

Figure. Temporal Characteristics Used for Inclusion, Matching, and MPR[a]



This figure is a temporal representation of factors used to determine the inclusion of cases and controls (A) and the characteristics to determine MPR and facilitate matching (B). Matching characteristics are also described in Table 2.
MPR indicates medication possession ratio.

to the controls to further limit the pool utilized in PSM (Table 1). Figure A shows a temporal depiction of inclusion characteristics.

PSM was performed on the refined pools of cases and controls, matching 2 controls to every case. PSM was computed using a logistic regression model that adjusted for covariates of patient age, sex, payer type, US Census region, all psychiatric condition(s), all medication type(s), Charlson Comorbidity Index score, and treating practitioner's specialty.[25-28] Binary variables were assigned for presence or absence of each central nervous system (CNS) diagnosis of interest as determined by the *International Classification of Diseases, Ninth Revision*, supplied at the time of testing for cases or the diagnosis code associated with private practitioner visits between 4 months pre to 60 days postindex (Appendix B). Separate binary variables were assigned for each pharmacologic category of interest (Appendix A). A standard mean difference between the 2 samples of less than 10% pre-post matching was considered indicative of good balance.[29,30] Figure B shows a temporal depiction of matching.

A separate replication analysis of medication adherence, which included different cases and controls, was conducted using the same selection criteria, with the exception of observation within medical claims following index date (Table 1). This criterion was necessary for cost evaluation in the primary analysis, but did not impact inclusion in a replication analysis regarding medication adherence.

Adherence Methods

Adherence was calculated using the medication possession ratio (MPR).[31,32] MPR was calculated at the active ingredient or generic drug level for each psychiatric product the patient filled during the respective periods: (1) preindex included dispensed scripts between 4 and 8 months pre-index (each product was tracked for 120 days from the time the first script was filled within this period); and (2)

postindex included dispensed scripts between days 5 and 120 postindex. Dispensed dates that did not allow for a 4-month observation window were excluded. At the generic molecule and patient level, the days of supply was summed over the respective observation period to represent the MPR numerator. The MPR denominator was the observation period duration of 120 days. Figure 1B shows a temporal depiction of pharmacy claims data utilized to determine MPR.

Overlapping days were considered early fills. Any prescription's days of supply that extended beyond the 120-day observation period was truncated to end on the 120th day of observation. MPR was calculated for all distinct drugs at the generic level, and the patient's maximum MPR among all products was used to represent the overall MPR for that period. Within sample comparison of the mean MPR 4-month pre-index versus 4-month postindex analysis was conducted. Additionally, a case versus control approach was utilized.

Statistical analyses were conducted using The Comprehensive R Network and a significance level of 0.05. χ^2 tests were conducted for categorical variables and Welch 2-sample 2-sided *t* tests for differences in means, assuming unequal variances; pre-post comparisons within a sample were calculated using 2-sided paired *t* tests. Propensity score matching utilized the MatchIt package.[33,34] Combined meta-analysis of the primary and replication cohorts was done using the weighted *z*-score method.[35]

Resource Utilization and Associated Costs Methods

Mean resource utilization and associated costs were calculated for each cohort. The total number and cost of dispensed prescriptions for all medications and the total number and cost of all outpatient medical visits were calculated for the 4-month pre- and postindex periods. Pharmacy costs and total cost data were analyzed as component and as composite utilization for cases and controls. Costs were calculated by using standard costs for the actual services and quantities received to control for variable costs within the data, and the inability to incorporate health plan–allowed amounts into the matching. Dispensed prescription cost was calculated using average wholesale unit price for the given national drug code (NDC) and quantity dispensed; medical costs were assessed using the 2012 CMS medical physician fee schedule, including the procedure's relative value units (work, practice expense, and malpractice) offset by geographic practice cost index (GPCI) based on the physician's location. Where a physician's zip code was missing or invalid, the national level GPCI of "1" was used.

Comparisons of the mean utilization and cost of the component and composite pre- versus postindex within each sample were conducted and reported. Additionally, a case versus control approach was utilized. The percent increase of case costs compared with control costs was assessed along with the gross cost change between cases and controls. In an attempt to account for the different baseline cost structures, percent cost increase between cases and controls on an averaged baseline was used to view the gross cost difference. Since this was a calculated baseline, and not an actual baseline, the conceptual basis for this part of the analysis is a theoretical approximation of the opportunity cost of a control taking the test, and a case not taking the test.

RESULTS

A total of 1016 patients met the inclusion criteria for cases (Table 1). After applying the selection criteria, 113 cases were identified. A total of 126,649 patients met all control inclusion criteria and were eligible for PSM. PSM yielded 111 cases and 222 well-matched controls, as indicated by a standard mean difference of less than 10% for matched variables (**Table 2**). The replication analysis included 128 cases and 402,868 controls prior to matching; 116 cases and 232 matched controls remained. This matched replication sample exhibited good concurrence, with only 2 variables having a standardized mean difference less than 10% (exposure to serotonin modulators [nonselective serotonin reuptake inhibitors] or atomoxetine pre-index). There were no significantly different characteristics postmatching.

Combining both analyses, the baseline adherence for cases was significantly lower (85.2%) than that of the controls (92.8%) despite the use of propensity score matching ($P = 4.83\times10^{-6}$; Cohen's d = 0.746, **Table 3**).[35] The improvement in medication adherence in cases was so substantial over the observation period that by the end of the postindex period, adherence was not statistically significantly different between the groups (Table 3). Overall, cases in the primary and replication analyses showed an average increase in adherence of 6.3% ($P = 2.40\times10^{-4}$; Cohen's d = 0.7068) versus controls who showed an average increase of 0.3% ($P = .5741$; Cohen's d = 0.1544). Thus, patients using the Genecept Assay showed a statistically significant increase in adherence compared with untested controls of 6.0% ($P = 1.56\times10^{-3}$; Cohen's d = 0.5108).

The increase in adherence in cases observed in the primary analysis was reflected in an increase in dispensed prescriptions (mean = 2.2 and 0.3 in cases and controls, respectively, for a mean difference of 1.9, $P = .022$). Over a

Table 2. Characteristics of Cases and Controls

	Pre-Matching			Postmatching		
	Cases	Controls	*P*[a]	Cases	Controls	*P*[a]
Unique patient count	113	126,649		111	222	
Patient gender						
Female	78/69.0%	102,367/80.8%	.0015	78/70.3%	151/68.0%	.6759
Male	35/31.0%	24,282/19.2%		33/29.7%	71/32.0%	
Patient age						
Mean	45.8	47	.4898	45.8	44.4	.4819
Median	50	50		50	49	
Standard deviation	18.5	15.7		18.7	15.6	
US Census region						
Northeast	31/27.4%	22,738/18.0%	.0153	31/27.9%	60/27.0%	.8785
Midwest	18/16.0%	24,625/19.4%		17/15.3%	40/18.0%	
West	7/6.2%	16,496/13.0%		7/6.3%	17/7.7%	
South	57/50.4%	62,790/49.6%		56/50.5%	105/47.3%	
Payer type[1]						
Commercial	45/39.8%	39,149/30.9%	.2457	44/39.6%	80/36.0%	.8012
Medicare	19/16.8%	23,398/18.5%		19/17.1%	42/18.9%	
Other (includes Medicaid, cash)	49/43.4%	64,102/50.6%		48/43.3%	100/45.1%	
Number of distinct treatment trials within observation window						
Mean	3.6	3.1	.0216	3.5	3.5	.9515
Median	4	3		4	3	
Standard deviation	2	1.8		1.9	1.9	
Number of distinct drug classes/agents						
Mean number of unique drug classes below	3.1	2.7	.0268	3	3.1	.5801
Median number of unique drug classes below	3	3		3	3	
Standard deviation	1.6	1.3		1.5	1.5	
Folate derivatives	10	4242	.0012	10	17	.6702
Mood stabilizers	43	49,028	.8858	43	91	.6928
Anxiolytics	68	75,317	.8782	67	122	.3479
TCAs	13	10,835	.2626	12	23	.8995
MAOIs	1	187	^	1	0	^
SSRIs	42	58,278	.0593	42	84	1
SNRIs	28	28,833	.61	28	56	1
Mirtazapine	9	5585	.0659	8	13	.6325
Bupropion	23	18,403	.0792	21	52	.349
Serotonin modulators	16	19,099	.7845	15	28	.8172
Stimulants	44	24,447	$<1.0e^{-5}$	42	93	.4775
Atomoxetine	0	1445	^	0	2	^
Alpha-2a-agonist	6	7666	.7405	5	14	.504
Antipsychotics	44	43,913	.341	44	103	.2418

(Continued)

Table 2. Characteristics of Cases and Controls *(Continued)*

	Pre-Matching			Postmatching		
	Cases	Controls	P[a]	Cases	Controls	P[a]
Psychiatric diagnosis groups						
Mean number of unique diagnosis groups below	1.8	1.5	.0003	1.8	1.9	.5684
Median number of unique diagnosis groups below	2	1		2	2	
Standard deviation	0.9	0.8		0.9	1.1	
ADHD	28	16,140	.0001	26	58	.5924
Anxiety disorder	34	44,785	.2412	33	78	.3239
Dementia	1	1335	^	1	3	^
Depression	38	36,952	.2981	37	60	.2325
Mood disorder	87	58,539	$<1.0e^{-5}$	85	175	.6396
Psychosis	5	5233	^	5	11	.8562
Schizophrenia	1	3046	^	1	1	^
All other psych	15	28,208	.0216	15	34	.6617
Charlson Comorbidity Index (CCI)[2]						
Mean score	0.3	0.4	.0041	0.3	0.3	.953
Median score	0	0		0	0	
Standard deviation	0.6	0.9		0.6	0.7	
Treating physician characteristics						
Physician specialty						
PCP (general practice, geriatrics, pediatricians, family, internal medicine)	15/13.3%	53,485/ 42.2%	$<1.0e^{-5}$	15/13.5%	30/13.5%	.8633
Psychiatry	83/73.4%	51,632/ 40.8%		81/73.0%	162/73.0%	
All others	15/13.3%	21,532/ 17.0%		15/13.5%	30/13.5%	
Physician gender						
Female	53/46.9%	44,529/ 35.2%	.0077	52/46.8%	75/33.8%	.0181
Male	57/50.4%	79,233/ 62.5%		56/50.5%	142/64.0%	
Unknown	3/2.7%	2887/2.3%		3/2.7%	5/2.2%	

ADHD indicates attention-deficit/hyperactivity disorder; MAOI, monoamine oxidase inhibitor; MPR, medication possession ration; PCP, primary care practitioner; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Statistical testing at alpha = 0.05 level. Chi-Square test for categorical variables. Welch Two Sample *t*-test for differences in means, assuming unequal variances.
^Indicates that at least one cell was <5, so stat testing could not be confidently preformed.
[1]Payer was identified based on the 30 days prior to and post the first study treatment of interest after Index. If there were multiple payers, they were hierarchically ordered as: Medicaid, Medicare, Commercial, Cash, Other. The substantial amount of Unknowns are attributed to claims being billed to a PBM with an unspecified plan. Medicaid and Cash were eventually aggregated to Other due to low sample sizes (<5%).
[2]The CCI is based on an adaption of the Deyo version. See references in the Analytical Rules."

4-month period, an increase in overall pharmacy costs was also observed for cases, averaging $886 per patient (a 14.2% increase from the pre- to postindex period), while controls showed a lesser increase of $222 dollars (a 5.5% increase, mean difference = $664, Table 4). At baseline, the average pharmacy cost for cases was 53.4% greater than for controls although the number of dispensed prescriptions was 29% less. However, between the pre- and postindex periods, outpatient visits declined by 1.2 visits for cases, resulting in a drop of $425 per patient for private practitioner medical costs (a 26.8% decrease), while controls maintained a similar number of outpatient visits (a reduction of 0.1 visit) and costs increased by $537 per patient on average (a 63.4% increase, Table 4). Overall, both cases and controls showed an increase in costs during the postindex period; however, cases increased costs by 5.9%, while controls more than doubled this finding with an increase in total costs of 15.4% (Table 4). This was seen as an overall comparative cost savings of $298 in cases over the 4-month postindex period. When these whole dollar cost savings were adjusted to reflect the considerably higher baseline costs of the cases, the relative cost savings for cases is 9.5% or $562 per patient over controls (Table 4).

DISCUSSION

This study provides real-world, observational, evidence that pharmacogenetic testing can inform treatment inter-

Table 3. Adherence Results

Combined Analysis	Pre-Index MPR	Postindex MPR	Change in MPR (Pre-Post)	*P*[a]	Cohen's d
All Cases (n = 227)	85.2%	91.5%	6.3%	2.40E-04	0.707
All Controls (n = 454)	92.8%	93.0%	0.3%	.574	0.077
Difference in MPR (cases vs controls)	–7.5%	–1.5%	6.0%		
P[a]	4.83E-06	.284	1.56E-03		
Cohen's d	0.746	0.154	0.511		

MPR indicates medication possession ratio.
[a]Weighted z-score method (2-tailed *t* test).

Table 4. Cost Data

	Difference (Post-Pre)				
Medical Cost Utilization (n = 333)	Per Patient Mean Difference (cases vs controls)	*P*	Cases Percent Change	Controls Percent Change	Mean Baseline Difference (cases vs control)
All Pharmacy Activity	$664	.108	14.2%	5.5%	$418
Private Practitioner Medical Activity	–$961	.105	–26.8%	63.4%	–$980
Total Costs	–$298	.705	5.9%	15.4%	–$562

ventions leading to increased patient adherence and reduced healthcare costs. In the present study, the observed increase in adherence in cases (Table 3) was associated with a significant *decrease* in overall costs associated with private practitioner medical activity (Table 4). While pharmacy costs for cases increased, the utilization of medical services decreased, leading to a reduction in total outpatient costs for cases. The increase in pharmacy costs among cases is likely due to consistent medication fills concomitant with improved medication adherence. Depression can lead to greater functional impairment, increased likelihood of discontinuing treatments, and inferior overall health, all of which contribute to higher medical costs associated with chronic illnesses.[36] This study provides evidence that the Genecept Assay is an effective tool to reduce the cost burden associated with depression and other mental illnesses.

Poor medication adherence is a problem common in the treatment of psychiatric illness, observed in an estimated 31% of patients with schizophrenia or schizoaffective disorders, 33% of patients with bipolar disorder, and 41% of patients with other severe mental illnesses.[37] A number of studies have shown that common genetic variations may be associated with increased side effect risk and medication intolerance which result in higher levels of medication discontinuation and nonadherence,[17,18] as well as higher overall medical costs.[38,39] The so-called "short" allele in the promoter of SLC6A4 has been associated with decreased adherence due to side effects.[17] Additionally, CYP2D6 poor metabolizers were more likely to experience tardive dyskinesia and extrapyramidal symptoms and had a significantly higher prevalence of noncompliance compared with intermediate or extensive metabolizers.[18] These data suggest that genetic testing can allow clinicians to determine which patients are likely to suffer from adverse effects and medication intolerability and provide them with alternative treatment plans which may increase medication adherence.

The increase in adherence and cost savings reported in this study for cases builds upon several studies which have previously found pharmacogenetic testing to be cost effective in psychiatry.[38-40] A study of Medicare beneficiaries found that for each additional prescription filled, hospital costs decreased by $104.[41] Several studies have found that although medication adherence results in higher pharmacy costs,[42] nonadherence results in increased overall healthcare costs via higher rates of hospitalization, more hospital stays,[37,42] and increased short-term disability claims.[43] One genetic test analyzing several genetic polymorphisms found that patients who had high-risk variations related to adverse outcomes had 69% more total healthcare visits, 67% more general medical visits, 3 times more medical absence days, and 4 times more disability claims compared with those without these polymorphisms.[39] The current study, however, is the first to demonstrate that pharmacogenetic testing can reduce healthcare utilization and increase adherence.

Randomized controlled trials remain the gold standard for clinical investigation; however, this retrospective ob-

servational study was able to use real-world clinical data to demonstrate effectiveness through adherence and resource utilization. The claims data utilized in this study may be suggestive of adherence, although 1 inherent limitation of claims analyses is that there is no way to definitively determine if a patient took the dispensed medication. In addition, the ability to assess the implementation of genetic information in clinician decision making was not possible. Although only randomized trials can fully address the contribution of confounding factors, propensity score analysis represents a well-accepted means to assess the effect of an intervention(s) when randomization is not possible.[25,26] One limitation of PSM was the inability to capture the duration for which cases and controls were prescribed the psychiatric drugs (Appendix A) prior to matching which may be an unmeasured confounding variable. The matching reduced the amount of standardized mean difference among these covariates and eliminated all statistical difference of attributes included in matching between the samples (Table 2). Lower baseline adherence rates for cases could also be linked with another unobserved confounder; patients who are less satisfied with their treatment are less likely to adhere to their regimen and may be more likely to be selected for genetic testing. Disparities in adherence may be a contributing factor to elevated baseline costs in cases. The difference in cost among cases and controls was a calculated rather than an observed finding and subsequently not a component of the propensity score matching. However, other confounding factors were likely at play as the post hoc analyses were unable to find any clear distinctions between cases and controls which would account for the disparity in baseline costs. These disparities were accounted for by calculation of relative changes in costs and adherence for each group.

In summary, these results suggest that the use of the Genecept Assay in psychiatric populations improves patient adherence while demonstrating cost effectiveness. Randomized, controlled trials will be necessary to better characterize the direct impact on clinical outcomes, to address potential confounding sources, and to identify the populations in which this testing may be most useful. Also, more data about clinician and patient attitudes and experiences with personalized medicine will further refine how pharmacogenomics is used in practice, and could further influence the effectiveness and cost savings of this type of testing in healthcare.

Acknowledgments

The authors would like to thank Catherine Balderston McGuiness for analytic assistance and Ali Tabibzadeh for programming assistance. Both are employees of IMS Health, Inc.

Author Affiliations: Genomind, LLC, Chalfont, PA (JF, RS, KRG, MK, FXP, JL); Symphony Health Solutions, Horsham, PA (EF, GPH); Leonard Davis Institute, University of Pennsylvania, Philadelphia, PA (GPH); Massachusetts General Hospital, Boston, MA (MF, RHP).

Source of Funding: This study was supported by funding from Genomind, LLC.

Author Disclosures: Drs Lombard, Brennan, and Scott, Ms Gardner, Mr Koffler, and Mr Fagerness were all employees of Genomind, LLC during the preparation, implementation, and analysis of the study. Dr Hess and Ms Fonseca were employees of IMS Health, Inc, a company that received funding to conduct this study, during the preparation, implementation, and analysis of the study. Both Drs Fava and Perlis were employees of Massachusetts General Hospital and currently serve as members of Genomind's Scientific Advisory Board. Dr Perlis also currently serves on scientific advisory boards or consults for Healthrageous, Pamlab, Perfect Health, Proteus Biomedical, and RIDVentures. He receives royalties/patent fees from Concordant Rater Systems (now UBC).

Authorship Information: Concept and design (JF, EF, GPH, RS, MK, FXB, JL); acquisition of data (JF, RS, FXB); analysis and interpretation of data (JF, EF, GPH, RS, KRG, MK, MF, RHP, FXB, JL); drafting of the manuscript (JF, RS, KRG, FXB); critical revision of the manuscript for important intellectual content (JF, EF, GPH, RS, KRG, MF, RHP, FXB, JL); statistical analysis (EF, GPH); provision of study materials or patients (EF, GPH); obtaining funding (MK); administrative, technical, or logistic support (JF, RS, KRG, MK, MF, RHP, FXB); supervision (x).

Address correspondence to: Rachel Scott, 100 Highpoint Dr, Ste 102, Chalfont, PA 18914. E-mail: Rachel.Scott@genomind.com.

REFERENCES

1. Mental health disorder statistics: statistics related to mental health disorders. Johns Hopkins Medicine website. http://www.hopkinsmedicine.org/healthlibrary/conditions/mental_health_disorders/mental_health_disorder_statistics_85,P00753/. Accessed February 8, 2013.
2. Insel TR. Assessing the economic costs of serious mental illness. *Am J Psychiatry.* 2008;165(6):663-665.
3. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on healthcare utilization and costs. *J Clin Psychiatry.* 2002;63(11):963-971.
4. Mathew SJ. Treatment-resistant depression: recent developments and future directions. *Depress Anxiety.* 2008;25(12):989-992.
5. Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry.* 2006;67(suppl 6):16-22.
6. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: Results from the national comorbidity survey replication (ncs-r). *JAMA.* 2003;289(23):3095-3105.
7. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D project results: a comprehensive review of findings. *Curr Psychiatry Rep.* 2007;9:449-459.
8. Greenberg P, Corey-Lisle PK, Birnbaum H, Marynchenko M, Claxton A. Economic implications of treatment-resistant depression among employees. *Pharmaco Economics.* 2004;22(6):363-373.
9. Gibson TB, Jing Y, Smith Carls G, et al. Cost burden of treatment resistance in patients with depression. *Am J Manag Care.* 2010;16(5):370-377.
10. Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. *J Natl Med Assoc.* 2002;94(10 suppl):1-26.
11. Chung-Feng K, Yu-Sheng F, Zhongming Z, Po-Hsiu K. Prioritization and evaluation of depression candidate genes by combining multidimensional data resources. *PLoS One.* 2011;6(4):18696.
12. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci.* 2011;36(2):87-113.
13. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *New Engl J Med.* 2003;348(6):538-549.
14. Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. *Biol Psychiatry.* 2013;73(7):679-682.
15. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Mol Psychiatry.* 2010;15(5):473-500.

16. Baune BT, Hohoff C, Berger K, et al. Association of the COMT val158met variant with antidepressant treatment response in major depression. *Neuropsychopharmacology.* 2008;33(4):924-932.

17. Murphy GM, Jr., Hollander SB, Rodrigues HE, Kremer C, Schatzberg AF. Effects of the serotonin transporter gene promoter polymorphism on mirtazapine and paroxetine efficacy and adverse events in geriatric major depression. *Arch Gen Psychiatry.* 2004;61(11):1163-1169.

18. Kobylecki CJ, Jakobsen KD, Hansen T, Jakobsen IV, Rasmussen HB, Werge T. CYP2D6 genotype predicts antipsychotic side effects in schizophrenia inpatients: a retrospective matched case-control study. *Neuropsychobiology.* 2009;59(4):222-226.

19. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry.* 2010;167(7):763-772.

20. Porcelli S, Fabbri C, Serretti A. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *Eur Neuropsychopharmacol.* 2012;22(4):239-258.

21. Zhang JP, Lencz T, Malhotra AK. D2 receptor genetic variation and clinical response to antipsychotic drug treatment: a meta-analysis. *Am J Psychiatry.* 2010;167(7):763-772.

22. Lencz T, Robinson DG, Napolitano B, et al. DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia. *Pharmacogenet Genomics.* 2010;20(9):569-572.

23. Bhat S, Dao DT, Terrillion CE, et al. CACNA1C (Cav1.2) in the pathophysiology of psychiatric disease. *Prog Neurobiol.* 2012;99(1):1-14.

24. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet.* 2011;43(10):977-983.

25. Baser O. Too much ado about propensity score models? comparing methods of propensity score matching. *Value Health.* 2006;9(6):377-385.

26. Luo Z, Gardiner JC, Bradley CJ. Applying propensity score methods in medical research: pitfalls and prospects. *MCRR.* 2010;67(5):528-554.

27. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol.* 2010;172(9):1092-1097.

28. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat.* 2011;10(2):150-161.

29. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med.* 1998;17(19):2265-2281.

30. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46(3):399-424.

31. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther.* 1999;21(6):1074-1090.

32. Woltmann EM, Valenstein M, Welsh DE, et al. Using pharmacy data on partial adherence to inform clinical care of patients with serious mental illness. *Psychiatr Serv.* 2007;58(6):864-867.

33. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis.* 2007;15(3):199-236.

34. Ho DE, Imai, K, King, G, Stuart, EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Soft.* 2011;42(8):1-29.

35. Whitlock MC. Combining probability from independent tests: the weighted z-method is superior to Fisher's approach. *J Evol Biol.* 2005;18(5):1368-1373.

36. Rubio JM, Markowitz JC, Alegria A, et al. Epidemiology of chronic and nonchronic major depressive disorder: results from the national epidemiologic survey on alcohol and related conditions. *Depress Anxiety.* 2011;28(8):622-631.

37. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatr Serv.* 2001;52(6):805-811.

38. Chou WH, Yan FX, de Leon J, et al. Extension of a pilot study: impact from the cytochrome P450 2D6 polymorphism on outcome and costs associated with severe mental illness. *J Clin Psychopharmacol.* 2000;20(2):246-251.

39. Winner J, Allen JD, Altar CA, Spahic-Mihajlovic A. Psychiatric pharmacogenomics predicts health resource utilization of outpatients with anxiety and depression. *Translational Psychiatry.* 2013;3:e242.

40. Herbild L, Andersen SE, Werge T, Rasmussen HB, Jurgens G. Does pharmacogenetic testing for CYP450 2D6 and 2C19 among patients with diagnoses within the schizophrenic spectrum reduce treatment costs? *Basic Clin Pharmacol Toxicol.* 2013;113(4):266-272.

41. Stuart BC, Doshi JA, Terza JV. Assessing the impact of drug use on hospital costs. *Health Serv Res.* 2009;44(1):128-144.

42. Gilmer TP, Dolder CR, Lacro JP, et al. Adherence to treatment with antipsychotic medication and healthcare costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry.* 2004;161(4):692-699.

43. Burton WN, Chen CY, Conti DJ, Schultz AB, Edington DW. The association of antidepressant medication adherence with employee disability absences. *Am J Manag Care.* 2007;13(2):105-112. ■

www.ajmc.com Published as a Web Exclusive

Appendix A. Psychotropic Agents

Medication Classes/Agents
Folate derivatives
Mood stabilizers
Anxiolytics
TCAs
MAOIs
SSRIs
SNRIs
Mirtazapine
Bupropion
Serotonin modulators (non-SSRIs)
Stimulants
Atomoxetine
Alpha-2a-agonists
Antipsychotics

MAOI indicates monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Appendix B. Psychiatric *ICD-9-CM* Diagnosis Codes

Diagnosis Group	*ICD-9-CM* Diagnosis Codes
ADHD	314*
Anxiety disorder	293.84, 300.3, 309.81, 300.0*, 300.2*
Dementia	292.82, 290*, 294.1*, 294.2*, 331.* EXCLUDING 331.3, 331.4, 331.5, 331.8, 331.81, and 331.83
Depression	300.4, 309.0, 309.1, 309.28, 311
Mood disorder	292.84, 293.83, 301.13, 296*
Psychosis	291-294.99 or 297-299.99 EXCLUDING 292.82, 293.83, 293.84, 294.1*, 294.2*
Schizophrenia	V110, 295*
All other psych	625.4, 296*, 300.1*, 300.5-310.9, 312-312.4, 312.8-313.9, 315-319.99, 625.4 EXCLUDING 301.13, 309.0, 309.1, 309.28, 309.81

ADHD indicates attention-deficit/hyperactivity disorder; *ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.*