Cost-Effectiveness of Combinatorial Pharmacogenomic Testing for Treatment-Resistant Major Depressive Disorder Patients

John Hornberger, MD, MS, FACP; Qianyi Li, MS; and Bruce Quinn, MD, PhD

ABSTRACT

Objectives: To describe the lifetime outcomes and economic implications of combinatorial pharmacogenomic (CPGx) testing versus treatment as usual (TAU) psychopharmacologic medication selection for a representative major depressive disorder patient who has not responded to previous treatment(s).

Study Design: Markov state-transition analysis based on clinical studies.

Methods: Clinical validity and utility were based on published findings in prospective clinical studies of a commercially available CPGx test. Data for quality of life, direct costs, and indirect costs were extracted from meta-analyses of published literature on clinical studies and claims databases. Outcomes were assessed from a societal perspective, and included differences between the CPGx and the TAU strategies in quality-adjusted life-years (QALYs), cumulative direct and indirect costs, and cost per QALY gained.

Results: CPGx improved the treatment response rate by 70% (1.7 times as high as that with TAU), increasing QALYs by 0.316 years. With these health benefits, CPGx is expected to save $3711 in direct medical costs per patient and $2553 in work productivity costs per patient over the lifetime. The cost-effectiveness of CPGx testing was robust over a wide range of variation in the input parameters, including the scenario when testing efficacy was set to its lower limit.

Conclusions: CPGx testing has been shown by prospective studies to modify treatment decisions for patients nonresponsive to previous treatment(s), with increased rates of treatment response. These effects are projected to increase quality-adjusted survival, and to save both direct and indirect costs to individual patients and society generally.

Am J Manag Care. 2015;21(6):e357-e365

Major depressive disorder (MDD) is associated with significant clinical and economic burden worldwide, with the United States[1] experiencing a 16.6% lifetime prevalence rate.[2] Although guidelines recommend antidepressants as well-validated treatment options, not all individuals will respond and/or achieve remission with an initial treatment and little evidence exists to guide next-step treatment, resulting in a trial and error approach to drug selection.[3] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the rate of response to an initial antidepressant treatment was only 49.6%, which declined with an increasing number of treatment trials.[4] A systematic review of published studies found that patients nonresponsive to 1 or more treatments have a 15% likelihood of suicide ideation, an approximately 17% likelihood of a suicide attempt, and a 10% incidence of severe adverse events; the net effect being a 0.26 absolute reduction in health utility compared with treatment-responsive patients.[5] Moreover, the annual medical costs for managing a patient nonresponsive to treatments were nearly $10,000 more than those for a treatment-responsive patient, in 2012 US$.[5]

Studies have indicated significant association of pharmacogenomic (PGx) stratification with patients' response to treatment, quality of life (QoL), work productivity, and the related costs.[6-12] Perlis et al found that a hypothetical PGx test for a newly diagnosed MDD patient was associated with a relative risk of recovery of 1.28, and the cost/quality-adjusted life-year (QALY) gained varied from $1000 to more than $50,000, depending on input parameters.[11] Because some studies indicated a weak association between certain single-nucleotide polymorphisms and antidepressant response,[9,13] an integrated analysis of multiple polymorphisms has been proposed as a solution to the pharmacotherapy "treatment odyssey," because this may allow the assessment of genetic variations that influence the activity of multiple enzymes in drug metabolism. Clinical data and adjunctive analyses are needed to estimate efficacy and to

enable pharmacoeconomic analysis of combinatorial tests.[11,14-16]

Prospective studies have recently provided evidence of improved antidepressant response rates associated with the use of a multi-gene combinatorial pharmacogenomic (CPGx™) test in real-world settings.[17-19] A retrospective analysis indicated a decrease in the use of healthcare and employer resources in patients treated with medications reported as likely to be effective.[20] The panel test assesses 6 genes (CYP2D6, CYP2C19, CYP2C9, CYP1A2, SLC6A4, and HTR2A) frequently shown to be important for neuropsychiatric disorders, from which an integrated report is generated to guide selection of 38 FDA-approved antidepressant and antipsychotic medications.[21] Given this new clinical data supporting CPGx testing, the aim of this study was to estimate the lifetime QoL effects and economic implications of CPGx testing compared with the treatment as usual (TAU) approach for medication selection. We focused on patients who were shown to be nonresponsive to at least 1 prior treatment, and primary outcome measures included QALYs, direct and indirect costs, and incremental cost-effectiveness ratio (ICER).

Take-Away Points

Combinatorial pharmacogenomic (CPGx) testing dominates the treatment-as-usual approach in managing major depressive disorder patients who did not respond to previous treatments.

- Prospective clinical studies across multiple settings have shown that CPGx testing helps to guide treatment decision-making, matching patients with the treatments that are most likely to be safe and effective.
- Further analysis indicates that CPGx testing is related to improved quality of life and cost savings.

METHODS

The research methods and analytic framework followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practices for Outcomes Research[22] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS).[23] The data were drawn from published clinical evidence and were validated by experts' opinions where published evidence was limited. The authors had independence in the design of the analytic framework, data sources, and interpretation.

Target Population

The analysis targeted patients nonresponsive to 1 or more treatments. The base-case scenario was a representative patient tested at age 44 years, the average age of participants in the 3 clinical studies.[17-19]

Analytic Framework

CPGx testing-guided treatment was compared with TAU from a societal perspective. TAU represents clinical decision making after evaluation of treatment history, physical examination, and interpretation of appropriate laboratory results.

A generalized, state-transition probability analysis was conducted of 4 states based on survival and treatment response (Figure 1), assessed quarterly in the first year and annually in subsequent years. Health outcomes assessed included QALYs and probability of death from suicide over the patient's lifetime. The patient's total QALYs were calculated as the sum of the QoL in the health states in each cycle within the time horizon.

Economic implications were evaluated by differences in direct medical costs and indirect costs, which included labor participation and employee productivity costs. Both benefits and costs were discounted at an annual fixed rate of 3%, correcting for accrued value at future dates. The ICER was calculated as the ratio of the difference in costs to the difference in QALYs.

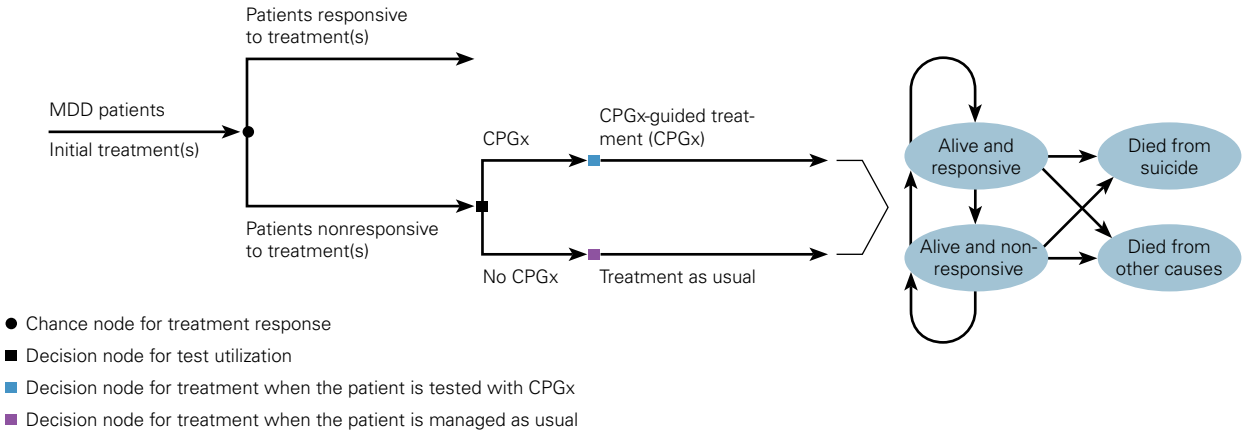
Input Parameters and Data Sources

Published peer-reviewed literature on MDD epidemiology and cost-effectiveness analyses was reviewed to identify data sources with relevant estimates. Gaps in this literature were augmented by additional searches in PubMed (National Center for Biotechnology Information, US National Library of Medicine). The quality of data was evaluated for inclusion using a hierarchy of evidence sources, ranging from literature review to population surveys and authors' assumptions (Table 1).

Response Rates

To estimate treatment response rates, we conducted a meta-analysis of 3 prospective clinical studies of the CPGx test carried out at different psychiatric outpatient clinics (eAppendix A, available at **www.ajmc.com**). STATA version 9.2 (Stata Corp, College Station, Texas) was used for all analyses. In the first quarter, the response rate was 24.7% for TAU and 42.2% for CPGx. Both rates increased during the next 2 quarters until reaching the plateau as the treating physicians tried different medications, based on the STAR*D response rates at different treatment levels.[24-26] We assumed TAU would catch up with CPGx after year 3, based on a published systematic review of randomized trials in which pharmacologic impacts have been shown to persist up to 36 months.[27]

Figure 1. Decision Diagram and State-Transition



CPGx indicates combinatorial pharmacogenomics; MDD, major depressive disorder.

Mortality Rates

Death from suicide was examined separately because suicide ideation and attempt are prevalent among treatment-resistant patients.[28,29] Probability of death from suicide was based on a US study that followed treatment-resistant patients treated with or without vagus nerve stimulation (VNS) for 5 years.[29] The annual suicide rate in the TAU group from this study was used to estimate the probability of suicide death for nonresponders in our analysis (0.16%), and the rate in the TAU+VNS group was used for responders (0.09%). The assumption that the TAU+VNS group is similar to responsive patients was substantiated by a study showing similar medical costs between VNS-treated patients and patients with managed depression.[28]

Non–suicide-related mortality was derived by subtracting suicide death from all-cause death. The literature review showed a lack of consistent evidence for an association between treatment resistance and increased all-cause mortality,[5,28,29] so all-cause mortality rate for responders and nonresponders was conservatively assumed to be the same as that in the general population (relative risk, 1.0).

Costs

Both direct and indirect costs were included in this analysis. The annual costs for management of depression per patient were based on a comprehensive meta-analysis of published claims databases.[5,28,30-32] Total costs were calculated by summing the costs from each simulation cycle, which equal the product of costs of the health state and the probability of being in this state in the corresponding cycle. Direct medical costs were composed of the costs of depression and non-depression drugs, inpatient and outpatient physician treatment, psychotherapy, and other costs. Indirect costs included productivity and absenteeism costs. Direct medical costs accumulated over the patient's lifetime, while indirect costs stopped accruing beyond the youngest full retirement age (65 years old) from the Social Security Administration Retirement Planner, reporting conservative results for the test benefit.[33] The list price of the test was included for the CPGx arm (provided by AssureRx Health, Inc, of Mason, OH). All costs were inflated to 2013 US$ using the medical care Consumer Price Index from the United States Bureau of Labor Statistics in 2013.[34]

Utilities

Utility values were assigned to each health state, ranging from 0 for death to 1 for perfect health. Utility data applied in this analysis were time trade-off utilities from a meta-analysis of published literature, with 0.67 for patients who had a response to treatment but not remission and 0.42 for patients nonresponsive to treatment.[5,35-37] The QALYs over the time horizon were calculated as the utility score-weighted sum of the probabilities of being responsive or nonresponsive to treatment.

Sensitivity Analyses

One-way (univariate) sensitivity analysis was conducted to assess the influence of uncertainty in input parameters on the outcomes. The range for parameters was based on 95% CIs, when available. If CIs were unavailable, ranges that had been commonly applied in similar depression-related analyses in the literature, or ranges equal to ± 25% of the mean, were used. Selective 2-way sensitivity analysis examined the effect of time-related variables—time horizon and catch-up year—and their interaction on

Table 1. Input Parameters and Base-Case Values

Analysis Parameters	Value
Test characteristics[17-19]	
Response rate – TAU	24.7%
Relative benefit ratio for response – CPGx	1.71
Clinical parameters	
Starting age of patient[17-19]	44
Mortality rates[29]	
Suicide rate – responders	0.09%
Suicide rate – nonresponders	0.16%
Relative risk of all-cause mortality – responders	1.0
Relative risk of all-cause mortality – nonresponders	1.0
Costs	
CPGx testing[21]	$2500
Direct medical costs, annual[5,28,30-32]	
Responders	$8542
Nonresponders	$14,571
Indirect employer costs, annual[5,30,31]	
Responders	$2932
Nonresponders	$7058
Utilities	
Response to therapy[5,35,36]	0.67
Nonresponse to therapy[5,35-37]	0.42
Policy parameters	
Time horizon	38
Discount rate	3%
Catch-up year[27]	3

CPGx indicates combinatorial pharmacogenomics; TAU, treatment as usual.

the total costs. Probabilistic sensitivity analysis (PSA) ran 10,000 simulations, in which the parameters took on values stochastically generated from their distributions.

RESULTS

In the base-case scenario, the higher response rate reported with CPGx testing compared with TAU was expected to increase QALYs by 0.316 years, or 3.8 months. A small but notable contribution to the difference in QALYs was due to the reduced probability of suicide mortality (Table 2). In the United States, this equates to 1460 fewer suicide-related deaths annually, if all eligible patients were tested.

Including the list price of testing ($2500), total cost savings versus TAU were $3764. The CPGx testing dominated the TAU strategy (ie, beneficial and cost-saving) with base-case inputs (Table 2). Direct medical costs were $211,971 with TAU strategy and declined to $208,260 with CPGx testing, for an average savings of $3711 over a patient's lifetime. Indirect costs declined from $64,544 for TAU to $61,991 with CPGx testing, with per patient savings of $2553.

Outcomes From Sensitivity Analyses

The 1-way sensitivity analysis ranked the 17 input parameters by their influence on difference in total costs (Figure 2 and eAppendix B). The incremental costs were most sensitive to the test effect on response rate, followed by the TAU catch-up year. The ranges for the test effect were based on the 95% CIs from our meta-analysis. The catch-up year(s) varied from 1 to 5.

The 1-way sensitivity analysis for ICER in total costs per QALY gained showed that CPGx testing dominated the TAU strategy when varying most of the parameters. The only 2 cost-increasing scenarios were when the test efficacy took the lower limit (CPGx $815 higher) or when the TAU catch-up year was 1 (CPGx $491 higher). However,

Table 2. Base-Case Results

	TAU	CPGx	Difference
Patient outcome – efficacy			
Probability of death from suicide at 5 years	0.625%	0.567%	–0.058%
QALYs	13.308	13.624	0.316
Costs			
CPGx testing	$0	$2500	$2500
Direct medical costs	$211,971	$208,260	–$3711
Indirect employer costs	$64,544	$61,991	–$2553
Total	$276,515	$272,751	–$3764
Incremental cost/QALYs gained			
Direct medical costs only			Cost-saving
Total costs (direct + indirect)			Cost-saving

CPGx indicates combinatorial pharmacogenomics; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TAU, treatment as usual.

the ICER values remained well below the commonly used willingness-to-pay (WTP) threshold of $50,000/QALY gained as cited in the literature of cost-utility analysis.[38,39]

Selective 2-way sensitivity analysis showed that the cost savings increased with a longer time horizon and a later catch-up year. These 2 time-related parameters work together to influence the difference in costs, and the calculation followed whichever had a shorter time period.

The joint distribution of incremental costs and incremental QALYs from the PSA is displayed with a scatter plot, in which the 4 planes represent different cost-effectiveness scenarios (**Figure 3**). The majority of the incremental cost-effectiveness pairs (74.7%) fell in the southeast quadrant, where CPGx testing dominated the TAU strategy, improving QALYs and saving costs. A proportion of the points (approximately 19.8%) lay under the WTP threshold ($50,000/QALY gained) in the northeast quadrant, indicating that CPGx improved QoL with acceptable costs. In summary, the probability of CPGx testing being cost-effective at the WTP of $50,000 is 94.5%.

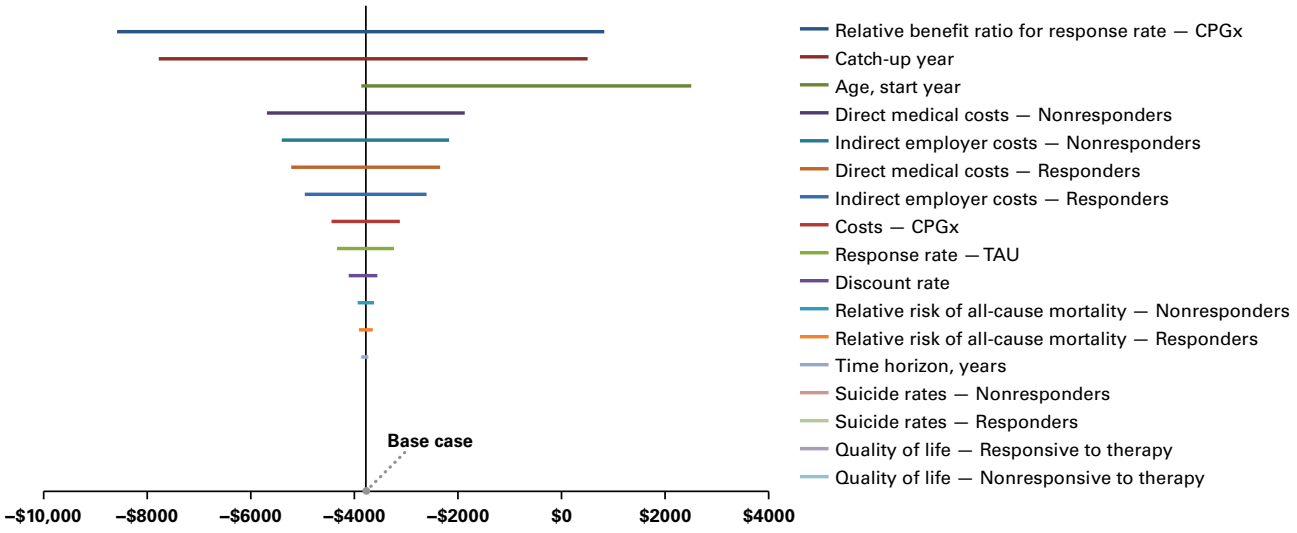
DISCUSSION

Difficult-to-treat patients with neuropsychiatric disease may undergo a long odyssey in the empirical search for optimal medications. Our analysis of the long-term clinical and economic implications projects that CPGx testing for MDD patients increases quality-adjusted survival while reducing costs associated with treatment nonresponse. The health effect measured in QALY is greater than that of adjuvant chemotherapies for women with node-positive breast cancer, or that of elective surgery as compared with expectant management for a 50-year-old with symptomatic gallstones.[40] Costs were estimated by combining the impact on response rates from 3 published clinical studies of CPGx testing with prior published costs for responders and nonresponders with MDD.

The results we obtained (cost difference of $6029) closely parallel findings from a retrospective claims analysis comparing patients' post hoc CPGx testing results to their actual clinical prescription history and healthcare utilization, which showed that the difference in annual direct medical costs between patients likely to respond without adverse drug reactions (ADRs) versus those unlikely to respond or likely to have an ADR was $5650 in 2013 US$.[20] This provides initial external validation of our analytic approach and study findings.

The association between genetic variants and treatment efficacy in depression has been supported by a number of studies. A comprehensive, systematic review of 268 candidate-gene studies revealed that analysis of nucleotide polymorphisms in some human cytochrome P450 (CYP) and pharmacodynamic genes predict metabolism, safety, or therapeutic efficacy of psychotropic medications commonly used to treat depression, schizophrenia, and bipolar disease.[12] For example, 93% of studies (37 of 41 studies) of CYP2C19 showed a significant association between genetically determined phenotypic variations and pharmacokinetic end points.[12] Other reviews of candidate-gene studies have also shown associations among some candidate genes and drug response.[9,15] The limitations of candidate-gene studies include the failure to detect relevant associations among many genomic loci, uncertain biological function of many potential genes, and absence of information on regulatory and epigenomic processes that could affect target gene expression.

Figure 2. Tornado Diagram for Total Costs



CPGx indicates combinatorial pharmacogenomics; TAU, treatment as usual.

Overall, the results of candidate-gene studies typically skew toward not finding potentially meaningful associations that may exist. In contrast to research on a priori targets, genome-wide association studies allow for genotyping of hundreds of thousands of polymorphisms, thus creating high-throughput screening of potential gene targets without relying on a priori information. The most notable of these studies in depression is the meta-analysis by the Genome-based Therapeutic Drugs for Depression (GENDEP), Munich Antidepressant Response Signature (MARS), and STAR*D investigators, who found "modest evidence" that common gene variations may contribute to individual differences seen in antidepressant response.[16]

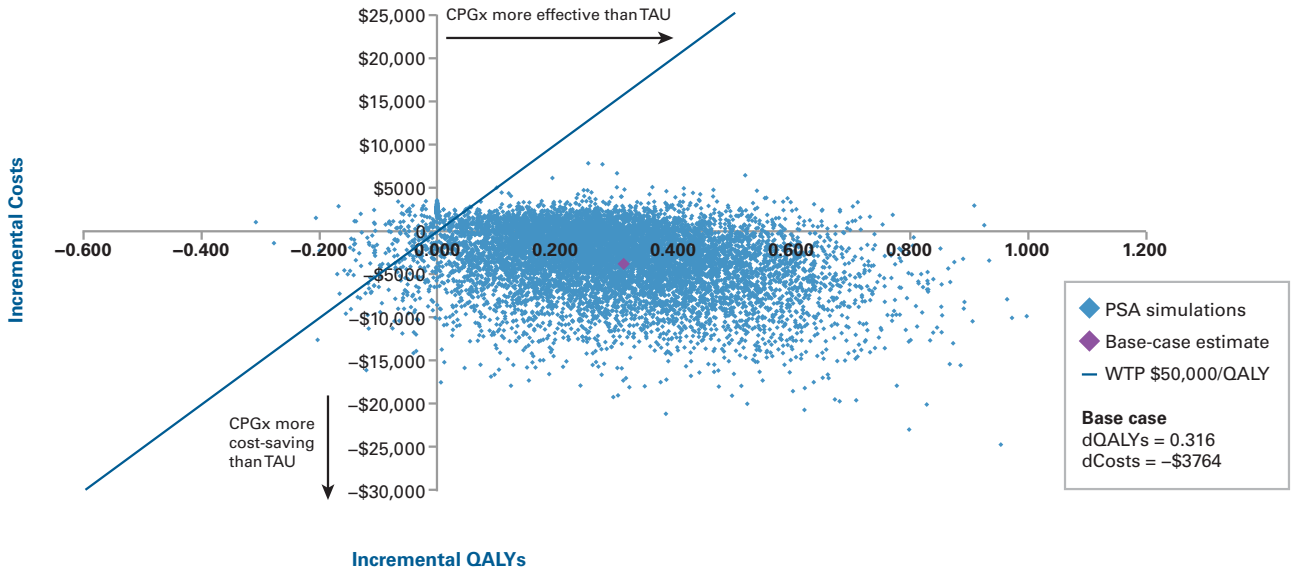
One limitation of genome-wide association studies involves large sample sizes needed to detect clinically meaningful associations[14,41,42]; "mega" studies may be required to detect significant associations, especially when the phenotype is complex as it is in MDD. In contrast to the body of literature based on candidate-gene studies that collectively enrolled more than 47,000 patients, the genome-wide association studies for depression collectively enrolled 2256 patients. In summary, expert reviewers expressed cautious optimism that clinically meaningful genotypic-phenotypic associations exist in major depression, and are open-minded about which genes are more relevant.[14,41]

A major limitation of studies conducted in the past is that they applied a single-gene analytic approach, in which individual genes were assessed for their association with clinical end points. For example, a genome-wide meta-analysis found no significant association of clinical outcomes with the single-gene analysis, but reported that the polygenic scores constructed based on GENDEP and MARS studies significantly predicted the clinical outcome in STAR*D.[16] Notwithstanding the limitations of single-gene studies in biological psychiatry, 2 studies have examined the cost-effectiveness of single-gene PGx testing for depression, one for 5-HTTLPR in SLC6A4 and the other using HTR2A as the base case to estimate the lower bound for PGx cost-effectiveness.[10,11] Both showed increased QoL with such tests, but costs were expected to increase.

A combinatorial multi-gene, multi-variant analysis has the potential to improve the predictive ability of psychiatric pharmacogenomics. Altar et al recently compared the outcome predictions of the combinatorial use of multiple allelic variations in genes included in a CPGx test with the outcome predictions for the very same subjects using traditional, single-gene analysis. The combinatorial approach achieved better discrimination and prediction of outcomes than did single genes. This greater clinical validity appeared to derive from the aggregation of effect sizes for all relevant alleles and relating the composite phenotype to the responses anticipated for each psychiatric medication.[43]

For this cost-effectiveness analysis, we focused on a CPGx test that has the most published evidence,[41] based on 3 studies, on its ability to influence treatment response. There are several possibilities for the cost savings pro-

Figure 3. Scatter Plot of Estimated Joint Distribution of Incremental Costs and Incremental Effects[a]



CPGx indicates combinatorial pharmacogenomics; d, difference; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year; TAU, treatment as usual; WTP, willingness to pay.
[a]Based on 10,000 simulations.

jected in this study but not reported previously. First, the CPGx test assessed here examined the interaction of multiple variants of multiple PGx genes that have been shown to be linked to pharmacokinetics/pharmacodynamics of up to 36 different medications. The greater range of potential gene variants and their effects on medication response and risk of ADRs may provide more accurate and precise targeting of effective therapies, thus leading to the greater impact on clinical response rates. Second, the test provides findings from the panel of gene variants in an integrated report, which stratifies potential medications into 3 classes: 1) likely to respond and low risk of ADRs; 2) unlikely to respond or high risk of ADRs; and 3) intermediate likelihood of response or risk of ADRs. This reporting approach may provide physicians with sufficient details to permit decision making (ie, actionable information), but not so much as to create information overload and potential confusion.

Medical geneticists have expressed concerns about the complexity in interpreting gene-panel tests with large numbers of genes and gene variants. They have suggested solutions to limit information conveyed by laboratories and physicians to patients, and thus have come under scrutiny by other professional societies.[44] Finding an appropriate balance between reporting necessary details of complex genetic analyses and making those analyses interpretable to busy practitioners and their patients remains an important challenge. The experiences highlighted in clinical validity and clinical utility studies of CPGx testing,[45] and in this comprehensive outcomes/economic analysis, may prove instructive for genetic testing.

Limitations

A key limitation of this study is the lack of a precise estimate of test efficacy related to availability of directly observed, long-term data on outcomes and costs, which is typically associated with any novel medical intervention. All-cause mortality rate for responders and nonresponders were conservatively assumed to be the same as that in the general population, because evidence supporting increased mortality associated with treatment resistance has not been consistent.[5,29] However, since depression is a condition that causes great burden of illness and a high prevalence of suicide ideation and attempt, it is expected that increased all-cause mortality would be observed in longer-term studies, which would be informative for the ICER measured with life expectancy change.

Another limitation is related to the potential heterogeneity across ethnic groups. The base-case test effect was derived from clinical studies in which the majority of participants were Caucasian, while other ethnicities, such as Asians, may present a different pattern.[9,46,47] Although

these publications were conducted on different genes from those we assessed, studies that include minorities or a more balanced mix of ethnic groups will provide more comprehensive information on the effect of CPGx testing across different ethnic and practice settings.

The present analysis is conservative in that it assumed the TAU group would catch up with CPGx testing within a few years. However, genetic information in the test report could provide guidance for subsequent drug selection and thus continue to impact clinical decision making further downstream. In the sensitivity analysis, delaying the TAU catch-up to year 5 would increase total cost savings to $7750. A conservative approach was also followed in estimating the test effect with the available case analysis (eAppendix A).

It is important to note that depression is a lifetime illness, composed of a complex mix of health states. Partial responders were not included due to lack of clinical data. The analysis did not distinguish response rates after different numbers of treatment trials, because data are limited on the dynamics of response rates for patients in subsequent years, and on the transition between response and nonresponse. Research is needed on subjects at various loci of the response spectrum to provide insights into the effects of CPGx testing for different patients. In addition, evidence-based psychotherapy, such as cognitive behavioral therapy, has been proven to bring long-term benefits to MDD patients,[48,49] which may be more effective when used adjunctively with CPGx approaches. Although beyond the scope of this analysis, future research may consider psychotherapy as an adjunct to TAU or CPGx testing, and assess the cost-effectiveness of these combined strategies to manage MDD patients.

CONCLUSIONS

In summary, a meta-analysis of 3 prospective clinical studies across different geographic locations has shown that CPGx testing compared with TAU modifies treatment decisions made for patients with MDD who did not respond to previous treatments, and led to higher rates of treatment response. By combining these data with published evidence on the effects of response on suicide rates and QoL, we established a representative scenario to estimate and compare the patient's health outcomes over lifetime between CPGx and TAU arms. We projected fewer depression-related suicides and increased quality-adjusted survival that is comparable to many effective medical treatments. Moreover, costs should be reduced because of the increased proportion of less-costly-to-manage responders; the effect influences both direct medical costs and indirect costs related to labor-force participation and employee productivity.

The conclusion that the test is cost-effective for a representative MDD patient nonresponsive to treatments over lifetime from the societal perspective is considered generalizable with the robust results from sensitivity analyses. As is recommended for any new approach to clinical management, more evidence, especially long-term follow-up data with larger sample sizes, will be useful to further validate these effects externally in other real-world settings.

Acknowledgments

The authors would like to thank James Burns, C. Anthony Altar, Bryan Dechairo, Jeff Bush, and Roy Perlis for their comments on this manuscript.

Author Affiliations: Cedar Associates LLC (JH, QL), Menlo Park, CA; Department of Internal Medicine, Stanford University School of Medicine (JH), Stanford, CA; Foley Hoag LLP (BQ), Boston, MA.

Source of Funding: AssureRx Health (Mason, Ohio) sponsored the study.

Author Disclosures: Dr Hornbeger and Qianyi Li are employees of Cedar Associates LLC, which received funding to be the research coordinating center for this study. Dr Quinn is an employee of Foley Hoag LLP, which provides paid legal services and policy consulting services for AssureRx Health, though no personal income is derived from this work. All the authors jointly conducted data collection, analysis, interpretation, and quality assurance. The authors attest that we have herein disclosed any and all financial or other relationships, and that all sources of financial support for this study have been disclosed.

Authorship Information: Concept and design (JH, QL, BQ); acquisition of data (JH, QL); analysis and interpretation of data (JH, QL, BQ); drafting of the manuscript (QL); critical revision of the manuscript for important intellectual content (JH, BQ); statistical analysis (JH, QL); obtaining funding (JH); administrative, technical, or logistic support (JH, QL); and supervision (JH).

Address correspondence to: John Hornberger, MD, MS, FACP, Cedar Associates LLC, 3715 Haven Ave, Ste 100, Menlo Park, CA 94025. E-mail: ujch@stanford.edu.

REFERENCES

1. Murray CJL, Lopez AD, eds. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Disease, Injuries, and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard University Press; 1996.

2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):593-602.

3. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

4. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.

5. Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv*. 2014;65(8):977-987.

6. McMahon FJ, Buervenich S, Charney D, et al. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. *Am J Hum Genet*. 2006;78(5):804-814.

7. Laje G, Perlis RH, Rush AJ, McMahon FJ. Pharmacogenetics studies in STAR*D: strengths, limitations, and results. *Psychiatr Serv*. 2009;60(11):1446-1457.

8. Villafuerte SM, Vallabhaneni K, Sliwerska E, McMahon FJ, Young EA, Burmeister M. SSRI response in depression may be influenced by SNPs in HTR1B and HTR1A. *Psychiatr Genet*. 2009;19(6):281-291.

9. Niitsu T, Fabbri C, Bentini F, Serretti A. Pharmacogenetics in major depression: a comprehensive meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;45:183-194.

10. Olgiati P, Bajo E, Bigelli M, De Ronchi D, Serretti A. Should pharmacogenetics be incorporated in major depression treatment? Economic evaluation in high- and middle-income European countries. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;36(1):147-154.

11. Perlis RH, Patrick A, Smoller JW, Wang PS. When is pharmacogenetic testing for antidepressant response ready for the clinic? A cost-effectiveness analysis based on data from the STAR*D study. *Neuropsychopharmacology*. 2009;34(10):2227-2236.

12. Altar CA, Hornberger J, Shewade A, Cruz V, Garrison J, Mrazek D. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int Rev Psychiatry*. 2013;25(5):509-533.

13. Miller DB, O'Callaghan JP. Personalized medicine in major depressive disorder—opportunities and pitfalls. *Metabolism*. 2013;62 Suppl 1:S34-S39.

14. Fabbri C, Di Girolamo G, Serretti A. Pharmacogenetics of antidepressant drugs: an update after almost 20 years of research. *Am J Med Genet B Neuropsychiatr Genet*. 2013;162B(6):487-520.

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. GENDEP Investigators; MARS Investigators; STAR*D Investigators. Common genetic variation and antidepressant efficacy in major depressive disorder: a meta-analysis of three genome-wide pharmacogenetic studies. *Am J Psychiatry*. 2013;170(2):207-217.

17. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet Genomics*. 2013;23(10):535-548.

18. Hall-Flavin DK, Winner JG, Allen JD, et al. Using a pharmacogenomic algorithm to guide the treatment of depression. *Transl Psychiatry*. 2012;2:e172.

19. Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. *Discov Med*. 2013;16(89):219-227.

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

21. AssureRx Health, Inc. GeneSight Multi-Gene Combinatorial Pharmacogenomic (CPGx™) Test is More Predictive of Antidepressant Response than Single Gene Tests. http://assurexhealth.com/genesight-multi-gene-combinatorial-pharmacogenomic-cpgx-test-predictive-antidepressant-response-single-gene-tests/. Published February 26, 2015. Accessed June 2015.

22. Ramsey SD, Willke RJ, Glick H, et al. Cost-Effectiveness Analysis Alongside Clinical Trials II—An ISPOR Good Research Practices Task Force Report. *Value Health*. 2015;18(2):161-172.

23. Husereau D, Drummond M, Petrou S, et al; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Int J Technol Assess Health Care*. 2013;29(2):117-122.

24. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry*. 2006;163(7):1161-1172.

25. McGrath PJ, Stewart JW, Fava M, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry*. 2006;163(9):1531-1541; quiz 1666.

26. Rush AJ, Trivedi MH, Wisniewski SR, et al; STAR*D Study Team. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006;354(12):1231-1242.

27. Geddes JR Carney SM, Davies C, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet*. 2003;361(9358):653-661.

28. Feldman RL, Dunner DL, Muller JS, Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. *J Med Econ*. 2013;16(1):62-74.

29. Olin B, Jayewardene AK, Bunder M, Moreno F. Mortality and suicide risk in treatment-resistant depression: an observational study of the long-term impact of intervention. *PLoS ONE*. 2012;7(10):e48002.

30. Corey-Lisle PK, Birnbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ. Identification of a claims data "signature" and economic consequences for treatment-resistant depression. *J Clin Psychiatry*. 2002;63(8):717-726.

31. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Curr Med Res Opin*. 2010;26(10):2475-2484.

32. Olchanski N, McInnis Myers M, Halseth M, et al. The economic burden of treatment-resistant depression. *Clin Ther*. 2013;35(4):512-522.

33. Retirement planner: full retirement age. Social Security Administration website. http://www.ssa.gov/retire2/retirechart.htm. Accessed May 20, 2013.

34. Consumer Price Index - All Urban Consumers, 2013. US Bureau of Labor Statistics website. http://data.bls.gov/cgi-bin/surveymost?cu [U.S. Medical Care, 1982-84=100 - CUUR0000SAM]. Accessed June 3, 2013.

35. Benedict A, Arellano J, De Cock E, Baird J. Economic evaluation of duloxetine versus serotonin selective reuptake inhibitors and venlafaxine XR in treating major depressive disorder in Scotland. *J Affect Disord*. 2010;120(1-3):94-104.

36. Nuijten MJ. Assessment of clinical guidelines for continuation treatment in major depression. *Value Health*. 2001;4(4):281-294.

37. Sava FA, Yates BT, Lupu V, Szentagotai A, David D. Cost-effectiveness and cost-utility of cognitive therapy, rational emotive behavioral therapy, and fluoxetine (Prozac) in treating depression: a randomized clinical trial. *J Clin Psychol*. 2009;65(1):36-52.

38. Earle CC, Chapman RH, Baker CS, et al. Systematic overview of cost-utility assessments in oncology. *J Clin Oncol*. 2000;18(18):3302-3317.

39. Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. *J Health Econ*. 1997;16(1):1-31.

40. Wright JC, Weinstein MC. Gains in life expectancy from medical interventions--standardizing data on outcomes. *N Engl J Med*. 1998;339(6):380-386.

41. Perlis RH. Pharmacogenomic testing and personalized treatment of depression. *Clin Chem*. 2014;60(1):53-59.

42. Klein C, Lohmann K, Ziegler A. The promise and limitations of genome-wide association studies. *JAMA*. 2012;308(18):1867-1868.

43. Altar CA, Carhart JM, Allen JD, Hall-Flavin DK, Dechairo BM, Winner JG. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes [published online ahead of print February 17, 2015]. *Pharmacogenomics J*. doi:10.1038/tpj.2014.85.

44. Green RC, Berg JS, Grody WW, et al; American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574.

45. Altar CA, Carhart J, Allen JD, Hall-Flavin D, Winner J, Dechairo B. Clinical utility of combinatorial pharmacogenomics-guided antidepressant therapy: evidence from three clinical studies. *Mol Neuropsychiatry*. In press. doi: 10.1159/000430915.

46. Mrazek DA, Rush AJ, Biernacka JM, et al. SLC6A4 variation and citalopram response. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(3):341-351.

47. Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. *Mol Psychiatry*. 2007;12(3):247-257.

48. Brunoni AR, Boggio PS, De Raedt R, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *J Affect Disord*. 2014;162:43-49.

49. Cuijpers P, Berking M, Andersson G, Quigley L, Kleiboer A, Dobson KS. A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *Can J Psychiatry*. 2013;58(7):376-385. Review.

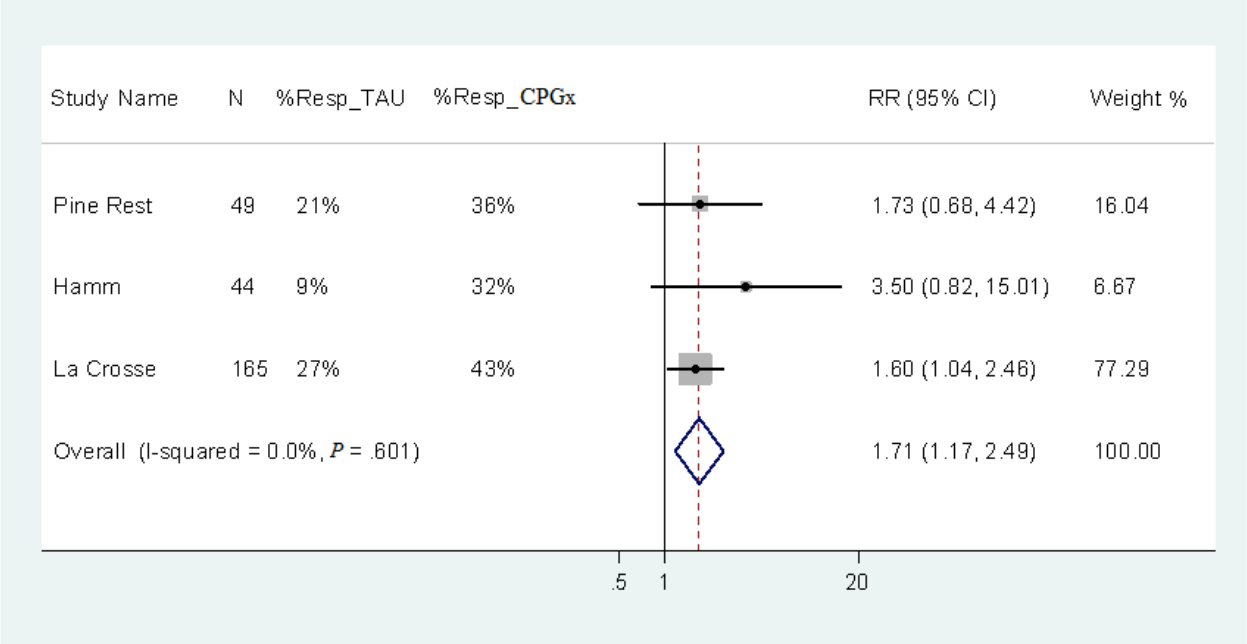
www.ajmc.com Full text and PDF

eAppendix. Supplementary Data

eAppendix A. Meta-Analysis

The meta-analysis of the effect of combinatorial pharmacogenomic (CPGx) testing was conducted with STATA version 9.2 (Stata Corp, College Station, Texas), which combined results from multiple studies. The fixed-effect model was used and response rates from individual studies were weighted using the inverse-variance methodology. The available case analysis (ACA) method was used to derive the base case relative risk (RR), showing that use of CPGx testing increased the response rate by 70% (**eAppendix A Figure**). The response rate with the treatment-as-usual strategy (24.7%) was calculated using rates from individual studies and weights calculated with the software. However, the drop-out rate of the largest study (La Crosse) was higher than that of the other studies, which should ideally be accounted for using the imputed case analysis by reasons for drop-out.[1] This was done through the expectation maximization algorithm and the last observation carried forward method in the La Crosse paper, confirming stronger improvement in response rate with CPGx testing when drop-out was considered.[2] This demonstrated that drop-out was not due to lack of test efficacy or safety. By using the ACA-derived RR, the analysis took a conservative approach.

eAppendix A Figure. Meta-Analysis of CPGx Effect on Response Rates



CPGx indicates combinatorial pharmacogenomics; RR, relative risk; TAU, treatment as usual; %Resp, % of subjects responsive to treatment.
The diamond represents the pooled result.
Area of squares corresponds to the weight of each study.
Horizontal bars indicate confidence intervals.

eAppendix B. 1-Way Sensitivity Analysis

Parameter Name	Base case	Range		Distribution	ΔCosts (Direct + Indirect + Test)		
		Lower	Upper		Left	Right	Difference
Relative benefit ratio for response rate – CPGx	1.71	1.17	2.49	Lognormal	$815	–$8543	$9358
Catch-up year	3	1	5	Uniform	$491	–$7750	$8241
Age, start year	44	18	82	Gamma	–$3835	$2500	$6335
Direct medical costs – Nonresponders	$14,571	$11,497	$17,645	Gamma	–$1872	–$5656	$3785
Indirect employer costs – Nonresponders	$7058	$4514	$9603	Gamma	–$2190	–$5338	$3148
Direct medical costs – Responders	$8542	$6257	$10,828	Gamma	–$5171	–$2357	$2814
Indirect employer costs – Responders	$2932	$1078	$4785	Gamma	–$4911	–$2617	$2293
Costs – CPGx	$2500	$1875	$3125	Gamma	–$4389	–$3139	$1250
Response rate – TAU	24.7%	17.5%	31.9%	Beta	–$3248	–$4280	$1032
Discount rate	3.0%	0%	5%	NA	–$4076	–$3561	$515
Relative risk of all-cause mortality – Nonresponders	1.00	0.75	1.25	Lognormal	–$3904	–$3627	$277
Relative risk of all-cause mortality – Responders	1.00	0.75	1.25	Lognormal	–$3650	–$3872	$222
Time horizon, years	38	5	68	NA	–$3843	–$3760	$83
Suicide rates – Nonresponders	0.16%	0.00%	0.56%	Beta	–$3764	–$3764	$0
Suicide rates – Responders	0.09%	0.00%	0.31%	Beta	–$3764	–$3764	$0
Quality of life – Responsive to therapy	0.67	0.51	0.83	Beta	–$3764	–$3764	$0
Quality of life – Nonresponsive to therapy	0.42	0.32	0.53	Beta	–$3764	–$3764	$0

CPGx indicates combinatorial pharmacogenomics; NA, not applicable; TAU, treatment as usual.

REFERENCES

1. Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials*. 2008;5(3):225-239.

2. Hall-Flavin DK, Winner JG, Allen JD, et al. Utility of integrated pharmacogenomic testing to support the treatment of major depressive disorder in a psychiatric outpatient setting. *Pharmacogenet Genomics*. 2013;23(10):535-548.