

# Cost Burden of Treatment Resistance in Patients With Depression

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**Objective:** To develop a claims-based scale for treatment-resistant depression (TRD) and estimate the associated direct cost burden.

**Study Design:** Retrospective, observational study of patients receiving antidepressant therapy between January 2000 and June 2007 (N = 78,477).

**Methods:** The Massachusetts General Hospital (MGH) clinical staging method for treatment resistance (assigning points for adequate trials of antidepressant medication, upward dose titration, extended duration, augmentation, and electroconvulsive therapy) was applied to claims data from the MarketScan Research Databases over a 24-month time period. Direct expenditures were measured over a subsequent 12-month period. Patients identified as having TRD (MGH score  $\geq 3.5$ ) (n = 22,593) were matched to depressed patients without TRD using propensity score methods. Regression models estimated the relationship between TRD and expenditures, controlling for sociodemographics, health plan type, and health status. Similar regression models estimated costs for an antidepressant-only version of the scale (MGH-AD).

**Results:** Treatment resistance among depressed patients was associated with 40% higher medical care costs ( $P < .001$ ). The MGH-AD score was associated with an increasing gradient in direct costs. Annual costs for patients with mild TRD (MGH-AD 3.5-4) were \$1530 higher than those for non-TRD patients, and costs for patients with complex TRD (MGH-AD  $\geq 6.5$ ) were \$4425 higher than those for non-TRD patients (all  $P < .001$ ). A 1-point increase in the MGH-AD score was associated with a \$590 increase in annual costs ( $P < .001$ ).

**Conclusions:** Early identification of TRD patients, using a claims-based algorithm, may support targeted interventions for these patients.

(*Am J Manag Care.* 2010;16(5):370-377)

For author information and disclosures, see end of text.

Major depression is the most common mental health disorder, with a lifetime prevalence of 16.2%.<sup>1</sup> Depression is associated with substantial economic costs, including increased direct medical and indirect productivity costs.<sup>2</sup> The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study found a remission rate for first-stage treatment (citalopram) of 27.5% or 32.9%, depending on the definition of remission<sup>3</sup>; at least 67.1% of patients failed to achieve remission in first-stage treatment. The estimated cumulative remission rate for up to 4 stages of treatment in STAR\*D was 67%, leaving an estimated 33% of patients without remission.<sup>4</sup> Furthermore, each additional unsuccessful course of therapy is associated with lower likelihood of remission<sup>5</sup> and higher relapse rates.<sup>4</sup>

Treatment-resistant depression (TRD) occurs when a patient with unipolar depression fails to respond to adequate antidepressant therapy; however, no consensus has yet emerged around a precise definition of TRD. Most clinical definitions of adequate antidepressant therapy require minimum thresholds of dose, duration, and patient compliance.<sup>6</sup> Claims-based definitions of TRD have been based on the number of medication switches, upward dose titrations, and flags for use of specific medication classes, electroconvulsive therapy (ECT), depression-related hospitalization, and suicide attempts.<sup>2,7-9</sup> Regardless of how TRD was defined, all prior claims-based studies found higher costs among patients with TRD compared with depressed patients without treatment resistance.<sup>2,7-9</sup>

Treatment resistance is not a dichotomous concept. Although some patients who fail to respond to the first antidepressant trial may respond to the second, others may respond after 3 or 4 trials, and others may require more trials. Several clinical staging algorithms have been developed in an attempt to characterize the type of treatment resistance, from mild to complex.<sup>10,12</sup> Thus far, only one such algorithm, the Massachusetts General Hospital (MGH) staging method, has been found to predict nonremission.<sup>13</sup>

The goal of this study is to develop a claims-based scale for TRD and estimate the associated direct cost burden. A replicable scale based on claims data may be used by providers and payers to identify treatment-resistant patients at an early stage, when targeted interventions have a greater potential to improve clinical outcomes and reduce future medical costs.

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## METHODS

We conducted a retrospective, observational study of the direct cost burden of TRD, using administrative claims data for patients with employer-sponsored commercial health insurance coverage. Propensity score weighting techniques were used to match TRD patients to depressed patients without TRD. Multiple regression models controlled for matching variables in order to isolate the effects of TRD and adjunctive therapies on costs.

The study sample was drawn from the 2000-2007 MarketScan Research Databases. Patients were selected from the MarketScan Commercial Claims and Encounters Database, which represents the healthcare experience of enrollees in commercial health insurance plans sponsored by more than 100 large- and medium-sized employers in the United States. The database includes monthly enrollment data, inpatient and outpatient medical claims, and outpatient prescription drug claims. Because the data conform to the Health Insurance Portability and Accountability Act of 1996 confidentiality requirements, the study did not require informed consent or institutional review board approval.

### Study Population

Depression was identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes (296.2x, 296.3x, 300.4, 309.0, 311.xx). Adult patients (age 18-64 years) were selected if they had at least 2 claims with a diagnosis of depression and at least 1 prescription fill for an antidepressant medication between January 1, 2000, and June 30, 2007. Continuous enrollment was required throughout a 24-month identification period following the first observed prescription fill for an antidepressant medication. Consistent with prior studies, patients were excluded from the study if they had any claim with a diagnosis of dementia (290.xx), schizophrenia (295.xx), delusional disorder (297.xx), other non-organic psychoses (298.xx), pervasive development disorder (299.xx), mental retardation (317.xx-319.xx), other cerebral degenerations (331.xx), Parkinson's disease (332.xx), senility without mention of psychosis (787.xx), or manic depression or bipolar disorder (296.0, 296.1, 296.4, 296.5, 296.7, 296.80, 296.81, 296.89).<sup>7,8</sup> A total of 106,139 patients met the initial selection criteria. The analysis of costs required an additional 12 months of continuous enrollment following the 24-month identification period; 78,477 patients met this criterion.

### Variables

In order to determine whether the TRD algorithm predict-

### Take-Away Points

A clinical staging algorithm for treatment-resistant depression (TRD) was applied to administrative claims data to measure the cost burden of mild to complex TRD.

- Patients with TRD incurred 40% higher direct medical costs than patients without TRD.
- Higher TRD scores predicted higher future direct medical costs.
- This claims-based algorithm can be used by providers and medical plans to find TRD patients at an earlier stage, when clinical interventions and programmatic interventions such as enrollment in disease management programs might improve clinical outcomes and reduce costs.

ed future costs, the 36-month study period was divided into 2 parts. Variables used to define treatment resistance and match patients were captured during a 24-month identification period following the first antidepressant prescription fill. Costs were measured during the subsequent 12-month follow-up period.

### MGH, MGH-AD, and Definition of TRD

Using 24 months of medical claims following the first observed antidepressant prescription fill, 2 claims-based versions of the MGH TRD staging method were created.<sup>12</sup> The full version of the MGH scale assigned 1 point for each adequate antidepressant trial (ie, 2 or more fills for the same antidepressant medication), half a point for each optimization strategy, and 3 points for any use of ECT. Optimization strategies included an extended duration (at least 3 fills), an upward titration in dose, and augmentation with an atypical antipsychotic, a mood stabilizer, or a stimulant.

The antidepressant-only version of the MGH score (MGH-AD) excluded ECT and the augmentation measures. ECT was excluded from the MGH-AD because it is not an early indicator of potential treatment resistance; rather, the use of ECT indicates that multiple prior treatment strategies have failed. Augmentation measures were excluded from the MGH-AD so that the effects of augmentation could be modeled independently. Accordingly, 3 dichotomous variables were created to indicate any use of atypical antipsychotics, mood stabilizers, or stimulants. (Detailed instructions on how to create the MGH-AD are available in a [Technical eAppendix](#) at [www.ajmc.com](http://www.ajmc.com).)

An MGH score exceeding 3 was established as a TRD threshold, consistent with the work of Berman and colleagues (2007)<sup>14</sup> and Marcus and colleagues (2008),<sup>15</sup> who used entry criteria that included a minimum of 2 antidepressant regimen failures prior to randomization to receive either adjunctive placebo or adjunctive aripiprazole in a clinical trial of inadequate responders to standard antidepressant therapy. An MGH score of 3 is the equivalent of 2 adequate antidepressant trials with 1 optimization strategy each (although other combinations are possible). Any additional optimization strategy, or an adequate trial of a third antidepressant, would increase the MGH score and meet the threshold for TRD.

### Explanatory/Matching Variables

Explanatory variables (measured during the 24-month identification period) included age, sex, US Census region, urban residence, health plan type, and health status. Health plan type included indemnity plans, exclusive provider organization/point-of-service plans, preferred provider organizations, health maintenance organizations, and capitated point-of-service plans. Health status was measured using the Deyo version of the Charlson Comorbidity Index, a numeric scale based on the presence or absence of 19 conditions (eg, diabetes, heart disease), each assigned a weight.<sup>16</sup> A count of the number of Psychiatric Diagnosis Groups (eg, organic mental disorders, substance user disorders), which are not included in the Charlson Comorbidity Index, ranged from 1 to 12.<sup>17</sup> The year of the first observed antidepressant prescription claim also was retained to control for trends in diagnosis, treatment, and medical spending.

### Direct Costs

The primary outcomes for this study were direct (medical) expenditures summed in the 12 months following the 2-year identification period. Medical expenditures included spending for hospitalizations, emergency department visits, outpatient services, and outpatient prescription drugs. Expenditures summarized patient out-of-pocket payments, health plan payments, and any additional third-party payers (eg, coordination of benefits). All dollar metrics were adjusted to 2006 values, using the medical component of the Consumer Price Index.<sup>18</sup>

### Statistical Analysis and Propensity Score Matching

Patients with TRD were matched one-to-one with non-TRD depressed patients by estimating a propensity score for each patient with depression using a logistic regression model of the probability of having TRD, controlling for sociodemographic variables, plan type, health status, and the year the index date occurred (time). Depressed patients with TRD were matched with non-TRD depressed patients using caliper matching.<sup>19</sup>

After matching, multivariate generalized linear models were used to adjust dollar comparisons for differences in sociodemographics, plan type, health status, and time. To estimate the independent cost effects of each augmentation strategy, the MGH-AD was used as a measure of TRD and indicator variables for treatment with atypical antipsychotics, mood stabilizers, or stimulants were included in the models. Separate models were estimated for the MGH-AD as a continuous variable and as a categorical variable. For use as a categorical variable, the MGH-AD was collapsed into 5 values (0-3, 3.5-4, 4.5-5, 5.5-6, 6.5+). As a sensitivity analysis, models with a single indicator variable for TRD were estimated. All models

controlled for age, sex, region, type of health plan, number of Psychiatric Diagnosis Groups, Charlson Comorbidity Index score, and year of index date.

Exponential conditional mean regression models were estimated for medical spending.<sup>20,21</sup> The percentage difference was calculated as  $\exp(\text{coefficient}) - 1$  (eg, 21.4% =  $\exp(0.194) - 1$ ). Incremental costs were estimated in dollars. For models using the categorical MGH-AD, the incremental cost is obtained by comparing costs for patients at each level of the MGH-AD to what their costs would have been if they were in the non-TRD (MGH-AD <3.5) category. For models using the continuous MGH-AD score, the incremental cost represents the potential savings (in dollars) per enrollee with depression from reducing the MGH-AD score by 1 point. For the adjunctive therapies, the incremental cost represents the additional cost of the adjunctive therapy for patients on an adjunctive therapy.

## RESULTS

We found 78,477 patients with depression who met all selection criteria. Analysis of the distribution of MGH and MGH-AD for these patients yielded no substantial differences (**Figure 1**). Removing ECT and adjunctive therapies from the MGH had no effect on the modal (1.5) or median (2.0) score, whereas the mean score decreased a trivial amount from  $2.56 \pm 1.66$  to  $2.51 \pm 1.59$ . The percentage of patients with scores above 3 (the cut-off for TRD) decreased by less than 1 percentage point from 28.8% (MGH) to 28.1% (MGH-AD). Fewer than 1% of patients had any use of ECT, and one-fifth of patients used adjunctive therapies (6.9% atypical antipsychotics, 12.8% mood stabilizers, 5.9% stimulants) (data not shown).

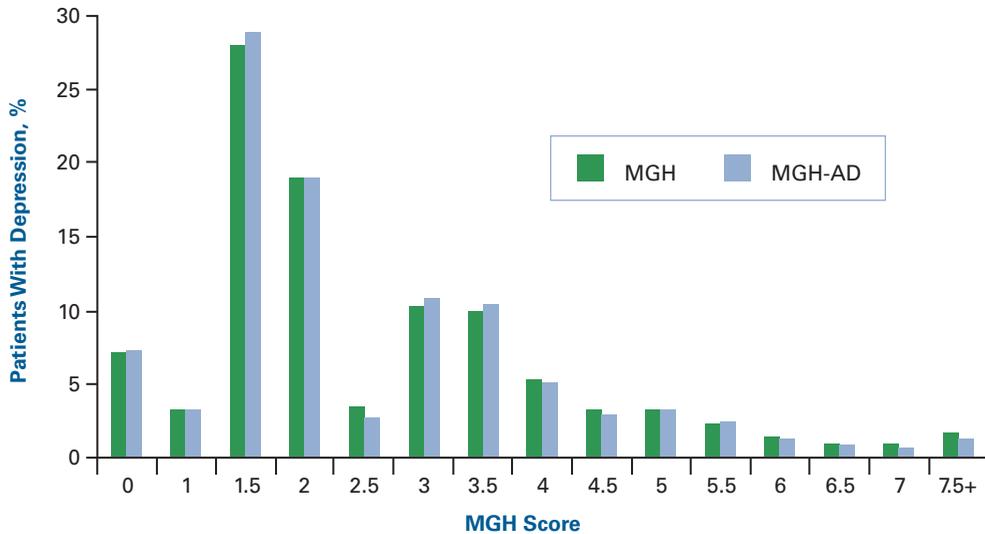
Medical/drug costs exhibited an almost linear relationship to the MGH-AD score, doubling from an annual average of \$5729 for a patient with a score of zero to \$13,167 for patients with a score of 7.5 or more (**Figure 2**). As the MGH-AD score increased, prescription drug and outpatient costs increased the most in absolute (dollar) terms.

After propensity score matching, the sample size was 45,186 (22,593 TRD and 22,593 non-TRD). Twenty-two TRD patients (0.1%) did not yield a match and were dropped from the analysis. **Table 1** describes characteristics of depressed patients with and without TRD, before and after matching. The matched groups had very few differences that remained statistically significant at the 95% confidence level. Among patients with TRD and their matches, 71.6% were female and 67.6% were between the ages of 35 and 54 years.

Multivariate regression results revealed a statistically significant, positive relationship between costs and MGH-AD

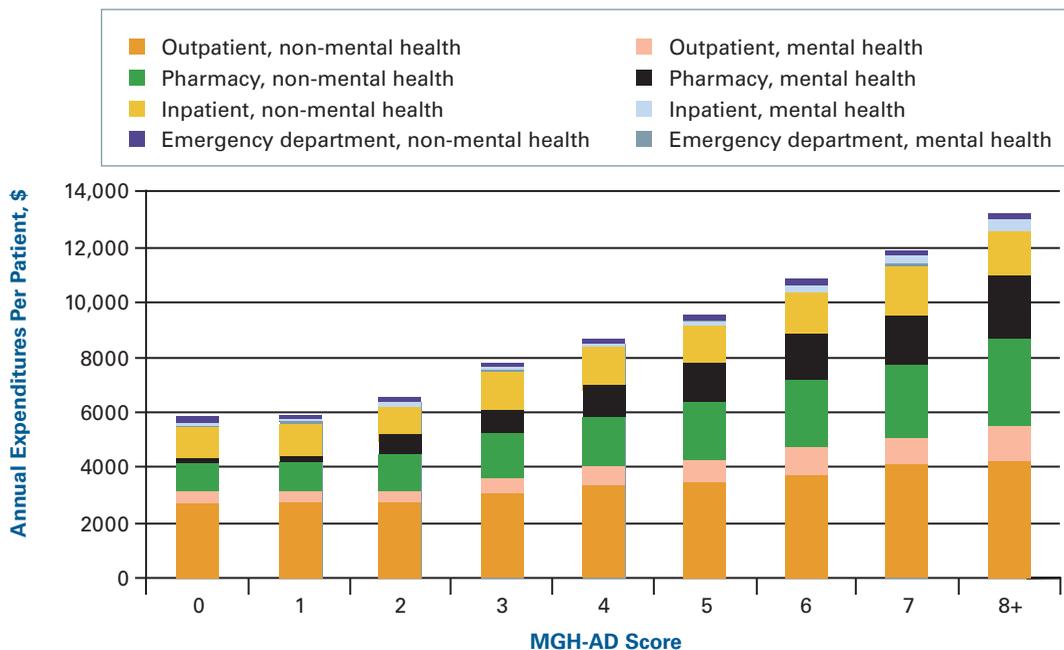
## Cost Burden of Treatment Resistance

■ **Figure 1.** Distribution of Patients With Depression by MGH Score (N = 78,477)



MGH indicates the Massachusetts General Hospital treatment-resistant depression staging method; MGH-AD indicates the antidepressant-only version.

■ **Figure 2.** Direct Medical Costs Per Patient With Depression by MGH-AD Score (N = 78,477)<sup>a</sup>



MGH-AD indicates the Massachusetts General Hospital treatment-resistant depression staging method, antidepressant-only version.  
<sup>a</sup>The pharmacy cost category represents outpatient pharmacy costs for medications delivered via retail and mail order distribution.

score, controlling for remaining differences in sociodemographic characteristics, plan type, health status, and index year (Table 2). Relative to patients with MGH-AD below 3.5, patients with MGH-AD 3.5 to 4, MGH-AD 4.5 to 5, MGH-AD 5.5 to 6, and MGH-AD above 6 had costs 21.4%, 27.0%, 39.7%, and 48.9% higher, respectively (all  $P < .001$ ). Costs also were 10.7% higher for patients using adjunctive atypical antipsychotics, 24.9% higher for patients using ad-

juvantive stimulants, and 59.8% higher for patients using adjunctive mood stabilizers (all  $P < .001$ ). When MGH-AD was expressed as a continuous measure, each 1-unit increment was associated with a 7.9% increase in medical costs. When expressed as a single indicator variable representing all TRD patients, treatment resistance among depressed patients was associated with 40% higher medical care costs (coefficient 0.336,  $P < .001$ , not shown).

■ **Table 1.** Population Characteristics for Patients With and Without TRD Before and After Matching (Direct Cost Analysis)

Characteristic	Unmatched			Matched <sup>a</sup>		
	TRD, % (n = 22,615)	Non-TRD, % (n = 55,862)	P	TRD, % (n = 22,593)	Non-TRD, % (n = 22,593)	P
<b>Year of first antidepressant prescription fill</b>						
2000	20.4	18.9	<.001	20.4	20.1	.433
2001	18.3	18.7	.199	18.4	18.5	.716
2002	23.2	23.5	.411	23.2	23.3	.806
2003	18.3	19.6	<.001	18.3	18.4	.865
<b>Age categories, y</b>						
18-34	19.6	22.7	<.001	19.7	19.4	.440
35-44	30.6	31.0	.304	30.6	30.6	.976
45-54	37.0	33.8	<.001	36.9	36.9	.961
55-64	12.8	12.5	.343	12.8	13.1	.347
<b>Sex</b>						
Female	71.6	69.4	<.001	71.6	71.9	.517
<b>Census region of residence</b>						
Northeast	13.4	12.1	<.001	13.4	13.4	.967
North Central (Midwest)	32.9	33.1	.449	32.8	33.0	.682
South	30.9	28.9	<.001	30.9	30.4	.217
West	22.3	25.3	<.001	22.4	22.8	.270
Unknown region	0.5	0.5	.360	0.5	0.4	.298
<b>Lives in urban area (metropolitan area)</b>						
Urban residence	80.9	80.3	.055	80.9	81.6	.048
<b>Type of health plan</b>						
Comprehensive	18.7	18.8	.570	18.7	18.4	.561
HMO	21.9	24.0	<.001	21.9	22.1	.691
POS	13.5	13.3	.453	13.5	13.3	.659
PPO	36.0	33.6	<.001	36.0	36.8	.068
Capitated POS	8.4	8.9	.038	8.4	8.0	.119
Other (includes unknown, CDHP, and EPO)	1.1	1.1	.396	1.1	0.9	.095
CDHP	0.1	0.1	.954	0.1	0.1	.435
EPO	1.0	1.0	.364	1.0	0.8	.134
<b>General health indices</b>						
Charlson Comorbidity Index	0.48	0.38	<.001	0.48	0.44	<.001
Number of Psychiatric Diagnosis Groups	2.10	1.53	<.001	2.09	2.08	.259

CDHP indicates consumer-driven health plan; EPO, exclusive provider organization; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; TRD, treatment-resistant depression.

<sup>a</sup>Patients were matched one-to-one via propensity score matching. Twenty-two patients with TRD could not be matched and were dropped. The final sample included 22,593 patients with TRD and a matched comparison group with depression (non-TRD) of the same size.

Table 2 also presents the marginal or incremental costs in dollars (the column on the right). A 1-unit increase in the MGH-AD score was associated with a \$590 increase in medical care costs (95% confidence interval = \$526, \$653). Costs for patients with MGH-AD scores of 3.5 to 4, 4.5 to

5, 5.5 to 6, and  $\geq 6.5$  were \$1530, \$2114, \$3183, and \$4425, respectively, higher than costs for patients without TRD. Costs for patients on adjunctive therapies were between \$1160 and \$5395 higher than costs for patients without augmentation.

**Table 2.** Models of Direct Cost Burden Associated With Treatment Complexity<sup>a</sup>

Model	Medical/Prescription Drug Expenditures (n = 45,186)				Incremental Cost, \$ <sup>c</sup> (95% CI)
	Coefficient	SE	Effect, % <sup>b</sup>	P	
<b>Model 1: Indicators for TRD score categories and use of adjunctive therapy</b>					
<b>Antidepressant-only TRD score categories (reference category is &lt;3.5)</b>					
MGH-AD 3.5-4	0.194	-0.018	21.40	<.001	1530 (1269, 1800)
MGH-AD 4.5-5	0.239	-0.025	27.00	<.001	2114 (1701, 2545)
MGH-AD 5.5-6	0.334	-0.031	39.70	<.001	3183 (2660, 3739)
MGH-AD ≥6.5	0.398	-0.036	48.90	<.001	4425 (3724, 5200)
<b>Adjunctive therapies</b>					
Add atypical antipsychotics	0.102	-0.026	10.70	<.001	1160 (668, 1652)
Add stimulants	0.222	-0.027	24.90	<.001	2338 (1857, 2820)
Add mood stabilizer	0.469	-0.021	59.80	<.001	5395 (4930, 5861)
<b>Model 2: Continuous measure of TRD score and indicators for adjunctive therapy</b>					
<b>Antidepressant-only TRD score continuous</b>					
MGH-AD	0.076	-0.004	7.90	<.001	590 (526, 653)
<b>Adjunctive therapies</b>					
Add atypical antipsychotics	0.096	-0.026	10.10	<.001	1108 (615, 1602)
Add stimulants	0.21	-0.028	23.40	<.001	2221 (1736, 2705)
Add mood stabilizer	0.467	-0.021	59.50	<.001	5399 (4931, 5867)

CI indicates confidence interval; MGH-AD, Massachusetts General Hospital treatment-resistant depression staging method, antidepressant-only version; TRD, treatment-resistant depression.  
<sup>a</sup>All models included controls for age, sex, region, type of health plan, number of Psychiatric Diagnosis Groups, Charlson Comorbidity Index, and year of index date.  
<sup>b</sup>Effect (%) was calculated as exp(coefficient) - 1 (eg, 21.4% = exp(0.194) - 1).  
<sup>c</sup>Calculation of incremental cost: For the continuous MGH-AD score, the dollar value shown represents the potential savings per enrollee with depression from reducing the MGH-AD score by 1 point. For the categorical MGH-AD, the dollar values shown are obtained by comparing costs for patients at each level of the MGH-AD with what their costs would have been if they were in the MGH-AD <3.5 category. For the adjunctive therapies, the dollar value shown represents the additional cost of the adjunctive therapy for patients on an adjunctive therapy.

## DISCUSSION

This study applied a clinical staging algorithm for TRD to claims data. Whether modeled as a flag for TRD, ordinal values, or a continuous measure, higher MGH and MGH-AD scores were associated with higher future direct medical costs. Use of adjunctive medication (ie, mood stabilizers, atypical antipsychotics, or stimulants) also was associated with higher future medical costs. This TRD scale shows promise for early identification of and intervention with TRD patients.

This study found TRD patients to have 40% higher medical costs than non-TRD patients. Other claims-based studies have found a larger difference. Corey-Lisle and colleagues found the costs of TRD-likely patients to be approximately twice the costs of TRD-unlikely patients.<sup>7</sup> Using the same definition of TRD-likely patients, Greenberg and colleagues found direct costs for TRD-likely patients to be more than

twice as high as for the TRD-unlikely patients.<sup>2</sup> Both prior studies used a more conservative definition of TRD; Corey-Lisle and colleagues classified 12% of depressed patients as likely to have TRD.<sup>7</sup> Our study used a definition that classified 29% of depressed patients as having TRD. Another important difference is that we measured costs in a subsequent period, whereas the prior studies measured costs contemporaneously with the TRD definition.<sup>2,7-9</sup>

Crown and colleagues created a simple classification by dividing patients into 3 disease severity groups, non-TRD, inpatient TRD, and outpatient TRD.<sup>8</sup> Patients in the inpatient cohort had costs that were more than 6 times those of the non-TRD group, and those in the outpatient cohort had costs that were 1.6 times those of the non-TRD group.

We found that higher scores on the MGH-AD predicted higher costs during the follow-up period. Although previous studies did not apply a scale, Russell and colleagues mea-

sured monthly costs after successive changes in treatment; they found significantly higher costs for the third through the eighth changes compared with costs for the second change.<sup>9</sup> They measured costs contemporaneously with the changes in treatment used to define TRD.<sup>9</sup>

It should be noted that other thresholds for TRD could have been used. As described above, a TRD threshold of MGH >3 is consistent with 2 antidepressant trials with 1 optimization strategy each. A minimum TRD threshold of MGH >2 would be consistent with 2 adequate antidepressant trials with no optimization strategies. Looking at the increase in costs (Figure 2), the direction of the relationship to costs would remain positive at a lower threshold; however, including patients with lower scores and costs would reduce the size of the cost burden.

Use of adjunctive atypical antipsychotics, mood stabilizers, and stimulants was associated with substantially higher direct medical costs during the follow-up period. Prior TRD studies did not model adjunctive medication use independently. In particular, the use of mood stabilizers during the screening phase was associated with 60% higher medical care costs in the following year. In contrast, use of atypical antipsychotics during the screening phase was associated with 11% higher medical costs. We could not establish whether patients receiving mood stabilizers had more complex cases than those receiving atypical antipsychotics, or whether atypical antipsychotics had a greater effect on costs than mood stabilizers. This topic warrants further study.

As with all claims-based studies, this study was limited by the level of clinical detail available in the data. Whereas a clinical trial or a retrospective study using chart review would assess a patient's response to treatment, a claims-based analysis can only assume treatment failure based on the existence of a subsequent treatment change. For the same reason, this study could not determine whether a change in treatment was due to factors such as treatment resistance, medication side effects, or a relapse after successful symptom relief. Patients may have had other psychiatric and medical comorbidities that were not captured within the claims data. For example, patients with undiagnosed bipolar disorder may have been included. Bipolar disorder has been suggested to account for a significant portion of antidepressant treatment resistance in patients with depression.<sup>22,23</sup> The extent of confounding resulting from such patients is unclear, though the relationship between MGH score and postindex health expenditures was consistent and robust. Our results do not constitute a diagnostic algorithm for TRD, but rather a means of finding patients who warrant greater diagnostic scrutiny and review of their treatment plan. Further research is necessary in order to validate the claims-based versions of the MGH staging algorithm. In addition, this study was based on patients receiving

employer-sponsored health insurance and the results may not be generalizable to other populations.

A clinically derived claims signature that measures mild to complex TRD may be useful to providers and plans that wish to find TRD patients at an earlier stage, when clinical interventions and programmatic interventions such as disease management programs might improve clinical outcomes and reduce costs.

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**Funding Source:** This study was supported by Bristol-Myers Squibb (Princeton, NJ) and Otsuka Pharmaceutical Co, Ltd (Tokyo, Japan).

**Author Disclosures:** Drs Jing and Kim are employees of Bristol-Myers Squibb (BMS), one of the funders of the study, and Dr Kim reports owning stock in the company. Dr Burton reports serving as a consultant to BMS and was paid by BMS for his involvement in the preparation of this manuscript. Drs Tran and Pikalov are employees of Otsuka America Pharmaceuticals, one of the funders of the study. Dr Goetzel reports receiving grants from BMS for this research and was paid by BMS for his involvement in the preparation of this manuscript. The other authors (TBG, GSC, JEB) report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

**Authorship Information:** Concept and design (TBG, YJ, GSC, EK, JEB, WNB, Q-VT, AP, RZG); acquisition of data (TBG); analysis and interpretation of data (TBG, YJ, GSC, EK, JEB, WNB, Q-VT, AP, RZG); drafting of the manuscript (TBG, YJ, EK, JEB, WNB, AP, RZG); critical revision of the manuscript for important intellectual content (TBG, YJ, GSC, JEB, WNB, Q-VT, AP, RZG); statistical analysis (TBG, YJ, GSC, JEB); obtaining funding (TBG); and supervision (YJ, AP).

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