Association Among Change in Medical Costs, Level of Comorbidity, and Change in Adherence Behavior

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ABSTRACT

OBJECTIVES: Interventions to improve medication adherence are effective, but resource intensive. Interventions must be targeted to those who will potentially benefit most. We examined what heterogeneity exists in the value of adherence based on levels of comorbidity, and the changes in spending on medical services that followed changes in adherence behavior.

STUDY DESIGN: Retrospective cohort study examining medical spending for 2 years (April 1, 2011, to March 31, 2013) in commercial insurance beneficiaries.

METHODS: Multivariable linear modeling was used to adjust for differences in patient characteristics. Analyses were performed at the patient/condition level in 2 cohorts: adherent at baseline and nonadherent at baseline.

RESULTS: We evaluated 857,041 patients, representing 1,264,797 patient therapies consisting of 40% high cholesterol, 48% hypertension, and 12% diabetes. Among those with 3 or more conditions, annual savings associated with becoming adherent were $5341, $4423, and $2081 for patients with at least diabetes, hypertension, and high cholesterol, respectively. The increased costs for patients in this group who became nonadherent were $4653, $7946, and $4008, respectively. Depending on the condition and the direction of behavior change, savings were 2 to 7 times greater than the value for individuals with fewer than 3 conditions. In most cases, the value of preventing nonadherence (ie, persistence) was greater than the value of moving people who are nonadherent to an adherent state.

CONCLUSIONS: There is important heterogeneity in the impact of medication adherence on medical spending. Clinicians and policy makers should consider this when promoting the change of adherence behavior.

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There is broad consensus that improving adherence to essential medications is central to better management of chronic conditions,[1,2] and there is an extensive body of literature that consistently demonstrates a strong relationship among better adherence, improved outcomes, and reduced medical costs.[3,4] The focus of researchers has shifted to developing a better understanding of how to best target and deliver interventions to improve adherence behavior. The principal challenge is that medication adherence is quite personal, and there are numerous reasons why patients fail to adhere, ranging from the complexity of therapy[5] to medication costs,[6] and to understanding the rationale for therapy and its appropriate administration.[7] No single intervention has proven effective at addressing all of the barriers experienced by patients.

As a result, payers and risk-bearing providers increasingly seek evidence concerning the clinical benefits and cost-effectiveness of targeted interventions to improve adherence and health outcomes, and, thus, reduce costs. Due to concern that the clinical and cost benefits may not be accrued by those making the investment, churn in insurance membership can influence decisions about investing in interventions to improve adherence. Studies that help characterize the value of improving adherence within patient subpopulations are essential, particularly in the short term, so payers and risk-bearing providers can be confident that investments to improve adherence will provide a positive return on their investment.

In this study, we used a de-identified longitudinal data set to assess the effect of adherence on healthcare costs, and then characterized the value of adherence in a 1-year follow-up period. We assessed the value of adherence by several key characteristics. We studied how patient comorbidity is associated with the value of adherence to better understand how targeting patients with multiple conditions might influence both health outcomes and the return on investment in adherence promotion programs. We also explored the differences in changes in medical spending between individuals who remain adherent and those who become adherent.

TAKE-AWAY POINTS

- Adherence to medication in patients with chronic disease leads to improved health outcomes and lower costs. Yet, physicians, health systems, and health plans continue to face significant challenges in promoting adherence among patients.
- There are considerable differences in the value created by improving adherence behavior and preventing nonadherence, with respect to the baseline level of comorbidity and the direction of behavioral change (ie, adherent to nonadherent or vice versa).
- Clinicians and policy makers determining how to cost-effectively deploy adherence promotion programs—particularly in the setting of providers at risk for medical service spending—should consider these findings in setting population health management priorities.

There has been no previous work, to our knowledge, examining this latter question; however, such evidence is critical for providers, pharmacies, and pharmacy benefits managers to develop and target interventions, and for payers and risk-bearing providers to make cost-effective investments in care improvement.

METHODS

Using a nationally representative de-identified medical claims data set with claims for 24 consecutive months, we examined the impact of change in medication adherence and change in the cost of medical care for 2 groups of patients: a) those who were nonadherent in the baseline year and became adherent in the second year compared with those who remained nonadherent, and b) those who were adherent in the baseline year and became nonadherent in the second year compared with those who remained adherent. Our study was limited to patients with at least 1 of 3 diseases: diabetes, hypertension, and high cholesterol (*hypercholesterolemia*). To gain additional insights into the relationship between change in adherence and change in medical spending, we stratified our analyses by the number of conditions included in the patient's claims in the baseline year. We also conducted a subanalysis examining whether there was a synergistic impact on spend when the patient is experiencing both hypertension and diabetes.

Study Sample

The study sample was drawn from a de-identified data set obtained from a national data aggregator, consisting of medical and pharmacy claims from more than 10 million commercially insured patients. No Medicare or Medicaid beneficiaries were included in the sample. The baseline period for analyses was April 1, 2011, to March 31, 2012; the follow-up period was April 1, 2012, to March 31, 2013. To be included in the cohort, we required that patients with a pharmacy or medical claim in the baseline period have benefits eligibility during the entire follow-up period and to have at least 1 of the candidate conditions—diabetes, hypertension, or hypercholesterolemia—during the baseline period. To insure that we were as sensitive as possible in case identification, we used both *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and medication profiles to identify patients with 1 of the 3 conditions (see **eAppendix**, available at **www.ajmc.com**).

The exposure of interest in this study was change in adherence status. For this purpose, adherence was measured using the medication possession ratio (MPR) calculated at the therapeutic class and averaged across the condition (eAppendix).[8] MPR is a commonly used outcome metric designed to measure medication adherence. It is a proportion consisting of the total days' supply of medication on hand divided by the elapsed time between the first fill of medication to the end of the year. Supply is prorated if the patient fills before the end of the year but won't exhaust the fill until after year's end. For our purposes, fill data time periods ran March to March, corresponding with eligibility data availability. Baseline MPR values spanned April 1, 2011, through March 31, 2012, and follow-up was measured between April 1, 2012, and March 31, 2013.

We created 2 cohorts based on prescription-filling behavior within the condition in the baseline period: a) patients adherent (MPR $\geq$0.80) to medication at the condition level, and b) patients not adherent (MPR $<$0.80). Adherence behavior was considered only at the condition level, with the weighted average of MPR considered when there were multiple medications taken. To gain additional insights into how the change in adherence status might affect spending on medical services, we also conducted a stratified analysis, splitting our sample into patients with a Charlson Comorbidity Index score greater than or equal to 3 and those with a score of less than 3.[9]

Finally, we conducted a descriptive analysis to examine whether the presence of comorbid hypertension modifies the relationship between change in adherence status and medical service utilization when diabetes is present. For this purpose, we compared the adjusted medical spend of 3 cohorts: a) patients with hypertension only, b) patients with diabetes only, and c) patients with both hypertension and diabetes. We evaluated the presence of effect modification by comparing the expected additive medical costs (ie, the spending of patients with hypertension plus the spending of patients with diabetes) with the actual observed spending of patients with diabetes and hypertension.

Outcome Measures and Model Covariates

The outcome modeled in these analyses was the spending on health services during the follow-up period. We captured allowed charges for all inpatient and outpatient services, regardless of whether they were paid by the insurer or patient. As our primary outcome was concerned with the impact of medication adher-

ence on medical service utilization, we did not include pharmacy costs in our outcome measure.

In the multivariable regression analyses of the post period medical spending, we adjusted for medical spending in the baseline period, age, gender, comorbidity (using the Charlson Comorbidity Index[9]), Census region, initiator/continuer medication use status, and preventive health service use. Initiator or continuer therapy utilization status was defined at the patient/condition level, where patients without a fill for a medication within the condition classification in the 6 months prior to the baseline period were considered initiators. Preventive health service use was included to adjust for "healthy user" bias,[10] and was defined as having a claim for 1 of 52 preventive services during the baseline period.[11] In this way, we controlled for the healthy user bias in 2 ways: a) by using each patient as his or her own historical control, and b) by adjusting for preventive service use.

Statistical Considerations

We constructed generalized linear models to describe the total spending on health services during the follow-up period (ie, April 1, 2012, to March 31, 2013). Our unit of analyses was patient/therapy combination; thus, it was possible in our preliminary analyses for patients with multiple conditions to be considered in more than 1 disease cohort. For instance, a patient with hypertension and high cholesterol would be included in both our hypertension and high cholesterol results. In our descriptive analyses examining the additive effect of comorbidity, patients are included in only 1 cohort. Thus, the hypertension group includes only patients with hypertension, while the diabetic/hypertensive group includes individuals with both conditions.

The impact of change in adherence status was estimated by comparing the adjusted spend of those who maintained their adherence status with those whose status changed. For instance, patients who maintained adherence at baseline and follow-up were compared with those who became nonadherent at follow-up. This difference (ie, increase in spending) was considered the impact on medical service spending of becoming nonadherent. Similarly, patients who newly achieved adherence at follow-up were compared with those who were nonadherent at baseline and during follow-up. This difference (ie, reduction in spending) was considered to be the impact on medical service spending of becoming adherent.

In modeling medical spending, the use of non-Gaussian distributions is common due to the skewed nature of healthcare utilization on a population basis. However, these cautions are typically the result of a large proportion of community members with no medical spending.[12] In the sample we evaluated, all patients were service utilizers, and we were modeling the change in medical spending among these patients between the 2 years. We examined this assumption empirically by testing the distribution of the change in spending in the follow-up year, and we found it to reflect a normal distribution. Therefore, we determined that ordinary least squares regression would be the most transparent and least biased approach to analysis.

All analyses were conducted using SAS Enterprise Guide 5.1 (SAS Institute, Cary, North Carolina). For this investigation, we used de-identified medical and pharmacy claims data from an external vendor; therefore, no institutional review board review for research on human subjects was required.

RESULTS

The 4 cohorts analyzed are described in **Table 1**. The 4 cohorts analyzed are described in Table 1. The combined sample of patients with at least 1 of the candidate conditions totaled 857,041 distinct patients and 1,264,797 patient therapies. Of these, 61% had only 1 condition: high cholesterol (23.7%), hypertension (34.1%), or diabetes (3.5%). The balance (39%) had multiple conditions: high cholesterol/hypertension (24.6%), diabetes/hypertension (2.8%), diabetes/high cholesterol (2.3%), or all 3 conditions (8.9%). Nonadherent patients who became adherent were more likely to be male, be a medication continuer, and have hypertension; on average, they were older and had higher baseline medical service cost than those who remained nonadherent. Adherent patients who became nonadherent were more likely to be female, live in the South, have point-of-service coverage, engage in fewer health-seeking behaviors, have high cholesterol, and be a medication initiator; on average, they were younger and had higher baseline medical service costs than those who remained adherent.

The results of the multivariable analyses are presented in the **Figure**. The number of conditions a patient had in the baseline period dramatically influenced the magnitude of change in spending when adherence behavior changed (**Table 2**). Patients having 3 or more conditions at baseline had up to 7 times greater savings (or increased spend) than patients with 1 or 2 conditions. Specifically, patients with 1 to 2 conditions who became adherent had a modest reduction in spending ranging from a reduction of $757 per year (diabetes) to an increase of $365 per year (high cholesterol). In contrast, the group that had 3 or more conditions had savings ranging from $2081 for high cholesterol to $5341 for diabetes. Among the adherent patients who became nonadherent, those with 1 or 2 conditions had increased spend ranging from $1045 for patients with high cholesterol to $1706 for those with hypertension; those with 3 or more conditions had increase spend ranging of $4008 for patients with high cholesterol to $7946 for those with hypertension. With the exception of high cholesterol in the overall sample, and hypertension among those with 1 to 2 conditions (both in the nonadherent to adherent cohort), all of these differences were statistically significant at the $P < .001$ level.

It is notable in the Figure that the increase in spend among patients who were adherent and became nonadherent was larger than

TABLE 1. Description of the Study Sample

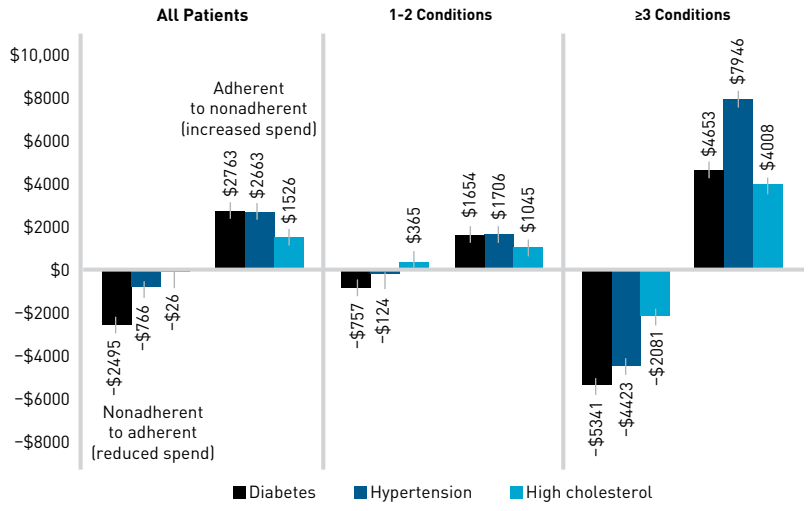
Characteristic	Strata	Nonadherents Who Remained Nonadherent		Nonadherents Who Became Adherent		Adherents Who Remained Adherent		Adherents Who Became Nonadherent	
		Number of Patient Therapies	%	Number of Patient Therapies	%	Number of Patient Therapies	%	Number of Patient Therapies	%
Total		523,315	41.4%	132,239	10.5%	450,321	35.6%	158,922	12.6%
Age, years	**0-44**	169,296	32.4%	30,667	23.2%	71,746	15.9%	40,049	25.2%
	45-54	206,108	39.4%	55,285	41.8%	181,852	40.4%	64,560	40.6%
	≥55	147,911	28.3%	46,287	35.0%	196,723	43.7%	54,313	34.2%
Gender	**Male**	265,176	50.7%	72,109	54.5%	256,882	57.0%	86,028	54.1%
	Female	258,139	49.3%	60,130	45.5%	193,439	43.0%	72,894	45.9%
Region	**Midwest**	107,044	20.5%	29,732	22.5%	113,451	25.2%	34,613	21.8%
	Northeast	89,004	17.0%	25,879	19.6%	94,908	21.1%	25,339	15.9%
	South	253,466	48.4%	60,098	45.4%	185,304	41.1%	78,076	49.1%
	West	73,801	14.1%	16,530	12.5%	56,658	12.6%	20,894	13.1%
Payer	**HMO**	64,331	12.3%	19,771	15.0%	68,438	15.2%	18,603	11.7%
	POS	396,520	75.8%	94,996	71.8%	318,355	70.7%	122,689	77.2%
	PPO	62,464	11.9%	17,472	13.2%	63,528	14.1%	17,630	11.1%
Charlson Comorbidity Index	**1**	439,019	83.9%	109,094	82.5%	373,424	82.9%	130,690	82.2%
	≥2	84,296	16.1%	23,145	17.5%	76,897	17.1%	28,232	17.8%
Healthy behaviors	**1**	104,670	20.0%	22,812	17.3%	73,598	16.3%	33,732	21.2%
	≥2	418,645	80.0%	109,427	82.7%	376,723	83.7%	125,190	78.8%
Therapy duration status	**Initiator**	214,900	41.1%	28,640	21.7%	41,247	9.2%	35,355	22.2%
	Continuer	308,415	58.9%	103,599	78.3%	409,074	90.8%	123,567	77.8%
Condition	**High cholesterol**	242,201	46.3%	50,430	38.1%	157,186	34.9%	60,494	38.1%
	Diabetes	70,008	13.4%	15,204	11.5%	44,733	9.9%	20,900	13.2%
	Hypertension	211,106	40.3%	66,605	50.4%	248,402	55.2%	77,528	48.8%
		Value (SE)		**Value (SE)**		**Value (SE)**		**Value (SE)**	
Continuous variables	**Baseline MPR**	50.2% (0.04)		60.0% (0.06)		94.7% (0.01)		92.4% (0.02)	
	Follow-up MPR	48.8% (0.04)		92.0% (0.02)		94.3% (0.01)		57.6% (0.05)	
	Baseline medical spend	$7445 (31)		$8321 (67)		$6862 (27)		$8001 (55)	
	Follow-up medical spend	$7935 (34)		$8080 (60)		$6798 (27)		$9021 (70)	

HMO indicates health maintenance organization; MPR, medication possession ratio; POS, point-of-service; PPO, preferred provider organization; SE, standard error.

the decrease in spending for patients who were nonadherent and became adherent. After adjustment, patients with diabetes who became adherent spent $2495 less on health services in the year they became adherent than those who remained nonadherent. In contrast, patients with diabetes who were nonadherent after being adherent had an increased spend of $2763. This relationship was more pronounced in patients with hypertension and high cholesterol. Among patients who were nonadherent who became adherent and had hypertension, the spending was $766 less per year than those who remained nonadherent, while those with high cholesterol spent $26 less. However, among those who were adherent who became nonadherent, patients with hypertension spent $2663 more and patients with high cholesterol spent $1526 more.

In Table 3, we present the results of the descriptive analyses examining the synergistic effect of hypertension and diabetes on medical service spending, and, here again, we see the dramatic

FIGURE 1. Adjusted Estimates of Changes in Medical Spending When a Patient Changes Adherence Behavior[a,b,c,d]



[a]Negative numbers indicate a reduction in medical spending between those who remain nonadherent and those who become adherent; positive numbers are an increase in spending between those who become nonadherent and remain adherent.

[b]All estimates adjusted for baseline medical spending, preventive health service utilization, age, gender, comorbidity (Charlson Comorbidity Index), initiator/continuer medication use status, and Census region.

[c]Reduced spending for a nonadherent patient with high cholesterol becoming adherent was $26, too small to be seen on the scale of the Figure.

[d]Count of conditions includes baseline condition.

impact of the presence of 3 or more conditions. Among patients with 2 conditions (ie, hypertension and diabetes only), there was modest impact above the expected contribution of the individual conditions alone. However, among those with 3 or more conditions, there were substantial differences between the expected (additive) spend and actual spend. For patients with 3 or more conditions who became adherent, the savings were $2418 greater than the expected. For patients with 3 or more conditions who became nonadherent, the increased spend was $1261 greater than the expected. In all cases, except for those patients with 1 to 2 conditions who became adherent, the difference between the additive (expected) and actual was significantly different at the $P < .001$ level.

DISCUSSION

In this study, we used a rigorous design to demonstrate that short-term changes in adherence have a meaningful and immediate impact on changes in healthcare spending. It is not necessarily surprising to learn that patients with multiple conditions have higher adherence-related savings potential than those with fewer conditions, but the magnitude of this difference demonstrates that the relationship is likely to be nonlinear. These results have key implications for targeting adherence interventions. In the Figure, we can clearly see that the change in spending associated with change in adherence behavior is much higher when the patient has 3 or more conditions. This would indicate that priority should be given to patients with multiple conditions when implementing adherence programs in resource-constrained settings.

Our findings have important implications in an era when we see new payment models moving risk for patient health status closer to physicians and health systems. If the adherence behavior and

TABLE 2. Year-Over-Year Change in Medical Service Spending for Patients Who Shift in Adherence Behavior Status

Cohort	Condition	N (% of all with condition)	Change in Spending Year 1 to Year 2						
			All Patients			Stratified by Comorbidity[a]			
			Unadjusted	Adjusted[a]	SE	1-2 Conditions[b]	SE	≥3 Conditions[b]	SE
Nonadherent to adherent	Diabetes	15,204 (10%)	−$1306	−$2495	$244	−$757	$189	−$5341	$592
	Hypertension	66,605 (11%)	−$898	−$766	$109	−$124	$88[d]	−$4423	$534
	High cholesterol	50,430 (10%)	$307	−$26	$98[c]	$365	$82	−$2081	$457
Adherent to nonadherent	Diabetes	20,900 (14%)	$1599	$2763	$180	$1654	$168	$4653	$403
	Hypertension	77,528 (13%)	$1239	$2663	$90	$1706	$72	$7946	$428
	High cholesterol	60,494 (12%)	$697	$1526	$93	$1045	$79	$4008	$399

SE indicates standard error.

[a]Adjusted for baseline medical spending, preventive health service utilization, age, gender, comorbidity (Charlson Comorbidity Index), initiator/continuer medication use status, and Census region. All estimates are statistically significant at the $P < .001$ level, except as noted.

[b]Count of conditions includes baseline condition.

[c]$P = .788$.

[d]$P = .160$.

results from our analyses were applied to a sample of 100,000 members with each disease, the plan savings would range from $38 million for patients with high cholesterol to $63 million for those with diabetes. Given the increasingly limited budgets that are available for providing medical services, it is essential that spending by payers and providers implementing healthcare programs represent an efficient use of resources. A key finding of our study was that a disproportionate share of these savings came from patients with 3 or more conditions. In this cohort, 17% of the patients would have 3 or more conditions, yet 31% of the savings among patients with diabetes, 53% of savings for patients with high cholesterol, and 60% of savings for patients with hypertension would come from patients with greater comorbidity.

TABLE 3. Year-Over-Year Change in Medical Service Spending for Patients With Diabetes, Hypertension, and Both[a]

Cohort	Conditions, n[c]	Change in Spend From Year 1 to Year 2[b]					
		Diabetes only[d]	HTN only[e]	Additive[f]	Actual[g]	SE	Excess[h]
Nonadherent to adherent	1-2	–$573	–$102	–$675	–$717	$616[i]	–$42
	≥3	–$2283	–$4336	–$6619	–$9037	$1400	–$2418
Adherent to nonadherent	1-2	$1241	$1734	$2975	$427	$427	$307
	≥3	$2503	$9452	$11,955	$13,216	$1020	$1261

HTN indicates hypertension; SE, standard error.
[a]All differences between additive and actual are significant at $P < .001$, except as noted.
[b]All estimates are adjusted for baseline medical spending, preventive health service utilization, age, gender, comorbidity (Charlson Comorbidity Index), initiator/continuer medication use status, and Census region.
[c]Count of conditions includes baseline condition.
[d]Change in spend for patients who have diabetes but no hypertension.
[e]Change in spend for patients who have hypertension but no diabetes.
[f]The simple sum of the change is spend for patients in the "Diabetes only" and "HTN only" columns.
[g]The actual change in spend for patients with both diabetes and hypertension.
[h]The difference between the actual and additive spend. This represents the difference in spend compared with the expected combined cost of nonadherence to diabetic and hypertension medications.
[i]$P = .244$ for difference between additive and actual.

Similarly, the findings point to the importance of persistence in programs promoting adherence. In our example of 100,000 patients with each condition, we found that between 50% and 80% of our savings, depending on condition and level of comorbidity, come from keeping people adherent rather than promoting adherence among those who are nonadherent. This is a nuance that has not been previously reported in the literature, but has profound implications in the targeting of adherence resources. It may be easier and more efficient to prevent nonadherence in a patient who is currently adherent to their medication than it is to treat nonadherence in a patient who is nonadherent. It follows that there will be a high return on investment from programs promoting persistency and in implementation of targeting algorithms that identify patients who are currently adherent but at risk of nonadherence, so that a successful early intervention can be made.[13]

Finally, the finding concerning the synergistic impact of comorbid hypertension and diabetes points to a particular case of the finding we made that surrounds the importance of 3 or more conditions. In this we see, not surprisingly, the importance of adherence in patients with diabetes regardless of the level of comorbidity or persistence status. The impact of comorbidity on the change in medical spend in patients with diabetes and hypertension is well in excess of that seen when we combine the impact of each condition standing on its own. This would indicate—as has long been recognized—that it is critical to take aggressive steps to ensure adherence among patients with diabetes, particularly among those with hypertension.

Taken together, our findings have important implications for insurers and provider groups, such as accountable care organizations, who are at risk for the cost of medical services. Although a number of studies have demonstrated convincingly that patients who are adherent to their medications incur lower costs, this study helps establish that "all adherence is not equal." Changing a patient's behavior is not a costless effort. This is particularly true in the field of adherence where the cost of interventions might range substantially based on the nature and comprehensiveness of the intervention. Our findings provide evidence that a carefully nuanced targeting program that tailors interventions to patients based upon their adherence history and comorbidities would result in greater benefit from these programs than would a program with a less focused approach.

Limitations

Our study has several limitations. First, in a cohort study such as ours, it is impossible to control for all potential sources of confounding. Despite our efforts to address this in multivariable analyses, there are likely to be several unknown factors separate from adherence that might account for the impact we have identified. Second, the presence of the healthy user bias challenges the validity of many studies examining the value of medication adherence. Some authors have made recommendations to resolve this through the inclusion of covariates identifying patients who engage in good health practices; however, we found that more than 80% of our cohort members engaged in preventive health services, thus limiting the usefulness of this as a method to adjust for this bias. Nevertheless, our study design addresses this bias by stratifying on baseline adherence behavior and examining the impact of behavior change within the cohort members. In this manner, each patient acts as their own control, limiting the impact of the healthy user effect. Third, we did not consider the cost of medications in our estimation of the impact of the change in adherence behavior on the cost of medical care. It was not our intention to conduct a cost-benefit study of the impact of phar-

macy care in these conditions; that study has been conducted previously, and it demonstrated a strong return on investment associated with pharmacy care.[4] Our intention was to examine the impact of heterogeneity in change in adherence behavior on medical spend, and we believe that we have clearly demonstrated the potential importance of heterogeneity in response to those considering implementation of adherence programs. Additional studies of the cost-benefit of pharmaceutical interventions may be the subject of future investigations.

Fourth, in our analyses, we have focused exclusively on the financial impact of medication adherence on payers, ignoring the detrimental impact that medication nonadherence might have on the quality of life of the patient or their family. However, we conducted these analyses from the payer's perspective—as it is the payer who makes coverage decisions in the United States—and there is considerable heterogeneity in the way that quality-of-life information is used by payers, as well as a multiplicity of quality-of-life measures used, even for the 3 conditions considered here. Thus, it is not clear how to properly measure quality of life related to medication adherence in a manner meaningful to a payer, or how meaningful the results might be for them. Therefore, we have taken the more conservative approach of considering only the financial impact, which might be considered the lower bound of potential impact of a change in adherence behavior. Finally, we have addressed the consequence of changes in adherence behavior and the importance of persistency, but we have not spoken to the long-term impact of the 40% of the cohort members who remained nonadherent. Finding methods to move these patients to healthy behaviors remains an essential and intractable public health challenge.

CONCLUSIONS

Medication adherence is a critical health problem worldwide. Resolving it requires careful targeting of effective programs, and one element of that targeting criteria must be the value of adherence to the patient and payer**.** What we have demonstrated will vary with the direction of adherence behavior change and the comorbid conditions; thus, thoughtful policy makers, investigators, and clinicians should take these factors into consideration when implementing their adherence programs.

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eAppendix

Table. ICD-9 and GPI Codes used to identify people with the candidate conditions

Condition	ICD 9 Code- Source CMS Website http://www.cms.gov/medicare-coverage-database/staticpages/icd-9-code-lookup.aspx	Rx-Based GPI Condition Codes
Diabetes	2490, 24901, 2491, 24911, 2492, 24921, 2493, 24931, 2494, 24941, 2495, 24951, 2496, 24961, 2497, 24971, 2498, 24981, 2499, 24991, 2500, 25001, 25002, 25003, 2501, 25011, 25012, 25013, 2502, 25021, 25022, 25023, 2503, 25031, 25032, 25033, 2504, 25041, 25042, 25043, 2505, 25051, 25052, 25053, 2506, 25061, 25062, 25063, 2507, 25071, 25072, 25073, 2508, 25081, 25082, 25083, 2509, 25091, 25092, 25093, 2535, 3572, 5881, 6480, 64801, 64802, 64803, 64804, 7751, V1221, V180, V771	2750, 2755, 279930, 279940, 2717, 2728, 2725, 279925, 279950, 279960, 279970, 279980, 2770, 2720, 2715, 2760, 279978
Hypertension	3482, 36504, 4010, 4011, 4019, 40501, 40509, 40511, 40519, 40591, 40599, 4160, 4593, 45931, 45932, 45933, 64211, 64212, 64213, 64214, 6422, 64221, 64222, 64223, 64224, 6423, 64231, 64232, 64233, 64234, 6427, 64271, 64272, 64273, 64274, 6429, 64291, 64292, 64293, 64294, 7962, 99791, V811	3610, 269915, 369918, 3615, 369930, 369940, 369945, 3310, 3330, 369920, 33200010, 33200020, 33200021, 33200022, 33200030, 33200040, 34000003, 34000010, 34000013, 34000015, 34000018, 34000020, 34000024, 34000030, 37500010, 37500030, 3760, 3799000230, 3617, 369960, 369967, 369968
High Cholesterol	2722 , 2724	3910, 3930003000, 3920, 3948, 3945, 3940, 399940, 409925