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ORIGINAL ARTICLE

Systematic bias in predictions of new drugs' budget impact: analysis of a sample of recent US drug launches

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ABSTRACT

Objective: Expectations about the budget impact of new drug launches may affect payer behavior and ultimately consumer costs. Therefore, we evaluated the accuracy of pre-launch US budget impact estimates for a sample of new drugs.

Methods: We searched for publicly available budget impact estimates made pre-launch for drugs approved in the US from 1 September 2010 to 1 September 2015 and compared them to actual sales. Accuracy was calculated as the ratio of pre-launch estimate to actual sales. Quantitative analyses, including multivariate regressions, were used to identify factors associated with accuracy.

Results: We identified 25 budget impact estimates: 23 for one of 14 individual drugs and 2 for the category of PCSK9 inhibitors. The ratios of predicted to actual budget impact ranged from 0.2 (estimate was 20% of sales) for secukinumab to 37.5 (estimate was 37.5 × sales) for PCSK9 inhibitors. Mean ratio was 5.5. In multivariate analyses, larger eligible population, more recent estimate year (e.g. 2015 vs. 2012), and being first in class, were associated with statistically significant, greater overestimation of budget impact.

Conclusions: For every $5.5 of predicted cost, there was $1 of actual cost to the healthcare system. This study, although based on a small, non-random sample, suggests possible cognitive bias on the part of the estimators. Overestimating budget impact may lead to early access restrictions, higher copays, and other changes that ultimately impact patients. Analysts and non-profits should be attuned to likely sources of error in order to improve their predictions.

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Introduction

Increased spending on prescription drugs is a major health system concern in the US and world-wide[1,2]. Although the rate of increase has moderated recently, spending on prescription drugs, adjusted for rebates, reached $310 billion in the US[3] and $800 billion across the Organisation for Economic Cooperation and Development (OECD) countries. Drug spending now accounts for 17% of US and 20% of OECD healthcare expenditures[4,5]. Widely reported dramatic increases in drug prices for both branded and generic products have recently become a particular focus of concern[6], although overall price growth (as opposed to volume growth) for branded drugs was only 2.8% in the US last year[7] and has slowed across most OECD countries[5].

One possible reason for the widespread belief that branded drug prices are the primary culprit in spending growth is that new drug launches have recently been accompanied by dramatic reports from multiple sources predicting their financial impact on the US healthcare budget. For example, the nonprofit Institute for Clinical and Economic Review (ICER) has recently begun publicly releasing analyses of costs and effectiveness of some new drugs, along with what they call "evidence-based calculations of prices"[8]. Steven Pearson, the founder of ICER, was widely quoted as saying the new class of cholesterol lowering medications, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, would cost $20 billion a year in the US alone[9]. A *New England Journal of Medicine* editorial predicted they would increase annual insurance premiums by $124 for every insured person in the US[10]. Similarly, a *JAMA* editorial predicted a $200–300 per person insurance premium increase from the introduction of sobusivir for hepatitis C virus (HCV) infection, and some analysts predicted US sales of $3 billion in the first year[11].

Budget impact predictions may do more than generate public alarm. In the US, the reimbursement system for drugs relies on health plans, which pay more than 40% of US drug costs[12], to constrain spending growth. Health plans wanting to hold costs in check, thus, often react to drug launches by increasing cost-sharing and restricting prescriptions. Commenting on HCV-related spending, Steve Miller, chief medical officer at Express Scripts, acknowledged that they were "asking for more prior authorization because we're having to scrutinize every penny we spend now"[13]. With payers cutting back, consumers bear an increasing cost burden. The average out-of-pocket cost for branded drugs is up 25% since 2010[7]. Seventeen percent of branded drugs now require a patient payment of more than $50 per prescription[7], and spending by individuals with out-of-pocket drug costs of

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$1000 or more now accounts for one-third of overall drug spending[14].

Expectations about the US budget impact of new drug launches may thus affect consumer cost sharing, and unrealistic predictions could cause harm. We therefore evaluated the accuracy of pre-launch estimates of the US budget impact of new drugs. Our goal was to determine the accuracy of these estimates with the hope of improving such estimates in the future. We hypothesized that policy-focused agencies would provide more accurate estimates than, for example, financial analysts.

Methods

We studied the accuracy of budget impact estimates by identifying publically available estimates made prior to drug launches, and comparing them to actual drug sales. The sample items selected for this study were all newly developed drugs that had been launched (i.e. released for sale) in the US from 2012 to 2016. To be included, the drug had to have been launched at least one year before the start of the study (September 2016) to allow post-launch data to be collected. Drugs were considered for inclusion if they were first approved by the Food and Drug Administration (FDA) during the 5 year period between January 2012 and September 2016. From this list, we attempted to identify a wide variety of drugs for inclusion, using characteristics such as indication, population size, and year of approval. For example, we categorized drugs as treating rare or common conditions, based on the FDA threshold of 200,000 affected persons in the US, and included a sample of each. We used a list of therapeutic areas (e.g. cardiovascular, endocrinology, oncology, anti-infectives, immunology) and attempted to sample from them broadly. We identified at least one drug from each year of our search window. In order not to restrict the analysis to pre-launch estimates provided by the financial services industry, we specifically searched ICER reports for drugs launched from 2012 to 2016, excluding those published in the year after launch or later.

For the selected drugs, we conducted a search for pre-launch US sales estimates and post-launch actual US sales. Launch dates were found in various media sources and were typically close to the FDA approval date. Pre-launch budget impact estimates were identified using a combination of keyword terminology and Google search filters. The search covered the timeframe from a year before the launch date to the launch date. We searched keywords such as: trade/generic drug name (e.g., "Opdivo"/"nivolumab"), "estimated sales", "predicted sales", "revenue", "annual sales", "sales forecast", launch year +1 (e.g. if launch was in 2013, then "2014" used to identify predictions for the post-launch year), "report", "US", and "United States". Reports by ICER were individually searched for all budget impact estimates related to recent launches. We used these sales estimates to represent the broad budget impact of the drug for the entire US population. Our goal was to find both formal and informal estimates of budget impact. A formal report was defined as one that described the methods used to make estimates of sales or one that aggregated the results of multiple unrelated estimates. Informal reports – reports that did not document their methods of arriving at their estimates, or included only a single estimate – were typically produced by financial analysts to project share price. Budget impact models of the type used by payers to estimate the impact of covering a particular drug were not included, as these often focus on a specific setting (e.g. one commercial payer, rather than the entire market), estimate cost on a per-member basis, and include reductions in other costs (e.g. substitution of one drug for another, or reduction in utilization associated with medication use).

We searched for post-launch measures of budget impact in terms of actual sales using a combination of the specific keyword terminology and search filters. The timeframe was from a year following launch (e.g. if launch was in 2013, then 2014 used) to the year of predicted sales estimate (e.g. if a 2013 pre-launch sales estimate identified predicted sales for 2015, then 2015 used). We searched the keywords trade/generic drug name (e.g. "Opdivo"/"nivolumab"), pharmaceutical company name (e.g. "Bristol-Myers Squibb", "Novartis"), "full year", "FY", "quarter 4", "Q4", "sales", "revenue", "annual sales", year following launch (e.g. if launch was in 2013, then 2014 used), year of predicted sales estimate (e.g. if a 2013 pre-launch sales estimate identified predicted sales for 2015, then 2015 used), "financial", "report", "US", and "United States". We looked for full year sales for drugs of interest as reported in annual or quarterly company financial statements. If a year was identified in the pre-launch sales estimate, we searched the sales report for that same year. For naltrexone HCl/bupropion HCl, full year sales reports were not available, and sales between January and September were used to estimate full year sales.

We identified the size of the eligible population for each drug by searching published literature and other authoritative estimates, such as those from specialty societies and government agencies. Typical treatment length was identified using the prescribing information and/or registration trials. Drugs were categorized as used to treat cancer based on their labeled indication and as "first in class" based on the FDA's Novel Drugs Summary[15–18]. Alirocumab and evolocumab were launched nearly simultaneously, and were both considered first in class.

Analysis

Each item in the sample contained the following information: 1) a pre-launch estimate of budget impact (predicted budget impact); 2) a measure of the actual estimated year sales (actual budget impact); 3) an indication of whether the pre-launch budget impact estimate came from a "formal" or "informal" source (formal/informal); 4) an estimate of the size of the population of patients with the target condition; 5) typical length of treatment with the drug (categorized as <3 months, 3–6 months, >6 months); 6) whether the drug was a first-in-class agent; 7) whether the drug was indicated for cancer treatment; and 8) the calendar year for which the actual budget impact was reported (sales report year).

The primary outcome measure was the degree of over (or under) estimation in terms of the ratio of predicted to actual budget impact of the drug. Ratios greater than 1 indicate overestimates and ratios less than 1 indicate underestimates of budget impact. A multiple regression analysis was performed with the log of the ratio of predicted to actual impact as the dependent variable. Log transformation was used to linearize this variable for the analysis. Six variables were included as the predictors: credibility of estimate, eligible population, length of typical treatment, first in class, oncology indication, and reporting year.

Results

Our initial list included 16 drugs launched in the five year timeframe of interest. We were able to identify both pre- and post-launch estimates for 14 drugs (excluding Nucala and Tresiba) in a variety of indications launched since 2012. There were two PCSK9 inhibitor cholesterol lowering drugs (alirocumab, evolocumab); three drugs to treat various cancers (nivolumab, ceritinib, palbociclib); three for hepatitis C (ledipasvir/sofosbuvir, sofosbuvir, ombitasvir/paritaprevir/ritonavir with dasabuvir); two for obesity management (naltrexone HCl/bupropion HCl, liraglutide); and one each for cystic fibrosis (ivacaftor), heart failure (sacubitril/valsartan), psoriasis (secukinumab), and diabetes (canagliflozin). We also included estimates of the budget impact of both PCSK9 inhibitors combined (PCSK9-combined) in our analysis. There were multiple budget impact estimates for several drugs: three each for nivolumab and ombitasvir/paritaprevir/ritonavir with dasabuvir, and two each for evolocumab, alirocumab, PCSK9-combined, secukinumab, sacubitril/valsartan, and sofosbuvir. As a result, there were 25 estimates in our sample.

Of these 25, 16 budget impact estimates were for 2016 sales; 7 estimates were for 2015; and 2 estimates were for 2014. Pre-launch estimates were from financial analysts (as reported by business news services), for-profit consulting companies (e.g. PwC Health), and a non-profit (ICER) (Table 1). All estimates were made less than 12 months before launch. Two estimates (1 for Zykadia, made in 2014, and 1 for Kalydeco, made in 2012) did not specify the year for which they were predicting sales, 1 specified the period as being 2 years after launch, and the remainder predicted first-year sales. The Predicted Budget Impact of all items in the sample ranged from a low of $50 million for liraglutide (2015) to a high of $7.2 billion for PCSK9-combined (2016). Actual budget impact (sales) was collected for the specific year predicted. For the two estimates that did not specify a year, sales data from 2015 was used. Actual budget impact ranged from a low of $35 million for liraglutide (2015) to a high of $8.5 billion for sofosbuvir (2014) (Table 1). The ratios of predicted to actual budget impact ranged from 0.2 for secukinumab (e.g. predicted sales were 1/5 of actual sales) to 37.5 for PCSK9-combined (predicted sales were 37.5 times actual) (Figure 1). The overall mean predicted budget impact for items in our sample was 5.5 times the actual budget impact of the drug (predicted/actual ratio of 5.5).

In regression analysis, the six predictor variables (credibility of estimate, size of the population, length of typical treatment, first in class, oncology indication, reporting year) accounted for 46% of the variance in log of the ratio of predicted to actual budget impact ($R^2 = 0.46$). While the overall regression analysis was not statistically significant ($F(7, 17) = 2.1$; $p = .10$), three of the six variables were statistically significant predictors of the ratio of predicted to actual budget impact: population size ($t(17) = -2.27$; $p = .04$), first in class ($t(17) = -2.20$; $p = .04$), and sales report year ($t(17) = 2.80$; $p = .01$). The beta weights for these variables were as follows: population size, beta $= -2.19$; first in-class, beta $= -3.21$; and report year, beta $= 0.65$ (Table 2). These beta weights indicate the relative strength and direction of the relationship of the predictor variable to the criterion variable. The sign of the beta weights indicates the direction of the association between predictor variables and the criterion variable.

Population size, with a beta weight of -2.19, was negatively related to the ratio of predicted to actual budget impact. The larger the population, the less the predicted budget impact overestimated the actual budget impact. The univariate correlation between these variables was only 0.004, which is neither significant nor negative. The significant negative relationship between population size and the ratio only showed up in this multiple regression analysis. This suggests that the "true" relationship is "masked" by a confounding variable (or variables). Being first in class, with beta weight of -3.21, was also negatively related to the ratio. Drugs that were first in class were associated with more overestimation of actual budget impact (Figure 2). Note that while the average ratio of predicted to actual budget impact was much higher for drugs that were first in class (6.5 vs. 2.2) the variance of these predictions was much greater (SD 95.5 vs. 4.1). Report year, with a beta of 0.65, was positively related to the ratio of predicted to actual budget impact. Thus drugs released later were associated with a greater overestimation of budget impact.

Since these results are based on data that were clustered over drug types, we performed a repeated measures regression analysis in order to determine the sensitivity of these results to this clustering. We found that taking clustering into account had little effect on the significance of population size ($p < .0001$) and post launch year ($p = .051$) but made first in class no longer significant ($p = .15$).

Discussion

Pre-launch predictions of the budget impact of newly developed drugs tend to be considerable overestimates of their actual sales: for every $5.5 of predicted cost, there is $1 of actual sales. Overall, ten estimates were off by more than $1 billion each; 8 of those were overestimates. The multivariate regression analysis produced several noteworthy findings, although these should be considered exploratory, given the small non-random sample. First, the smaller the estimated

Table 1. Descriptive statistics of 14 drugs evaluated.

Drug	Predicted Budget Impact ($, millions)	Actual Budget Impact ($, millions)	Sales Report Year	Predicted/ Actual Ratio	Estimation Method[a]	Population Size (thousands)	Typical Length of Treatment	First in Class	Cancer Treatment
PCSK9-combined[b,c]	7200[19]	192[d]	2016	37.5	Formal	650[20]	>6 months	Yes	No
Sofosbuvir[b,c]	6600[21]	1895[22]	2016	3.5	Formal	3200[11]	<3 months	Yes	No
PCSK9-combined[b,c]	5000[23]	192[d]	2016	26.1	Informal	650[20]	>6 months	Yes	No
Ombitasvir/paritaprevir/ritonavir with dasabuvir[b,c]	3000[24]	804[25]	2015	3.7	Informal	3200[24]	<3 months	Yes	No
Ombitasvir/paritaprevir/ritonavir with dasabuvir[b,c]	3000[26]	342[27]	2016	8.8	Formal	3200[24]	<3 months	Yes	No
Sofosbuvir[b,c]	3000[11]	8507[28]	2014	0.4	Formal	3200[11]	<3 months	Yes	No
Ombitasvir/paritaprevir/ritonavir with dasabuvir[b,c]	2900[29]	804[25]	2015	3.6	Formal	3200[24]	<3 months	Yes	No
Nivolumab[c]	1800[26]	2664[30]	2016	0.7	Formal	12[31]	3–6 months	No	Yes
Nivolumab[c]	1700[31]	2664[30]	2016	0.6	Formal	12[31]	3–6 months	No	Yes
Ledipasvir/sofosbuvir	1600[32]	2001[28]	2014	0.8	Informal	3200[32]	<3 months	Yes	No
Alirocumab[b,c]	1300[26]	91[33]	2016	14.3	Formal	650[20]	>6 months	Yes	No
Sacubitril/valsartan[b,c]	1200[34]	170[35]	2016	7.1	Formal	6200[34]	>6 months	Yes	No
Sacubitril/valsartan[c]	844[36]	170[35]	2016	5.0	Formal	6200[34]	>6 months	Yes	No
Palbociclib[b]	800[26]	2068[37]	2016	0.4	Formal	82[e]	>6 months	Yes	Yes
Nivolumab[c]	652[38]	823[39]	2015	0.8	Formal	12[31]	3–6 months	No	Yes
Ivacaftor	550[40]	632[41]	2015	0.9	Informal	30[40]	>6 months	Yes	No
Canagliflozin	468[42]	1273[43]	2016	0.4	Informal	25,800[42]	>6 months	Yes	No
Evolocumab[c]	426[36]	101[44]	2016	4.2	Formal	650[20]	>6 months	Yes[f]	No
Alirocumab[c]	353[36]	91[33]	2016	3.9	Formal	650[20]	>6 months	Yes	No
Ceritinib	350[45]	79[46]	2015	4.4	Informal	16[g]	3–6 months	No	Yes
Evolocumab[c]	300[26]	101[44]	2016	3.0	Formal	650[20]	>6 months	Yes[e]	No
Naltrexone HCl/bupropion HCl	200[47]	39[h]	2016	5.1	Informal	90,437[i]	>6 months	No	No
Secukinumab[c]	200[26]	1128[35]	2016	0.2	Formal	1500[j]	>6 months	Yes	No
Secukinumab[c]	120[38]	261[46]	2015	0.5	Formal	1500[j]	>6 months	Yes	No
Liraglutide[k]	50[48]	35[49]	2015	1.4	Informal	90,437[i]	>6 months	No	No

[a]Formal defined as reporting either the methods used to make the estimate, references to the sources of the estimates, or summaries of estimates made by multiple analyses.
[b]Predicted budget impact off actual budget impact by >$1 billion.
[c]Multiple reported estimates.
[d]Alirocumab and evolocumab actual sales combined.
[e]Proportion of hormone receptor positive, human epidermal growth factor receptor 2 negative metastatic breast cancer is 2.7% of all breast cancer patients[50]; there are 3,069,231 breast cancer patients in the US[51].
[f]First in class in Europe and introduced a month after alirocumab.
[g]Proportion of non-small-cell lung cancer (NSCLC) with anaplastic lymphoma kinase gene rearrangements is about 4%–5% of all NSCLC patients[52]; NSCLC accounts for 85% of all lung cancer cases in the US[53]; there are 415,707 lung cancer patients in the US[54].
[h]Sales estimated using available 2016 Q1–2[55] and August–September sales[56] of $26.3 million.
[i]Of US adults 36.5% are obese[57]; adult population in US is 247,773,709[58].
[j]Approximately 7.5 million people in the United States have psoriasis; 20% have moderate to severe psoriasis[59].
[k]No US sales prediction broken out, therefore world-wide predicted and actual sales are reported. Predicted and actual sales converted from Danish crowns to USD.

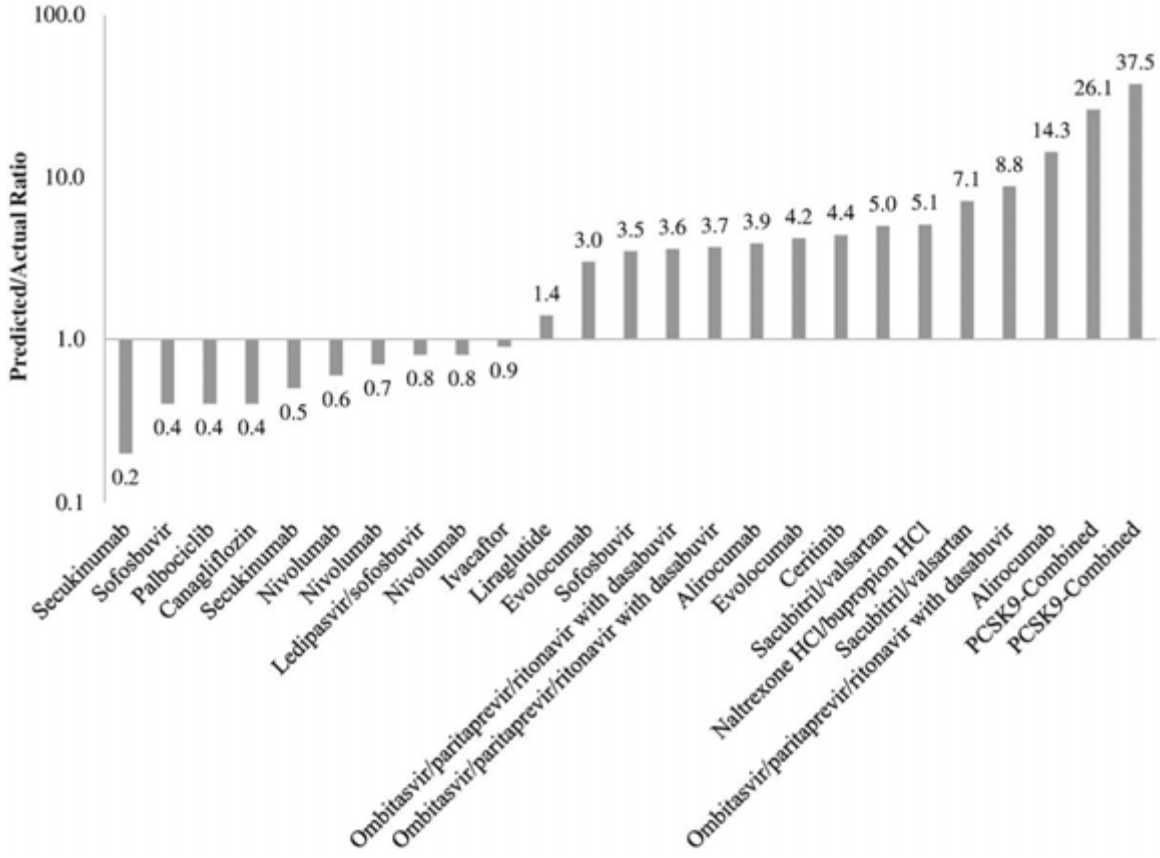

Figure 1. Predicted and actual budget impact ratios of 14 evaluated drugs.

Table 2. Results of multiple regression analysis.

	Coefficients	Standard Error	*t* Stat	*p* Value	Beta
Intercept	−1243.16	445.19	−2.79	0.01	
Estimation Method	−0.45	0.30	−1.50	0.15	
Population Size	0.00	0.00	−2.27	0.04	−2.19
3–6 Month Treatment Cycle vs. <3 Month Treatment Cycle	−4.22	2.21	−1.91	0.07	−2.55
>6 Month Treatment Cycle vs. <3 Month Treatment Cycle	−0.31	0.32	−0.97	0.35	−0.25
First in Class vs. Not First in Class	−4.57	2.07	−2.20	0.04	−3.21
Cancer Indication vs. Not Cancer Indication	−1.09	0.57	−1.92	0.07	−0.72
Sales Report Year	0.62	0.22	2.80	0.01	0.65

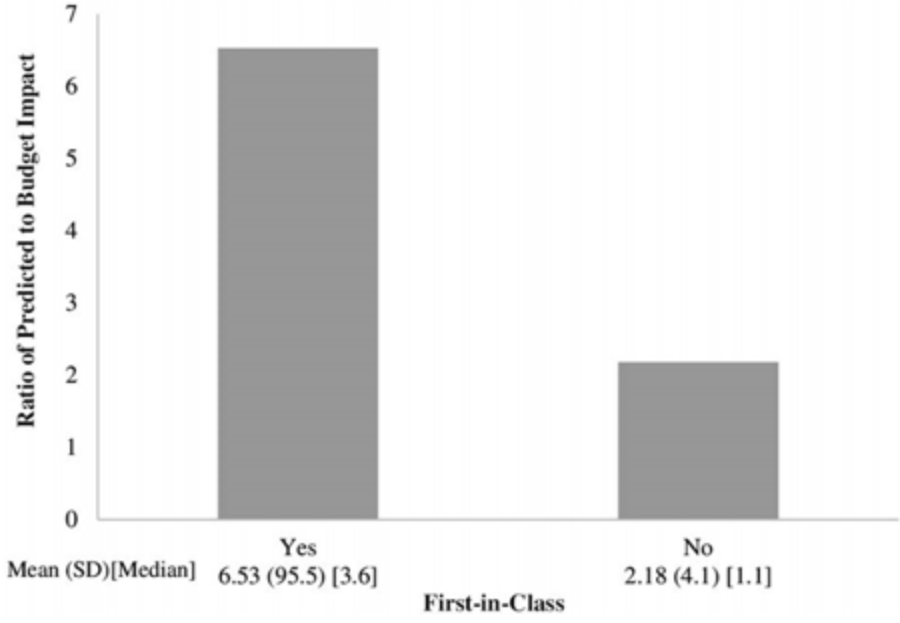

Figure 2. Average accuracy of budget impact estimates (in terms of the ratio of predicted to actual budget impact) for drugs that are and are not first in class.

population, the larger the overestimate of budget impact, independent of other characteristics. One plausible explanation for this finding is that estimates of the proportion of the potential population that will actually use the drug vary with population size. The smaller the potential population, the more inclined analysts may be to overestimate the proportion of that population who will use the drug. This hypothesis could be tested by examining whether the proportion of the estimated population that actually ends up using the drug is inversely related to the estimated treatment population size. Such an analysis was beyond the scope of this project, but we hope to undertake such analysis in the future by extending the current data set.

Although not quite statistically significant in the repeated measures regression analysis, the results do suggest that the budget impact of first-in-class drugs is overestimated more than that of other drugs. We hypothesize that this reflects an assumption that the market for first-in-class drugs will be a greater proportion of the eligible population than for other drugs. We were able to identify two cases in which this appeared to explain at least a portion of the overestimate, but most estimates did not provide enough detail to confirm this hypothesis systematically. This possible upward bias may be based on an assumption that doctors and patients are attracted to new treatments. A related hypothesis is that eventually first-in-class drugs might command a larger market share, but it may take longer to reach this share than estimated. Thus, the larger overestimation would reflect lower early sales, but in later years, as sales increased, overestimation would be reduced. This explanation is supported by the work of Cha *et al.*[60] who found no difference in the accuracy of predictions of first-in-class and follow-on drugs when assessing "peak" sales.

We were surprised that formal sources, using well documented, quantitative methods, were no more accurate than those made by informal sources. These sources overestimated budget impact to the same degree as informal sources. The consistency with which budget impact predictions overestimate actual cost suggests that predictions may be biased. An earlier study[60] focusing on forecasts of drug sales concluded that there is a natural tendency to be biased towards overestimating future sales (and, hence, budget impact) of newly developed drugs. ICER, a non-profit that performs and disseminates analyses on effectiveness and costs[9], contributed two estimates that were among the least accurate, so systematic bias is not restricted to financial analysts[61,62]. Availability bias – the tendency to overweight more readily available information (e.g. drug list price, epidemiology of disease, first-in-class status) and underweight less available information (e.g. effect of competition on rebates and discounts, proportion of individuals who actually use the drug, realistic estimate of prescriber knowledge and adoption)[62] may lead health policy research groups to make inappropriately high estimates of the budget impact of a newly released drug.

Overestimating budget impact can directly impact patients. Forty-two state Medicaid fee-for-service programs restricted sofosbuvir reimbursement[63], three-quarters in a manner inconsistent with recent treatment recommendations[64]. In the Medicaid program these restrictions may even be illegal[65]. Recent industry reports and Amgen officials suggested that the "complicated and lengthy" prior authorization required to prescribe PCSK9 inhibitors has "severely limit[ed]" the availability of these drugs[66,67]. Most patient access restrictions are less well publicized, but are likely driven by similar information on budget impact. For example, although this is far from proving causality, Express Scripts 2016 Medicare formulary shows restrictions (tier 5 or prior authorization) on four of the five drugs with the highest pre-launch estimates in our study[68], highlighting the importance of accurate estimates to a well functioning healthcare system.

This study had limitations. First, we focused on the US, although increased spending on prescription drugs is a major health system concern globally[69]. Prescribing restrictions for high cost medicines may limit patient in Europe, as well as the US[70]. An analysis using data from Europe would be informative, but was beyond the scope of this study. Second, we used a small, non-random sample comprising 8% of the new molecular entities launched in the last 5 years[13–18,71], and findings could be different with more or different drugs. We attempted to include drugs for a variety of illness types, approved in different years, used for varying lengths of time, and for populations of different sizes. Our goal in using a purposive sampling technique was to be able to explore whether various drug characteristics were associated with prediction accuracy. This approach could lead to bias if the sample we selected was systematically different from the underlying population. A larger study, using a larger proportion of approved drugs, or done using a random sampling technique, would be methodologically superior. Nonetheless, research done over a longer period with a larger sample generally supports our conclusions[60]. Third, most pre-launch estimates do not state whether they estimated prices before rebates or other price concessions. Rebates are opaque, but have been reported to average about 30% of list prices[72]. Adjusting all the predicted numbers as though they reported unrebated cost, the mean (SD) ratio of predicted to actual budget impact was reduced to 3.8 (6.1), which reduces but does not negate our findings. Fourth, one actual budget impact (for naltrexone HCl/bupropion HCl) was estimated based on less than a full year of sales. Fifth, drugs may take time to reach peak sales. A follow-up analysis using later sales data might produce a lower ratio of predicted to actual. Finally, high sales estimates may themselves lead to stringent controls on access. The "inaccuracy" we identified may have resulted from the impact of initial estimates on managed care decision makers. That is, high sales predictions could drive down sales. Given the retrospective nature of this research, we could not determine whether this mechanism explains our findings. Future studies should examine formulary decisions resulting from formal and informal reports of budget impact.

Conclusions

In this sample of newly approved drugs, for every $5.5 of predicted cost, there was $1 of actual cost to the healthcare system. Overestimating budget impact may lead to early

access restrictions, higher copays, and other changes in plan design that would ultimately impact patients. Our study, while based on a small, non-random sample, is the first to identify factors associated with overestimation of cost, including being first in class and being used in a smaller population. These systematic errors may result from cognitive biases on the part of the estimators. Analysts and non-profits promulgating estimates should examine likely sources of error in order to improve their predictions.

Transparency

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Declaration of financial/other relationships

M.S.B., J.M.Z., and J.L. have disclosed that they are employees of Partnership for Health Analytic Research LLC, a health services research company paid by Amgen to conduct this research. R.S.M. has disclosed that he has no significant relationships with or financial interests in any commercial companies related to this study or article.

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