Understanding Price Growth in the Market for Targeted Oncology Therapies

Jesse Sussell, PhD; Jacqueline Vanderpuye-Orgle, PhD; Diana Vania, MSc; Hans-Peter Goertz, MPH; and Darius Lakdawalla, PhD

ABSTRACT

OBJECTIVES: The causes of oncology drug price growth remain unclear. Analyzing corresponding trends in revenue can help understand these causes. This study seeks to assess changes over time in prices, patient counts, and drug-level revenues in the US market for oncology therapies and to investigate whether price growth is driven by an increased ability by pharmaceutical firms to capture profits.

STUDY DESIGN: Nineteen-year retrospective study (1997-2015).

METHODS: We used panel regression to investigate trends in prices, patient counts, and revenues within a US national data set consisting of targeted oncology therapies launched in different eras.

RESULTS: We find that prices have roughly tripled, whereas average patient counts per therapy have fallen by 85% to 90% over this period. However, the entire distribution of annual revenues has fallen: For instance, median revenues for drugs launched in the early 2010s are about half of what they were for drugs launched in the late 1990s.

CONCLUSIONS: Future research on the causes of quantity decline can help inform pharmaceutical policy.

Am J Manag Care. 2019;25(6):273-277

Insurers, healthcare providers, and others have noted that prices for novel oncology treatments are rising over time.[1-3] Price per episode of treatment has risen steadily, and prior research suggests that although the efficacy of cancer therapies (as measured by gains in overall survival) is certainly improving over time, prices are rising even faster.[4] If improved efficacy or effectiveness does not provide the dominant explanation, then what else might be contributing to the observed increase in prices?

One possibility is that firms today possess greater market power and use it to earn greater rewards for their drugs. If true, higher prices would coincide with higher revenues. At first blush, the magnitude of price growth in the oncology market may make growth in revenues seem self-evident. However, it becomes more difficult to assess when one considers the fact that newer drugs tend to treat fewer patients, as we document later. This decline in patients treated may be due to greater personalization of therapy, slower incremental progress that fails to force older drugs out of the market, or other factors. Regardless, rising prices alongside falling quantities make the trend in revenues an empirical question.

An empirically interesting context for this investigation is the market for targeted oncology therapies, first introduced in the late 1990s. Prior research has documented that targeted therapies have quickly come to dominate the market: For example, targeted therapies accounted for about two-thirds of all chemotherapy expenditures by 2011.[5] In this study, we investigate trends in prices, quantities, and revenues for targeted oncology therapies. We aim to determine whether higher prices have coincided with higher revenues and rewards for innovation or whether, instead, price growth has coincided with flat or falling revenues. Analyzing a sample of targeted therapies intended to treat common tumor types, we estimate the growth in price per patient-year, the reduction in the average size of the annual patient base using each drug, and the resulting change in revenue. In auxiliary analysis, we also estimate the implied increase in costs of drug development per patient-year.

TAKEAWAY POINTS

Comparing targeted oncology therapies launched in the intervals 1997-2002, 2003-2009, and 2010-2015, we investigate trends over time in prices, the number of patients using each drug, and revenues within the US market.

- We confirm the previously documented result that prices are rising over time.
- However, revenues are not rising concurrently with prices.
- This decline is attributable to contemporaneous declines of 85% to 90% in per-drug average patient counts.

METHODS AND DATA

We focused on targeted cancer drugs launched since 1997, when the first targeted agent (monoclonal antibody) was approved by the FDA. We considered all drugs primarily aimed at extending survival and/or progression-free survival for patients with cancer and focused on the 6 most common tumor types: breast, colorectal, melanoma, non-Hodgkin lymphoma, non–small cell lung, and prostate.[6] As some drugs are indicated for more than 1 tumor type, the unit of analysis for this study was therapy–tumor pair. To account for the fact that many drugs have more than 1 indication, and that approvals for new indications are frequently granted subsequent to the initial approval, we computed estimates for all possible therapy–tumor pairs, including all indications known at the time of this analysis. We estimated relative usage of a single agent for different indications by assuming usage proportional to relative disease incidence. After we dropped data for indications not of interest, our final sample consisted of 29 therapies and 33 therapy–tumor pairs (see **eAppendix Table 1** [eAppendix available at **ajmc.com**]).

Using data for each of these therapy–tumor pairs, we defined 3 measures of interest: therapy price, the number of patients using each drug for each indication, and annual revenues. We estimated each of these quantities for each therapy–tumor pair of interest, for each year in our analysis sample (1997-2015), and then used panel regression to investigate how they changed with respect to drug launch year. In supplementary analysis presented in the eAppendix, we also estimate trends in per-patient research and development (R&D) cost.

Therapy Price, Patient Count, and Revenues

We estimated the total number of patients and the estimated price of treatment using the IQVIA National Sales Perspective (NSP) data set.[7] The NSP reports nationally representative estimates of the total annual units of individual therapies distributed in the United States and of the total related revenues received by manufacturing firms. We combined these data with monthly dose and average length of treatment values specific to each therapy–tumor pair (obtained from FDA labels and clinical trials) to derive our price and patient count outcomes. Price was calculated as the cost for a full course of treatment (ie, the total revenue estimated to return to the manufacturer as a result of 1 patient being treated). Patient counts were imputed through analysis of the total number of therapy units distributed in combination with label information on dosing for a full course of treatment. Revenues were calculated within-year as the product of price and patient count. Revenues were calculated at the therapy, rather than therapy–tumor, level because this captures the total return on launching a new drug. Complete details on the construction of these measures are provided in the eAppendix.

To validate our findings regarding trends over time in the average number of patients, we separately analyzed patient counts in an independent data set, the Medicare Current Beneficiary Survey (MCBS). The MCBS is a survey of a representative sample of Medicare beneficiaries and contains data on diagnosis and drug utilization.[8] For each of the therapy–tumor pairs of interest, we counted the number of individuals in the MCBS sample who (1) had an indication for that tumor type and (2) reported using that therapy. We then used sampling weights to inflate these counts to the population level. We note that the MCBS results are estimates of counts for the Medicare population only and should not be construed as separate estimates for the aggregate US population. We repeated this process for the individual years between 1997 and 2012. (At the time of this analysis, 2012 was the most recent year for which MCBS data were available.) Finally, we compared trends over time in average patient counts as estimated in the IQVIA and MCBS analyses.

Analytic Approach

We sought to determine whether each of our main outcomes (therapy price, number of patients, and annual revenues) was correlated with therapy launch year. To do this, we fit a series of regression models using the above measures as outcomes and therapy launch period as the key independent variable. We converted therapy launch year into a categorical variable with 3 groups: drugs launched between 1997 and 2002 (reference category), drugs launched between 2003 and 2009, and drugs launched between 2010 and 2015. We present results from 2 sets of regressions. In the first, we regress each of our outcomes of interest on this categorical variable corresponding to launch time period. In the second, we include an additional regressor (years post launch) to control for life cycle trends in the price and quantity of a drug following its market entry. We report trends in average regression-adjusted price and quantity and then report movement over time in the entire distribution of regression-adjusted annual revenues per therapy. We conducted sensitivity analyses involving (1) adding covariates to the base-case model, (2) using alternative values for key parameters related to the cost of R&D, and (3) asserting a linear relationship between launch year and outcomes, rather than the period fixed-effects structure described above. These are discussed in detail in the eAppendix.

FIGURE 1. Plot of Launch Period Dummy Coefficients: Therapy Price

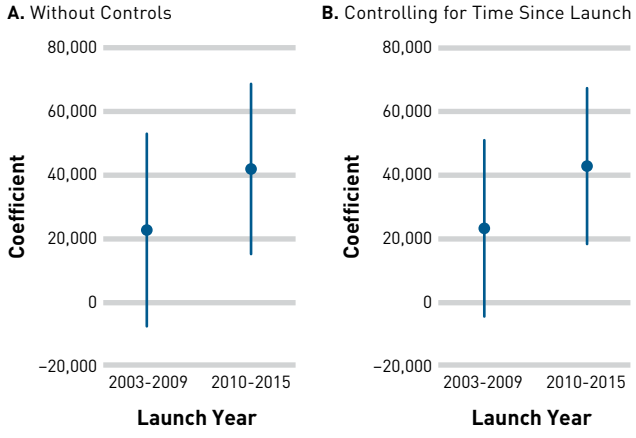
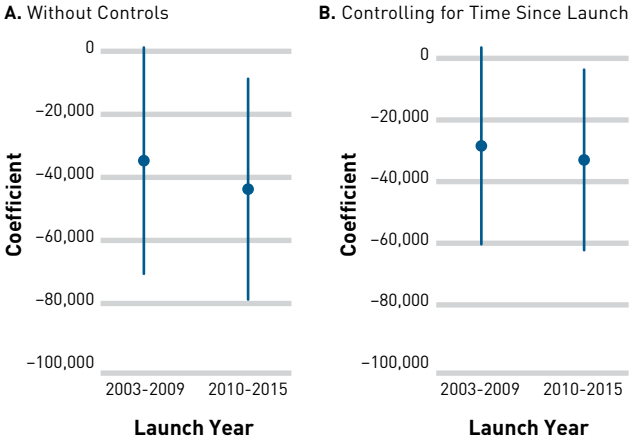


FIGURE 2. Plot of Launch Period Dummy Coefficients: Patient Count



RESULTS

Therapy Price

We begin with an analysis of the first study outcome, episode treatment price. The fact that newer oncology products are increasingly costly has been extensively documented in the literature.[9,10] This trend is also readily apparent in our data on targeted agents. **Figure 1** presents the results of a series of regressions that use therapy price as the dependent variable and launch year as the key independent variable and that follow the specifications defined previously.

We find a statistically significant positive correlation between price and launch year. The episode treatment cost for drugs launched between 2003 and 2009 was, on average, $23,000 greater than that for drugs launched between 1997 and 2002. The difference was even greater for drugs launched between 2010 and 2015—a statistically significant average difference in episode treatment cost of about $43,000.

Patient Count

This study sought to examine whether price growth has coincided with revenue growth. Thus, trends in annual average patient counts play a crucial role.

Figure 2 presents the results of the regressions for the patient count outcome, first without and then with the control for time since launch. Figure 2 demonstrates a strong negative relationship between launch year and average patient count. Relative to therapies launched in the early period, the dummy models suggest that therapies launched in the middle period were used by, on average, 28,000 to 35,000 fewer patients annually, whereas therapies launched in the late period were used by 33,000 to 44,000 fewer patients. Detailed time-series plots of patient counts for individual therapy–tumor pairs, and for average values within launch period, are presented in **eAppendix Figures 1-4**.

To confirm these results, we conducted a separate analysis of patient counts by therapy–tumor pair in the independent MCBS data set. Comparative results are presented in **Figure 3**.

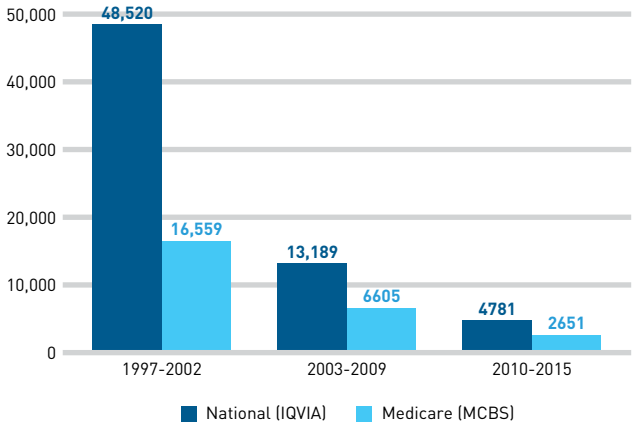
Note that the IQVIA data set covers the entire US population, whereas MCBS covers Medicare patients only. Each is designed to be nationally representative for its particular sample frame.

There is clear evidence that annual patient populations are smaller for more recently launched drugs: In the main analysis using IQVIA data, the average patient count fell from 48,520 per drug for drugs launched in the early period to 4781 per drug for drugs launched in the late period, a decline of 90%. A decline of similar magnitude (85%) is observed in the Medicare data.

Annual Revenues

The reduction in quantity seems to have offset growth in price. The entire distribution of annual revenues has fallen over time. We use the regression-adjusted (ie, predicted) revenues from our regression model of revenues as a function of years since launch and time period. We also aggregate this up to the therapy level to eliminate the possibility that newer drugs spawn more indications and thus artificially lower revenues per tumor type. This permits uniform comparisons over time that account for the way in which revenue evolves over the life cycle of a drug. **Figure 4** (A and B) presents the distribution of regression-adjusted annual revenues (at the therapy level) for each of the 3 launch periods; the difference between the 2 panels is that Figure 4B removes a single influential outlier—bevacizumab—from the data set. Both panels show that the distribution of regression-adjusted annual revenue has shifted left over time. In both cases, the most recent distribution ranges from $250 million to $500 million, whereas the earliest period shows a distribution from about $250 million to more than $900 million (all values are reported in 2015 US$). The sole difference between the distributions lies in the middle period. In the full sample, the

FIGURE 3. Average Patient Count per Therapy–Tumor Pair, by Launch Period and Data Source



MCBS indicates Medicare Current Beneficiary Survey.

main mass of the distribution lies between those of the early and late launch periods, but significant right skew is present. This long right tail is caused by the presence of a single drug, the blockbuster bevacizumab. Annual revenues for that drug (limited to the 6 indications of interest to this study) routinely exceeded $1 billion, in part because it was approved for more than 1 of those tumor types.

The **Table** presents the shifts in the distributions at key percentile points. Because bevacizumab is such an outlier, the Table accurately describes the distributions in both panels of Figure 4 (ie, the bevacizumab data points lie beyond the 90th percentile).

Annual adjusted revenues for the median drug have fallen from about $580 million to $287 million, a decline of about 50%. There is a decline of roughly 40% at the 25th percentile and nearly 60% at the 75th percentile. The only region of increase occurs at the 10th percentile, where revenues increased from the early to middle period, only to fall back down in the final period.

Results from the sensitivity analyses are presented and explained in the eAppendix.

DISCUSSION

The rising cost of novel oncology therapies has been a source of great controversy in recent years.[11-13] Our analysis confirms that prices of oncology drugs are indeed rising rapidly. We show that the number of patients taking each drug has dropped substantially over the same period of time. As a result, revenues have fallen at every point in the distribution, after accounting for life cycle growth in revenues over years since launch. This suggests that price growth is unlikely to have resulted from greater pricing power, at least within this market segment. Profit-maximizing firms with more pricing power would never willingly make decisions that lead to lower revenues for each drug launched. One exception to this point might occur if costs of drug discovery or production have fallen significantly. Although the extant academic literature on the costs of drug discovery remains controversial, all of it points to rising costs.[14] We know of no academic publications on trends in the costs of oncology drug production; more research is called for in this area.

Limitations

This study has several important limitations. The IQVIA NSP data set, which provided much of the source data for this study, contained "restrictions" (partially missing values) for some therapies in some years; we recoded these as missing. This step will not affect the results of the study, as long as the circumstance of missing data is not correlated with our outcomes of interest. Also, our measure of the cost of individual therapies contains only the component of total cost that returns to pharmaceutical manufacturers; it does not incorporate markups by wholesalers or hospitals, nor does it include any confidential rebates paid by manufacturers to purchasers. In addition, we focus on only treatments for the 6 most common tumor types; as such, our results have limited generalizability to other forms of cancer. Finally, to estimate therapy prices, we assume that average treatment duration is equal to the duration indicated on the drug label. In practice, individual patients' duration of therapy may be longer or shorter than is suggested by the label because of factors such as mortality, discontinuation, and extended treatment at the discretion of the physician.

CONCLUSIONS

Previous research has suggested that we should be skeptical of the notion that prices are rising solely because effectiveness is rising.[4] Our study also casts doubt on an explanation for price growth that relies solely on rising R&D costs: If this were so, firms would necessarily respond by launching drugs capable of earning higher revenues. Our findings suggest instead a relationship between price growth and average patient counts, although the precise nature of this relationship is not fully clear. One possible explanation for declining patient counts is relatively slow growth in effectiveness over time; this would improve the ability of older drugs to remain on the market. The consequences of this longevity would be reduced market share and reduced revenue for newer drugs. A second possible hypothesis for declining patient counts would be increased competition: All else being equal, an increase in the number of drugs approved for a given tumor type would lead to a decline in the average number of patients per drug. This explanation, however, would also suggest an increase in price competition, which is inconsistent with the observed data.

A final possible explanation for the trends we observe is growth in the development of drugs that target patients with specific biomarkers (sometimes referred to as personalized medicine) within the targeted oncology market. By design, these drugs target subsets of the total population of patients with the indicated cancer. Shrinking patient counts might be in part the result of more personalized therapies that treat narrower indications. For example, trastuzumab is indicated for human epidermal growth factor receptor-2–overexpressing

FIGURE 4. Changes in the Distribution of Regression-Adjusted Annual Revenues Over Time

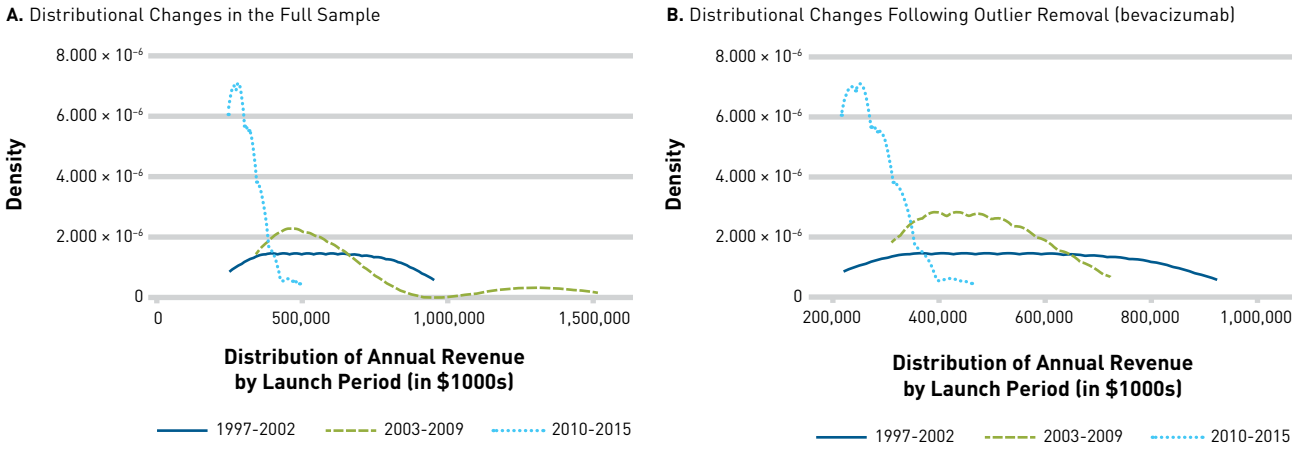


TABLE. Percentiles of Revenue Distributions by Launch Period (in $1000s)

Regression-Adjusted Revenue	1997-2002	2003-2009	2010-2015
10th percentile	290,920	339,764	245,262
25th percentile	415,136	381,169	245,262
50th percentile	580,757	505,385	286,667
75th percentile	746,378	588,196	328,073
90th percentile	870,594	671,006	369,478

breast cancer, which comprises only 15% to 20% of invasive breast cancer cases.[15] Mechanically, personalization leads to lower revenue when we hold prices constant. From another perspective, this is a cost to society of personalization: Without significant offsetting price growth, personalized therapies generate lower revenues and returns to innovators; this reduction in returns may reduce the rate of drug discovery in the long run.[16] More research is needed on these and other hypotheses for the causes of drug price growth and the observed decline in average patient counts.

Despite acknowledged limitations, this study provides surprising new data on declining patient populations treated by targeted cancer agents. This pattern is likely an important and, to our knowledge, previously undescribed factor that lies behind trends in revenues and rewards from innovation in oncology. ■

Author Affiliations: Precision Health Economics (JS, JV-O, DV, DL), Oakland, CA; Genentech (HPG), South San Francisco, CA.

Source of Funding: This study was funded by Genentech.

Author Disclosures: Dr Vanderpuye-Orgle is an employee of and owns stock in Amgen, Inc, which manufactures oncology therapies. Mr Goertz is employed by Genentech/Roche and owns Roche stock; Genentech manufactures and sells several of the oncology therapies covered in this manuscript. Dr Lakdawalla is a consultant to Precision Health Economics, a healthcare consultancy with clients in the life science and insurance industries, including firms that market oncology treatments; he holds equity in Precision Medicine Group, parent company of Precision Health Economics. The remaining authors 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 (JS, JV-O, HPG, DL); acquisition of data (JS, DV); analysis and interpretation of data (JS, JV-O, HPG, DL); drafting of the manuscript (JS, DV); critical revision of the manuscript for important intellectual content (JS, JV-O, HPG, DL); statistical analysis (JS); provision of patients or study materials (HPG); obtaining funding (HPG); administrative, technical, or logistic support (JS, DV); and supervision (JS, HPG, DL).

Address Correspondence to: Jesse Sussell, PhD, Precision Health Economics, 555 12th St, Ste 1725, Oakland, CA 94607. Email: jesse.sussell@pheconomics.com.

REFERENCES

1. Chhatwal J, Mathisen M, Kantarjian H. Are high drug prices for hematologic malignancies justified? a critical analysis. *Cancer*. 2015;121(19):3372-3379. doi: 10.1002/cncr.29512.
2. Lotvin AM, Shrank WH, Singh SC, Falit BP, Brennan TA. Specialty medications: traditional and novel tools can address rising spending on these costly drugs. *Health Aff (Millwood)*. 2014;33(10):1736-1744. doi: 10.1377/hlthaff.2014.0511.
3. Kantarjian H, Rajkumar SV. Why are cancer drugs so expensive in the United States, and what are the solutions? *Mayo Clinic Proc*. 2015;90(4):500-504. doi: 10.1016/j.mayocp.2015.01.014.
4. Howard DH, Bach PB, Berndt ER, Conti RM. Pricing in the market for anticancer drugs. *J Econ Perspect*. 2015;29(1):139-162.
5. Shih YC, Smieliauskas F, Geynisman DM, Kelly RJ, Smith TJ. Trends in the cost and use of targeted cancer therapies for the privately insured nonelderly: 2001 to 2011. *J Clin Oncol*. 2015;33(19):2190-2196. doi: 10.1200/JCO.2014.58.2320.
6. American Cancer Society. *Cancer Facts & Figures 2015*. Atlanta, GA: American Cancer Society; 2015. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2015/cancer-facts-and-figures-2015.pdf. Accessed March 1, 2018.
7. IMS Institute for Healthcare Informatics. HSRN data brief: national sales perspectives. 162.44.221.25/files/web/IMSH%20INstitute/NSP_Data_Brief-.pdf. Published 2011. Accessed March 1, 2018.
8. 2016 data user's guide: public use file. CMS website. download.cms.gov/Research-Statistics-Data-and-Systems/Downloadable-Public-Use-Files/MCBS-Public-Use-File/downloads/2016MCBSpufuserguide.pdf. Published December 6, 2018. Accessed March 1, 2018.
9. Dusetzina SB. Drug pricing trends for orally administered anticancer medications reimbursed by commercial health plans, 2000-2014. *JAMA Oncol*. 2016;2(7):960-961. doi: 10.1001/jamaoncol.2016.0648.
10. Kantarjian H, Steensma D, Ruis Sanjuan J, Elshaug A, Light D. High cancer drug prices in the United States: reasons and proposed solutions. *J Oncol Pract*. 2014;10(4):e208-e211. doi: 10.1200/JOP.2013.001351.
11. Frances A. Why are most cancer drugs so expensive and so ineffective? *HuffPost* website. huffpost.com/entry/why-are-most-cancer-drugs_b_8294392. Published October 15, 2015. Accessed March 1, 2018.
12. Pollack A. For profit, industry seeks cancer drugs. *New York Times*. September 1, 2009. nytimes.com/2009/09/02/health/research/02cancerdrug.html. Accessed March 1, 2018.
13. Whitehead N. Doctors press for action to lower 'unsustainable' prices for cancer drugs. NPR website. npr.org/sections/health-shots/2015/07/23/425387299/doctors-press-for-action-to-lower-unsustainable-prices-for-cancer-drug. Published July 23, 2015. Accessed March 1, 2018.
14. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi: 10.1016/j.jhealeco.2016.01.012.
15. Burstein HJ. The distinctive nature of HER2-positive breast cancers. *N Engl J Med*. 2005;353(16):1652-1654. doi: 10.1056/NEJMp058197.
16. Dubois P, de Mouzon O, Scott-Morton F, Seabright P. Market size and pharmaceutical innovation. *Rand J Econ*. 2015;46(4):844-871. doi: 10.1111/1756-2171.12113.

Visit **ajmc.com/link/3994** to download PDF and eAppendix

eAppendix

Therapy-tumor pairs included in the study

eAppendix Table 1. List of included therapies and tumor types

Therapy	Tumor Type
Abiraterone	Prostate
Ado-trastuzumab emtansine	Breast
Afatinib	NSCLC
Bevacizumab	Breast
Bevacizumab	Colorectal
Bevacizumab	NSCLC
Cabazitaxel	Prostate
Ceritinib	NSCLC
Cetuximab	Colorectal
Crizotinib	NSCLC
Dabrafenib	Melanoma
Enzalutamide	Prostate
Erlotinib	NSCLC
Everolimus	Breast
Exemestane	Breast
Fulvestrant	Breast
Gefitinib	NSCLC
Ipilimumab	Melanoma
Lapatinib	Breast
Letrozole	Breast
Nivolumab	Melanoma
Nivolumab	NSCLC
Panitumumab	Colorectal
Pembrolizumab	Melanoma
Pertuzumab	Breast
Ramucirumab	Colorectal
Ramucirumab	NSCLC
Regorafenib	Colorectal
Rituximab	Non-Hodgkin's Lymphoma
Toremiifene	Breast
Trastuzumab	Breast
Vemurafenib	Melanoma
Ziv-aflibercept	Colorectal

Note: NSCLC, non-small cell lung cancer

Estimating number of patients and episode price of treatment from the IMS data

To our knowledge, no dataset exists which contains estimates of the total number of patients in the United States using individual therapies for specific indications. Claims datasets such as Truven MarketScan have large samples (typically numbering in the tens or hundreds of millions of patients). However, these samples are obtained on a convenience basis, typically being collected from participating plans and/or employers working with the claims data vendor, and there are no validated mechanisms for inflating these data to represent the US population as a whole. We elected to estimate the number of patients using individual therapies for individual tumor types using the IQVIA/IMS National Sales Perspective (NSP) dataset, which provides 100% coverage of the US pharmaceutical market. The NSP provides two inputs at the therapy/year level: Revenue (R) and Eunits (tablets/mL) (U) – essentially the total number of units of the therapy sold in a given period. As described below, we combine these inputs to estimate the number of patients using each therapy. This calculation requires imposing the assumption that real world patient dosing is consistent with what is described on the label, and this raises a concern of dosing measurement bias. Data are not disaggregated to individual indications, i.e. tumor types. Because NSP data does not include information on tumor type, for therapies with more than one indication, we assumed that utilization was distributed in proportion to the relative incidence of the co-indicated tumor types. We dropped all cases where only partial year data (<12 months) were available. In addition, the NSP contained "restrictions" (incomplete data for either the total revenues or total units sold) for some therapies in some years. For the purposes of this study, these instances were coded as missing.

Because therapies were typically indicated for more than 1 condition (including conditions not of interest to this study), it was necessary to estimate tumor-specific utilization and episode treatment cost. To do this, we took the approach described below. This example is for a therapy indicated for 2 conditions, but it is generalizable to T conditions.

First, we identified the population incidence rates for tumor type 1 and tumor type 2, and denote these I_1 and I_2. Next, we compute the relative incidence rate RIR_1 and RIR_2:

$$RIR_i = \frac{I_i}{(I_1 + I_2)} \tag{A1}$$

Using FDA label information, we identify the total treatment dose (entire course) for a single user of a given drug for tumor 1 and tumor 2 and define these quantities as TTD_1 and TTD_2. These quantities are weighted by gender-specific incidence rates if dosing varies by gender, BSA, or weight.

Next, we assume the relative incidence rate for users of the drug is identical to the population relative incidence rate:

$$\frac{N_1}{(N_1 + N_2)} = RIR_1 = \frac{I_1}{(I_1 + I_2)} \tag{A2}$$

We define "price per unit" as

$$\frac{Revenue}{eUnits} = \frac{R}{U} \tag{A3}$$

We define total Eunits as

$$U = N_1 * TTD_1 + N_2 * TTD_2 \tag{A4}$$

Given two equations (A4 and A2) in two unknowns (N_1 and N_2) we solve these quantities as:

$$N_1 = \frac{U}{\frac{I_1}{I_1 + I_2} * TTD_1 + \frac{I_2}{I_1 + I_2} TTD_2} * \frac{I_1}{I_1 + I_2} \quad \text{(A5)}$$

and

$$N_2 = \frac{U}{\frac{I_2}{I_1 + I_2} * TTD_2 + \frac{I_1}{I_1 + I_2} TTD_1} * \frac{I_2}{I_1 + I_2} \quad \text{(A6)}$$

The total episode cost of treatment is defined as

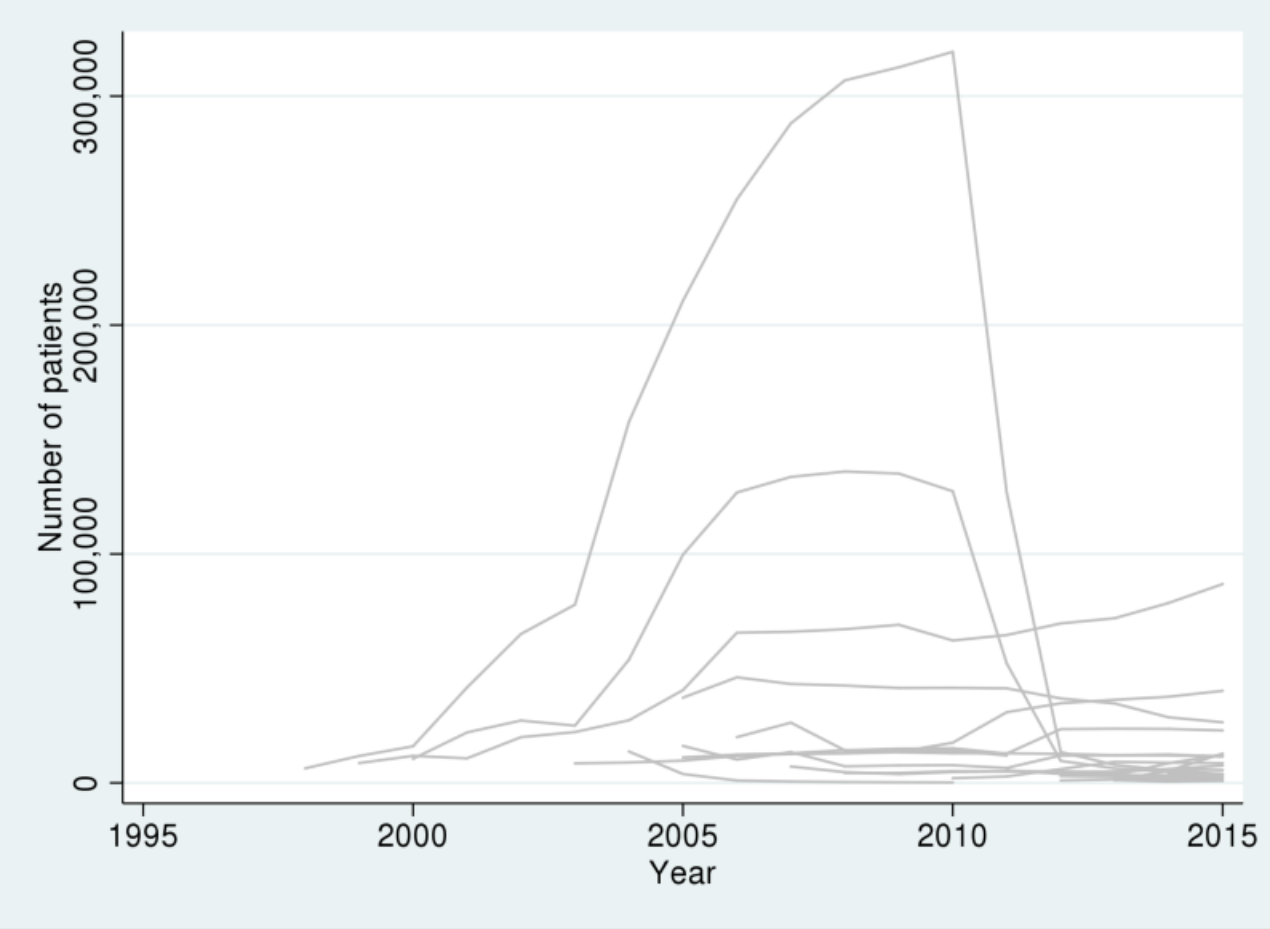
$$\textit{Price for indication i } (P_i) = TTD_i * \left(\frac{R}{U}\right) \quad \text{(A7)}$$

This framework is generalizable to therapies with >2 indications. In many instances, therapies were also approved for indications beyond our six tumor types of interest. (for example, Bevacizumab for age-related macular degeneration) that usage was estimated and then omitted from the analysis.

Time series plots of average patient counts by launch period

The following exhibits portray time-series plots of the number of patients using therapies by launch period. In eAppendix Figure 1, the patient counts for each of the 33 therapy-tumor pairs considered in our study are portrayed.

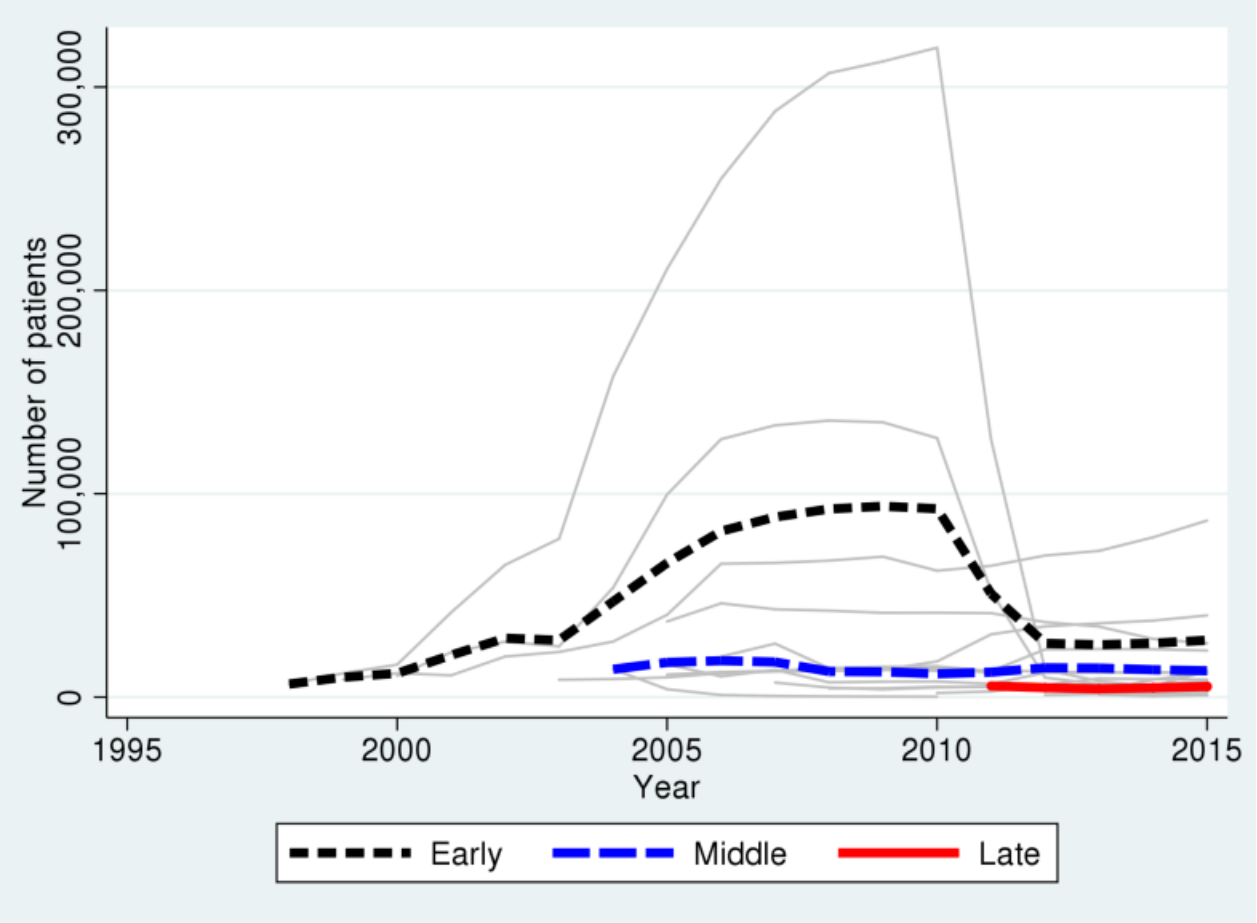
eAppendix Figure 1. Time-series plots of patient counts by year and therapy-tumor pair



Because of the large number of time series portrayed, individual data labels would render the chart difficult to interpret and are thus omitted. The general pattern of a decline over time is clearly evident – drugs which launched in the early period (1997-2002) appear to have generally higher patient counts than do drugs which launched in the late period (2010-2015). For reference, the large outlier which peaks at above 300,000 patients in 2010 is letrozole, for breast cancer. The steep subsequent decline for that drug is caused by loss of exclusivity in 2011.

Below, eAppendix Figure 2 overlays on eAppendix Figure 1 plots of average patient counts for the early, middle, and late launch periods, respectively.

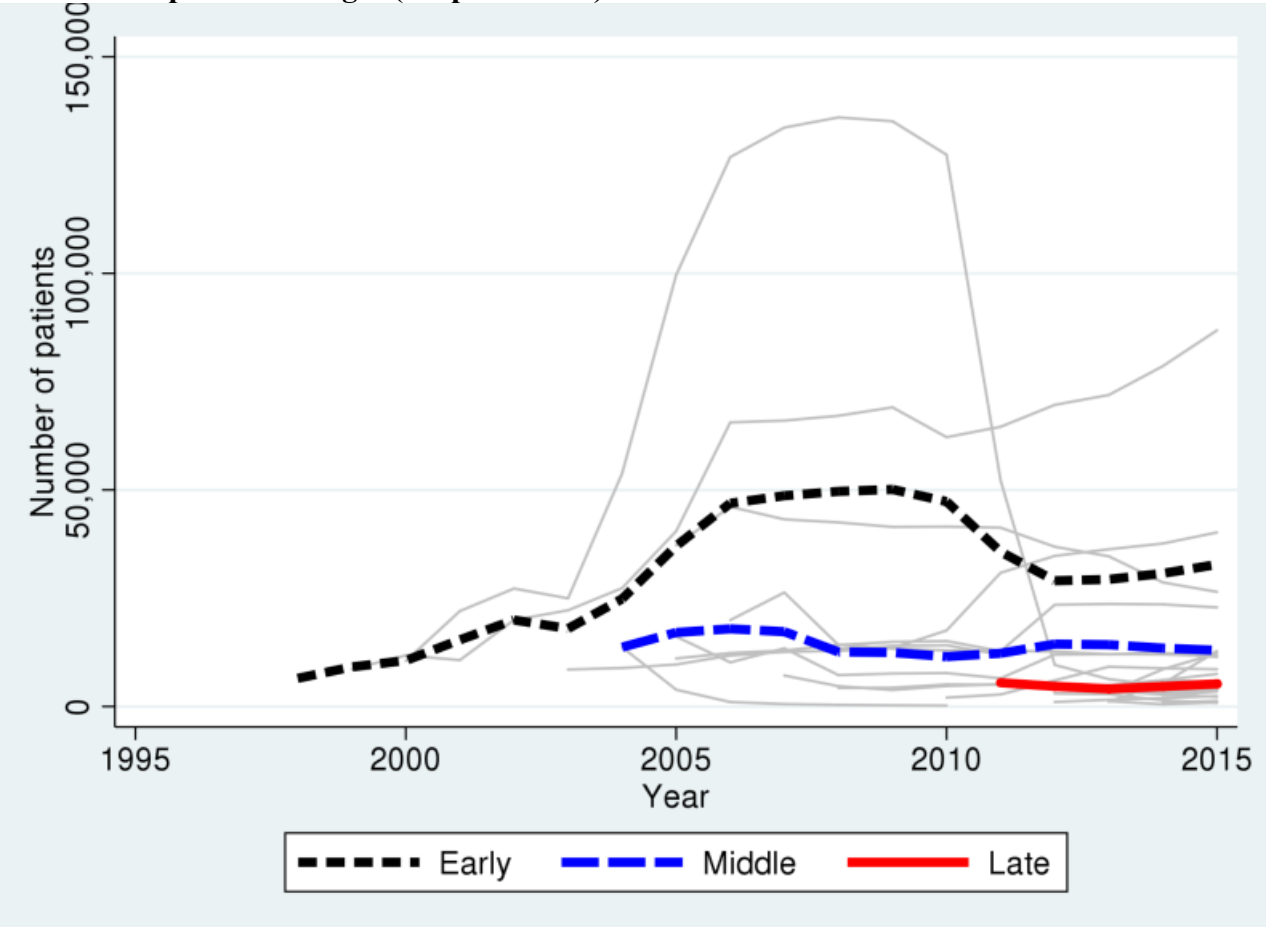
eAppendix Figure 2. Time-series plots of patient counts by year and therapy-tumor pair, with launch period averages



The key finding of the paper – the large decline in average patient counts over time – is evident here. The average patient count for drugs launched in the early period (black series with short dashes) is larger than the average count for drugs launched in the middle period (blue series with long dashes), which is in turn larger than the average count for drugs launched in the late period (red series).

Letrozole is clearly an outlier and thus has disproportionate influence on the computed average patient count for drugs launched in the early period. eAppendix Figure 3 provides a robustness check for this influence by re-rendering the data presented in eAppendix Figure 2 after dropping letrozole.

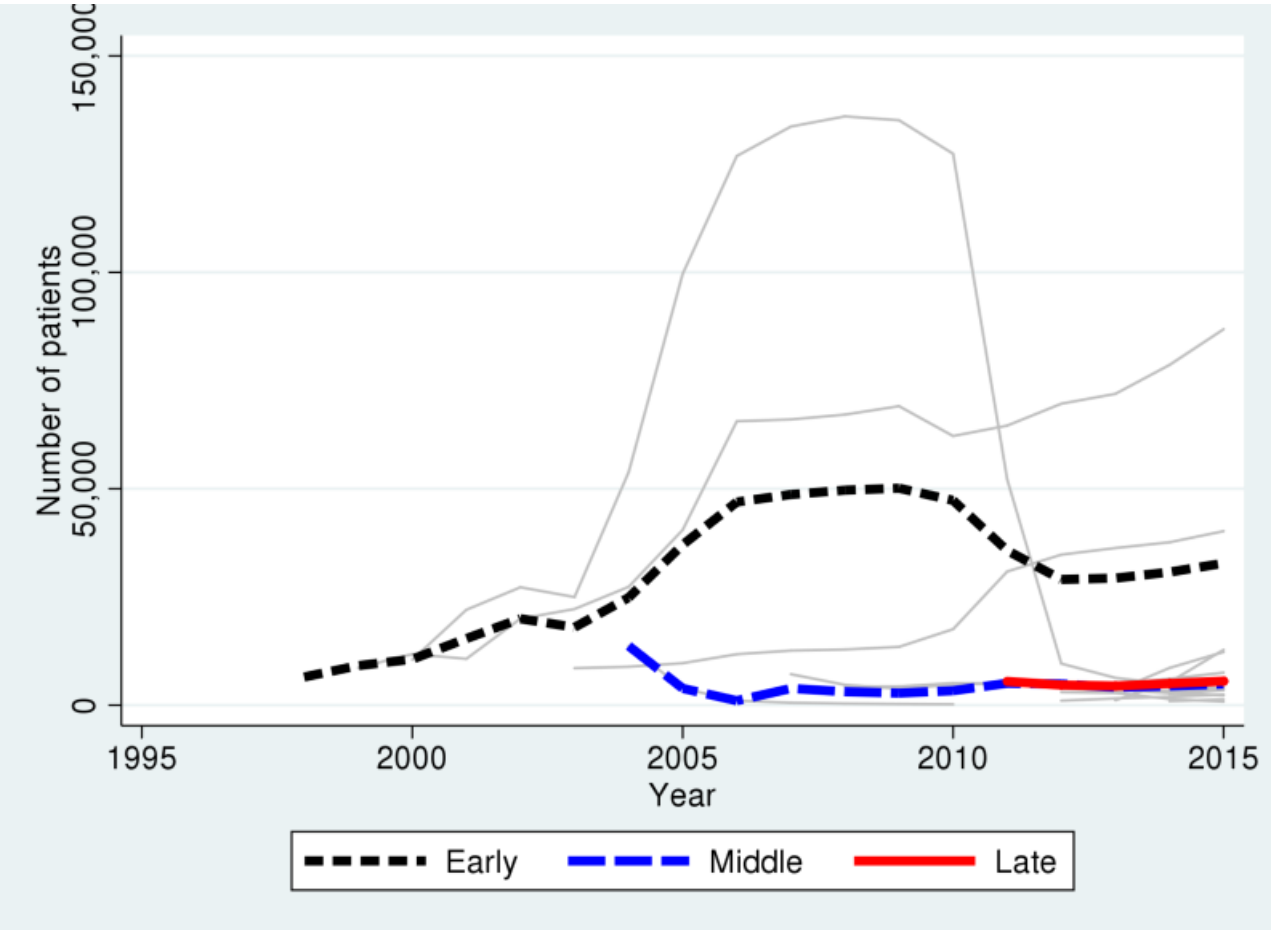
eAppendix Figure 3. Time-series plots of patient counts by year and therapy-tumor pair, with launch period averages (drop letrozole)



eAppendix Figure 3 demonstrates that the finding of a decline in average patient counts over time is robust to the exclusion of letrozole.

As noted above, when drugs are indicated for more than one condition, our base case analysis estimates indication-specific usage by assuming relative usage is proportional to relative disease prevalence. One concern with this approach is that to the extent drug usage is *not* proportional to relative disease prevalence, our results may underestimate the number of patients using drugs for specific conditions. eAppendix Figure 4 portrays a version of the plot of individual and average patient counts following a single change: All therapies with more than one indication which launched in the middle and late periods are dropped. By retaining multi-indication drugs in the early period, this approach is conservative, in the sense that average patient counts in the early period may be biased downward, while average patient counts in the middle and late periods are accurately estimated (for drugs with a single indication).

eAppendix Figure 4. Time-series plots of patient counts by year and therapy-tumor pair, with launch period averages (drop letrozole and multi-indication drugs in the middle/late periods)



Here, a comparison of the average patient count for drugs launched in the early period versus the late and middle periods still shows a substantial decline. By contrast, the estimated average patient counts in the middle and late periods appear to be substantially equivalent.

Regression equations

With Y^a denoting the three outcomes of interest (price, number of patients, and per-patient R&D cost), the regression results presented in this paper are of the forms:

Model 1:

$$Y^a = \theta_0 + \theta_1 * Middle_{ij} + \theta_2 * Late_{ij} + \varepsilon_{ijt}$$

Model 2:

$$Y^a = \theta_0 + \theta_1 * Middle_{ij} + \theta_2 * Late_{ij} + \theta_3 * Year_{ijt} + \varepsilon_{ijt}$$

Model 3 (sensitivity):

$$Y^a = \theta_0 + \theta_1 * Middle_{ij} + \theta_2 * Late_{ij} + \theta_3 * Year_{ijt} + \theta_4 * IV_i + \theta_5 * Biologic_i + \varepsilon_{ijt}$$

Model 4 (sensitivity):

$$Y^a = \beta_0 + \beta_1 * launch\ year_{ij} + \beta_2 * Year_{ijt} + \beta_3 * IV_i + \beta_4 * Biologic_i + \varepsilon_{ijt}$$

Where

"Middle" is an indicator for drugs launched between 2003 and 2009

"Late" is an indicator for drugs launched between 2010 and 2015

"Year" = time since launch year

“IV” is an indicator for drugs that require intravenous administration

“Biologic” is an indicator for biologic compounds

Sensitivity analyses

To determine the extent to which price growth is due to changing prevalence of intravenous and biologic compounds, we added two indicator variables to model 2: one that denotes drugs requiring intravenous administration and a second that identifies biologic compounds. We also present another model in which launch period enters linearly, rather than as a set of period indicators.

Main model regression results, with sensitivity analyses

eAppendix Table 2. Regression results: therapy price

	(1) Dummy	(2) Dummy with time control	(3) Sensitivity: Dummy with time and indicator controls	(4) Sensitivity: Linear trend
Launched 2003-2009	22,798	23,326*	16,575*	
	(14,751)	(13,504)	(9,665)	
Launched 2010-2015	41,957***	42,860***	36,268***	
	(13,036)	(11,939)	(10,812)	
Number of years after launch		131	80	158
		(426)	(353)	(243)
Intravenous drug			7,231	3,265
			(5,852)	(6,790)
Biologic			24,697**	28,377***
			(9,667)	(9,789)
Current year				2,435***
				(840)
Constant	18,585*	17,411*	5,756	-4.860e+06***
	(10,874)	(8,987)	(4,393)	(1.680e+06)
Observations	222	222	222	222
R-squared	0.298	0.298	0.545	0.538
Number of therapies	29	29	29	29

Cluster-robust standard errors in parentheses

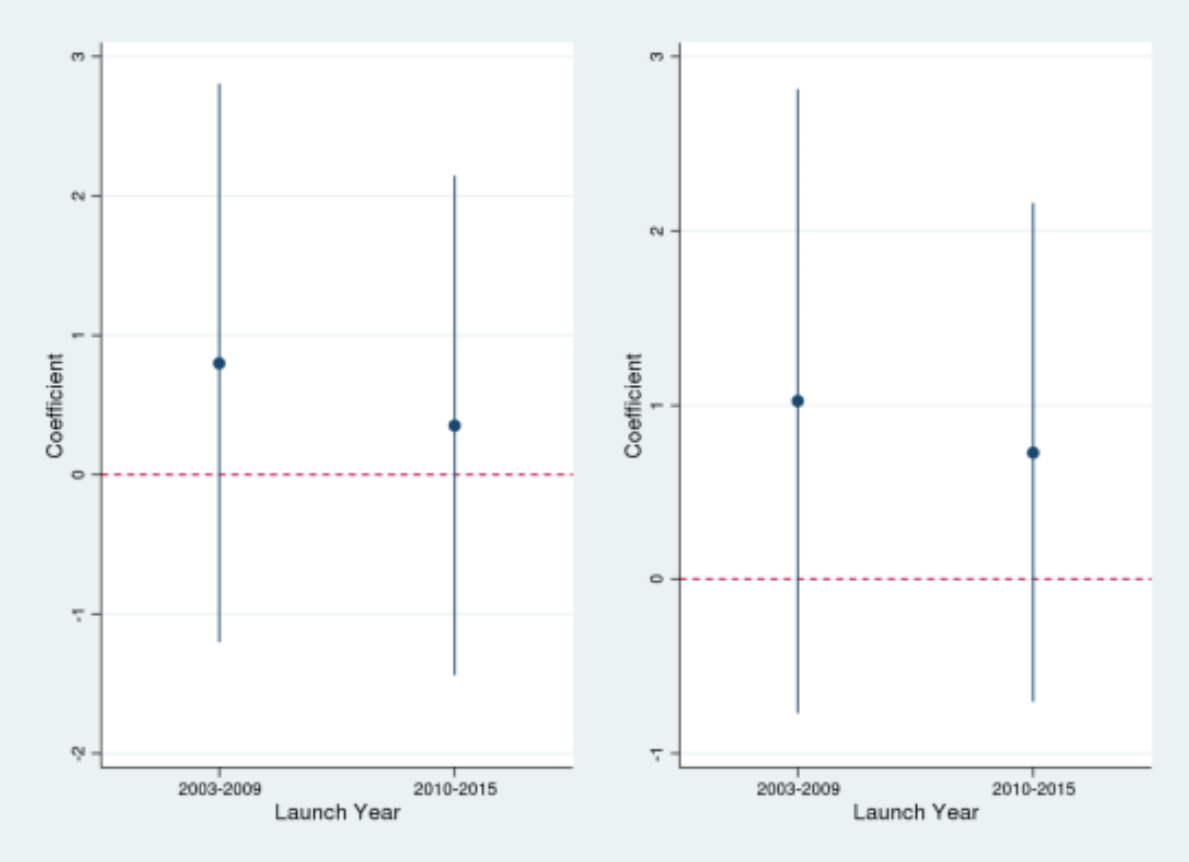
*** p<0.01, ** p<0.05, * p<0.1

eAppendix Table 3. Regression results: patient count

	(1) Dummy	(2) Dummy with time control	(3) Sensitivity: Dummy with time and indicator controls	(4) Sensitivity: Linear trend
Launched 2003-2009	-34,701*	-28,408*	-27,763**	
	(17,524)	(15,587)	(13,352)	
Launched 2010-2015	-43,739**	-32,964**	-34,343**	
	(17,096)	(14,303)	(12,830)	
Number of years after launch		1,570	1,507*	1,433*
		(930)	(876)	(778)
Intravenous drug			-18,586	-15,016
			(15,201)	(13,009)
Biologic			4,449	52.28
			(8,212)	(5,062)
Current year				-2,618**
				(1,229)
Constant	48,520***	34,500**	42,427**	5.270e+06**
	(17,054)	(13,887)	(17,587)	(2.473e+06)
Observations	222	222	222	222
R-squared	0.142	0.156	0.179	0.173
Number of therapies	29	29	29	29

Cluster-robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

eAppendix Figure 5. Plot of launch period dummy coefficients: log revenue, without controls and controlling for time since launch



eAppendix Table 4. Regression results: log revenue (000's of dollars)

	(1)	(2)	(3)	(4)
VARIABLES	Dummy	Dummy with time control	Dummy with time and indicator controls	Sensitivity: linear trend
Launched 2003-2009	0.802	1.023	0.875	
	(0.977)	(0.874)	(0.647)	
Launched 2010-2015	0.351	0.728	0.538	
	(0.875)	(0.699)	(0.556)	
Number of years after launch		0.055	0.055*	0.0525**
		(0.030)	(0.027)	(0.046)
Intravenous drug			1.460***	1.394***
			(0.450)	(0.493)
Biologic			0.910**	0.984**
			(0.403)	(0.404)
Current year				0.0454
				(0.0447)
Constant	11.75***	11.25***	10.24***	-94.646
	(0.831)	(0.579)	(0.534)	(91.577)
Observations	206	206	206	206
R-squared	0.037	0.051	0.422	0.403
Number of therapies	29	29	29	29

Cluster-robust standard errors in parentheses.
Log revenue computed as ln(n_patients*price_therapy/1,000)
*** p<0.01, ** p<0.05, * p<0.1