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Health Policy Analysis

# Trends in the Price per Median and Mean Life-Year Gained Among Newly Approved Cancer Therapies 1995 to 2017

Alice J. Chen, PhD,[1,2,*] Xiaohan Hu, MPH,[2] Rena M. Conti, PhD,[3] Anupam B. Jena, MD, PhD,[4,5] Dana P. Goldman, PhD[1,2,5]

[1]Sol Price School of Public Policy, University of Southern California; [2]Leonard D. Schaeffer Center for Health Policy and Economics, University of Southern California, Los Angeles, CA; [3]Questrom School of Business, Boston University; [4]Department of Health Care Policy, Harvard Medical School, Boston, MA; [5]National Bureau of Economic Research, Cambridge, MA, USA

## ABSTRACT

*Background:* The prices of newly approved cancer drugs have risen over the past decades. A key policy question is whether the clinical gains offered by these drugs in treating specific cancer indications justify the price increases.

*Objectives:* To evaluate the price per median and mean life year gained among newly approved cancer therapies from 1995 to 2017.

*Methods:* We collected data on the price (in 2017 USD) per life-year gained among cancer drug-indication pairs approved by the US Food and Drug Administration (FDA) between 1995 and 2017. We modeled trends using fractional polynomial and linear spline regression models that controlled for route of administration and cancer type fixed effects.

*Results:* We found that between 1995 and 2012, price increases outstripped median survival gains, a finding consistent with previous literature. Nevertheless, price per mean life-year gained increased at a considerably slower rate, suggesting that new drugs have been more effective in achieving longer-term survival. Between 2013 and 2017, price increases reflected equally large gains in median and mean survival, resulting in a flat profile for benefit-adjusted launch prices in recent years.

*Conclusions:* Although drug costs have been rising more rapidly than median survival gains, they have been rising at about the same rate as mean survival gains. This suggests that when accounting for longer-term survival gains, the benefits of new drugs are roughly keeping pace with their costs, despite rapid cost growth.

*Keywords:* cancer drug, cost, mean life-year gained, median life-year gained, price trends, survival.

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## Introduction

High and rising launch prices of new cancer drugs have raised American public stakeholder and policy concern.[1-3] For example, sipuleucel-T (Provenge, Dendreon Corp, Seattle, WA), an immunotherapy for prostate cancer, launched in 2010 at $93 000 for a complete course of treatment.[4] A year later, in 2011, ipilimumab (Yervoy®, Bristol-Myers Squibb Co, Princeton, NJ) was introduced for metastatic melanoma at $120 000 per year of treatment, and, in 2014, blinatumomab (Blincyto®, Amgen Inc, Thousand Oaks, CA), a treatment for lymphoblastic leukemia, was priced at $178 000 per year.[5,6]

Although prices are high and appear to have increased over time, these drugs may also result in better health as measured by incremental survival or other health gains for those taking them.[7-9]

One previous study examined trends in the price of health associated with new cancer drugs. Howard et al considered trends in the price per health gained among all cancer drugs approved in the United States between 1997 and 2013.[10] They found that the price per life-year gained increased by approximately $8500 per year.

As the measure of health gained, Howard et al used the median survival estimates reported in the clinical trials accepted by the US Food and Drug Administration (FDA) for approval. Median survival is a clinical trial endpoint that is met when 50% of the trial sample has died. It is often considered the most reliable cancer endpoint because it is precise and unambiguously documented by the date of death.[11] Nevertheless, median survival estimates may mask gains in longer-term survival, thereby representing an underestimate of the true survival gain.[12]

Unlike median survival, mean survival estimates capture the presence of longer survival gains by taking into account the survival-curve distribution after 50% survival has been achieved, known as the right-tail of survival. Capturing longer-term benefits of survival may be particularly valuable because existing evidence

* Address correspondence to: Alice J. Chen, PhD, Sol Price School of Public Policy, University of Southern California, 635 Downey Way, Los Angeles, CA 90089-3333, USA. Email: alicejc@price.usc.edu


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suggests that for decisions involving poor odds of survival, each additional day of survival is worth more than the last.[13,14] Moreover, the importance of these longer-term gains has been acknowledged by several institutions, including the American Society of Clinical Oncology (ASCO), the Institute for Clinical and Economic Review (ICER), and the United Kingdom's National Institute for Health and Care Excellence (NICE). In their scoring of net health benefits, American Society of Clinical Oncology awards bonus points to cancer drugs that generate meaningful survival gains at a time point that is twice the median.[15] Endorsed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), ICER's current value framework assesses potential clinical gains over the lifetime of patients eligible for treatment with new drugs and includes consideration for the presence of right-tailed survival gains reported in supporting studies.[16,17] The presence of potential right-tailed survival gains was an important feature in the institute's assessment of the effectiveness and value of Poly ADP-Ribose Polymerase inhibitors.[18] In 80% of cancer drug assessments, NICE incorporated mean survival estimates into their reimbursement decisions, whereas median survival was incorporated into only 36% of cases.[12]

Estimating mean survival requires information on the survival times for all individuals, but those times are generally unobserved. As a result, statistical models are used to approximate the survival distribution and extrapolate findings up to the point at which all patients have died.[19,20] Mean estimates are calculated by fitting the existing data to parametric models that can differ by assumed distribution (eg, exponential, log-normal, etc).[12,21] Although different models are appropriate in different contexts, model assumptions can affect survival estimates.[12] Consequently, guidelines issued by International Society for Pharmacoeconomics and Outcomes Research and NICE suggest that publications should provide justification for the specific extrapolation approach used and demonstrate that the modeling choice meets the accepted best-fit criteria.[17,22] Quality of mean survival estimates can also differ depending on the underlying data used. We focused on mean survival estimates that were extrapolated from clinical trials data because they are considered more rigorous than extrapolations based solely on patient-level claims data.[22-24]

In this article, we examine trends observed between 1995 and 2017 in the price of health associated with new cancer drug-indication pairs. Given the different benefits between median and mean survival estimates, we employed both measures and tested for differences. Unlike previous articles, we also included in our sample first and follow-on cancer indications and tested for model robustness for inclusion of the latter. Because cancer drug prices are generally uniform across indications, accounting for follow-on approvals may offer a more complete picture of drug prices relative to survival gains.[25,26]

We used a fractional polynomial model to flexibly estimate trends over time and identify possible breaks in trend over the 24-year study period. Based on detected trend changes around 2013, we estimated separate trends from 1995 to 2012 and 2013 to 2017. The latter time period has not yet been analyzed by existing studies. It is also an interesting focus, given significant stakeholder scrutiny on the high prices of recently launched cancer drugs.[2,10,14,15,22,27-37]

## Study Data and Methods

### Data

We constructed a data set of approved cancer drugs and their approved indications by month and year, route of administration, median and mean survival gains, and prices from 1995 to 2017. We briefly describe the data—which is at the drug-indication level—here and document additional details in Appendix Section A in Supplemental Materials, which can be found at https://doi.org/10.1016/j.jval.2019.08.005. Figure 1 provides a flow chart that illustrates the data collection process.

First, we used CenterWatch—a source cited by several studies on drug innovation—to construct a list of cancer drugs approved between January 1995 and May 2017.[10,38,39] We excluded drugs treating only cancer-related symptoms or treatment side effects (eg, diarrhea, anemia, etc). For each drug, we used FDA-approved drug labels to identify the relevant cancer indications, defined as a combination of cancer type and line of therapy (eg, first-line treatment of advanced breast cancer). Approval dates for each drug-indication pair were checked against those listed in the FDA Orange Book and the National Cancer Institute. The route of administration for each cancer drug-indication pair was collected from the FDA Orange Book.

We examined efficacy using measures of life-years gained (LYG). Median data were obtained from published trials; these trials were referenced by the FDA drug label in its "Full Prescribing Information" section. We calculated survival gains by differencing median overall survival between treatment and comparator arms.

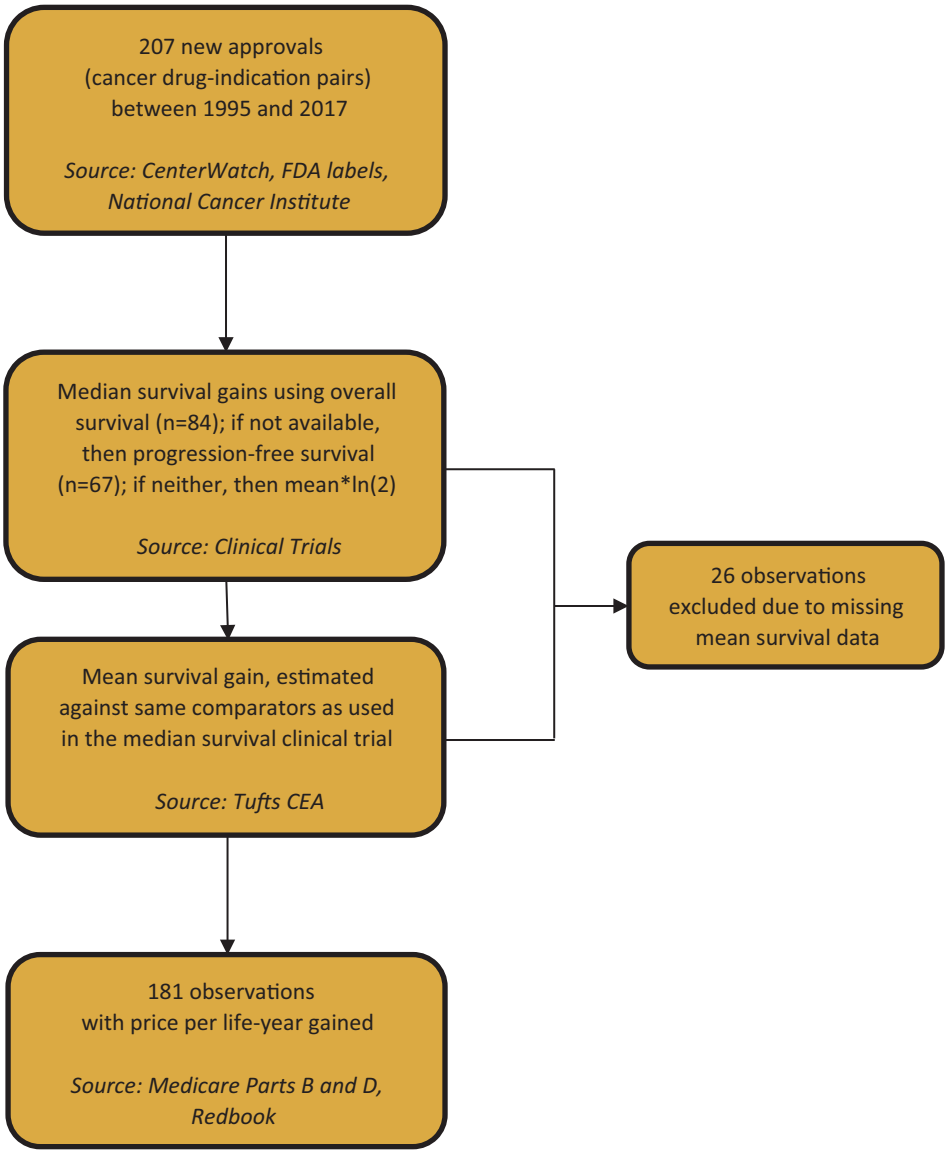
When overall median survival was not reported, we used progression-free median survival, which is defined as the period of time when the cancer is under control. Our use of this alternative metric is consistent with previously published studies.[10] These progression-free survival estimates are used by the FDA as a basis for approval, and they provide a useful signal of quality to the manufacturer who must set prices for a new drug in the absence of data on overall survival. Moreover, previously published studies suggest that progression-free survival is highly correlated with overall survival especially in cancers with short survival post-progression.[40-42]

When neither overall nor progression-free survival was available—for instance, when only a symptom-based endpoint was reached (eg, hazard ratios, complete or partial response rates, or cytogenetic responses rates) or when drug-indication pairs were approved on the basis of single-arm trials, we obtained estimates of median LYG by assuming an exponentially distributed survival curve—which has been well-validated by the literature—and dividing mean survival estimates by $\ln(2)$.[10,43-45]

Mean LYG were obtained from a search of previously published economic evaluations reported in the Tufts Cost Effectiveness Analysis (CEA) Registry.[46,47] Continuously updated since 1976, the Tufts CEA Registry provides a comprehensive database of 5655 CEAs across various diseases, and the data has been used in more than 50 peer-reviewed publications.[48] All mean LYG estimates were obtained from extrapolations of the corresponding clinical trials used for drug approval, and the results of these extrapolations were published in peer-reviewed journals. To further ensure a consistent comparison between median and mean LYG estimates, we selected mean LYG estimates from models that compared the drug therapy to the same comparator as those used in the median survival data. We also utilized progression-free-survival mean LYG estimates when a progression-free-survival measure was used in the median LYG data. If no economic modeling could be identified, the drug-indication pair was dropped.

Finally, we calculated a "treatment-episode price" for each indication-drug pair in the sample by multiplying the drug's monthly price by the typical duration of treatment for the specific indication.[22,49,50] As detailed in Exhibit A2 of the Supplemental Materials, we followed the literature by calculating each drug's monthly price, at the time of approval of earliest price observed after approval, according to the Medicare program (ie, Medicare

**Figure 1.** Data collection flowchart.




reimbursements).[51,52] All prices were inflation-adjusted and expressed in 2017 USD. These prices represent the actual dollar amounts that Medicare, the largest public insurer, pays for drugs. In most cases, these prices will be greater than the prices that hospitals, physicians, and pharmacies pay to acquire the same drugs.[10]

### Statistical Analysis

We computed the price per median and mean LYG for each drug-indication pair and analyzed trends in these variables using two approaches. First, we estimated the trends using a fractional polynomial model, which allowed us to flexibly parameterize trends without imposing a pre-determined specification.[53] We considered 44 different degree-2 polynomials and selected the model with the lowest deviance. All models were additionally controlled for route of administration and cancer type fixed effects (16 categories).[54] Details regarding all models tested are provided in Appendix Section B of the Supplemental Materials.

Second, informed by the results of the fractional polynomial model, we estimated a linear spline regression model with a knot (ie, a point of separation in the piecewise regression system) at 2013. The knot allowed slopes to differ between 1995 to 2012 and 2013 to 2017. The linear spline models for drug-indication pairs $d$ in year $t$ is of the form:

$$Y_{dt} = \beta_0 + \beta_1 \min(Time, 18) + \beta_2 \min(0, Time - 18) + \alpha \mathbf{1}(Oral)_{dt} + \eta_{i(d)} + \epsilon_{dt}$$

$Y_{dt}$ measures either the price per median LYG or price per mean LYG. *Time* equals the approval date minus 1995, so times 0, 18, and 22 correspond to January 1 in 1995, 2013, and 2017, respectively. Again, we additionally controlled for route of administration ($1(Oral)_{dt}$) and 16 cancer type fixed effects ($\eta_{i(d)}$). Thus $\beta_1$ identifies the average annual change in price per median or mean LYG from 1995 to 2013, and $\beta_2$ identifies the average annual change in price per median or mean LYG from 2013 to 2017.

To identify whether changes in trend were driven by prices changes or changes in survival gain, we estimated the linear spline

regression model with price, median LYG, and mean LYG as separate dependent variables ($Y_{dt}$).

We tested the sensitivity of our estimates by examining several alternative price-per-LYG metrics. In addition to dropping outliers and data points approximated by dividing mean survival by ln(2), we considered specifications using logged price per LYG and monthly Medicare price per LYG (which ignored the duration of treatment episodes). To assess whether changes in trends from 1995 to 2012 and 2013 to 2017 were associated with the 2012 budget sequester, which reduced Part B reimbursements starting April 2013 from average sales price (ASP) plus 6% to ASP plus 4.3%, we additionally examined a specification that kept the part B pricing formula constant (eg, ASP plus 6%). If results persisted in that specification, then they could not be driven by the change in pricing policy.[55] Finally, abstracting from fluctuations in Medicare pricing policies, we estimated our results using the average wholesale price (AWP) per LYG, with AWP data from the earliest post-approval date observed in IBM's Micromedex Red Book.[56]

All analyses were performed using the statistical software Stata, version 15.1, and estimates with $P < .05$ using two-tailed tests were considered significant.

## Study Results

### Sample Characteristics

During the study period, the FDA approved 91 distinct cancer drugs, of which 38 (41.8%) were approved for a single indication and 53 (58.2%) for multiple indications. In total, our sample included 181 cancer drug-indication approved pairs. Table 1 shows each drug-indication pair included and provides characteristics of our analytic sample. Annual counts of drug-indication pairs are shown in Appendix Figure A1 (in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.005).

The average treatment-episode price ranged from $25 274, with a standard deviation (SD) of $28 828, for pancreatic cancer to $171 448 (SD $73 835) for thyroid cancer. Pancreatic cancer also had the lowest monthly price at $4222 (SD $3439), but owing to differences in treatment duration, the indication with the highest monthly price was the "other" category, which included indications with few approvals over the study period. Within the "other" category, high prices were driven by dinutuximab for the treatment of neuroblastomas (with a monthly price of $84 561) and polifeprosan with carmustine implant for the treatment of brain cancer (with a monthly price of $51 621).

Across all drug-indication pairs, the average treatment-episode price was $82 260 (SD $100 174), and average median and mean LYG estimates were 0.56 and 0.91 years (SD 0.63 and 0.98), respectively. After dividing the treatment-episode price by the mean and median LYG for each drug-indication pair, we found that the average price per median and mean LYG were $195 355 (SD $196 748) and $131 889 (SD $149 259), respectively.

### Overall Trends

Estimates from the fractional polynomial indicated that the real price per median LYG, adjusted for drug indication and route, had been increasing until approximately 2013, when the trend changed (Fig. 2). Specifically, from 1995 to 2013, the adjusted real price per median LYG rose from $81 648 per LYG to almost $176 867 per LYG. From 2013 to 2017, however, the adjusted price per median LYG fell to $126,950 per LYG. The observed break in trend in price per median LYG is apparent when examining both first and follow-on indications (see Appendix Figure A2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.08.005).

The adjusted price per mean LYG exhibited a slower rise. The price per mean LYG initially declined, perhaps because of the small sample sizes in earlier years. From 2002 to 2012, the adjusted price per mean LYG increased from $108 250 per LYG to $129 798 per LYG, and it continued to increase to $143 891 per LYG in 2017. Although there was no clear break in trend in the price per mean LYG across all drug-indication pairs, Appendix Figure A1 in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.08.005) suggests a break in trend did occur in 2013 among the price per mean LYG for follow-on indications.

The fractional polynomial estimates suggested that trend changes can be approximated by a linear spline regression model, which allowed for a trend change around 2013 (Fig. 2). The adjusted price per median LYG of a drug increased by $6129 ($P = .14$) each year from 1995 to 2012 (Table 2, Panel A), whereas the adjusted price per mean LYG increased at a markedly slower rate of $476 ($P = .88$) per year.

The positive trend, particularly in the price per median LYG, slowed in recent years. From 2013 to 2017, neither the adjusted price per median LYG ($10 488 reduction per year, $P = .44$) nor the adjusted price per mean LYG ($412 increase per year, $P = .97$) increased significantly.

These findings remained robust to several alternative price metrics (Table 3). Our results were not driven by outliers (ie, we dropped two observations that, as Figure 3 indicates, were clear outliers), and they persisted even when we considered only trials that reported overall or progression-free survival. The natural logarithm specification indicated a 10% ($P < .001$) annual increase in price per median LYG from 1995 to 2012 and a slower price per mean LYG growth at 8.8% ($P = .001$) per year. In the recent period from 2013 to 2017, price per median LYG fell by 16% ($P = .04$) per year, and price per mean LYG fell by 12% ($P = .17$) per year.

The recent halt in price-per-LYG growth was not due to the 2012 budget sequester because our results persisted in the specification that ignored the budget sequester. Moreover, estimates in the recent period continued to be negative and statistically insignificant when using monthly price per LYG and Red Book–derived AWP per LYG measures.

Although market dynamics surrounding first indications can differ from follow-on indications, our findings are robust to focusing only on first indications: the growth in price per median and mean LYG between 2013 and 2017 was negative and statistically insignificant when examining only first indications (Table 2, Panel B).

Finally, we show that our results are robust to adding additional knots in the spline regression. In Appendix Table A3 in Supplemental Materials, we show the results from adding a knot in 2003 to account for possible changes in the price per mean LYG in the earlier period. We also consider knots for each 5-year time period (eg, knots in 2000, 2005, 2010, and 2015). Although some imprecision in the results are introduced, estimates in the recent period are persistently negative and statistically insignificant.

Table 2 also shows the trends in price and LYG separately. During the recent period, launch prices, which have not been benefit-adjusted, rose at a rate of 18.5% per year ($15 274 per year from a mean of $82 260, $P = .016$). In contrast, gains in median survival increased at a faster rate of 22% per year (0.12 LYG from a mean of 0.55, $P = .001$). These findings suggest that on average, median survival gains have outstripped price increases from 2013 to 2017. Mean survival increased at 16% per year (0.15 LYG from a mean of 0.91, $P = .017$). These observations again hold when examining only first indications. From 2013 to 2017, the median survival gain increased by 41% per year (0.24 LYG from a mean of 0.59, $P = .004$), whereas the price increased by a statistically insignificant 13% per year ($12 845 from a mean of $82 261, $P = .31$).

**Table 1.** Treatment-episode price and life-year gained by cancer indication, 1995-2017.

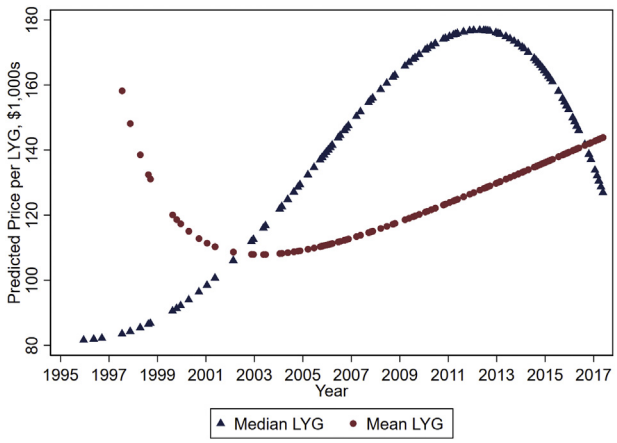
| Indication | Treatment- episode price | Monthly price | Median LYG | Mean LYG | Drug names |
|---|---|---|---|---|---|
| Breast | $54 255 | $4762 | 0.47 | 0.55 | Ado-trastuzumab, anastrozole, capecitabine, docetaxel, eribulin mesylate, everolimus, exemestane, fulvestrant, gemcitabine, ixabepilone, lapatinib, letrozole, palbociclib, pertuzumab, ribociclib, trastuzumab |
| Cervical | $29 368 | $6125 | 0.22 | 0.27 | Bevacizumab, topotecan hydrochloride |
| Colorectal | $36 007 | $7412 | 0.23 | 0.36 | Bevacizumab, capecitabine, cetuximab, irinotecan, oxaliplatin, panitumumab, ramucirumab, regorafenib, trifluridine and tipiracil, ziv-aflibercept |
| Gastric | $90 956 | $8183 | 0.36 | 0.81 | Docetaxel, everolimus, imatinib mesylate, ramucirumab, regorafenib, sunitinib, trastuzumab |
| Head and neck | $70 561 | $9967 | 0.61 | 0.89 | Cetuximab, docetaxel, nivolumab |
| Kidney | $78 531 | $10 638 | 0.33 | 0.562 | Axitinib, bevacizumab, cabozantinib, everolimus, lenvatinib, nivolumab, sorafenib, sunitinib, temsirolimus |
| Leukemia | $149 247 | $13 974 | 1.30 | 1.82 | Alemtuzumab, bendamustine hydrochloride, dasatinib, ibrutinib, idelalisib, imatinib mesylate, midostaurin, nelarabine, nilotinib, obinutuzumab, ofatumumab, rituximab |
| Lung | $74 005 | $9514 | 0.31 | 0.52 | Afatinib, alectinib, atezolizumab, bevacizumab, ceritinib, docetaxel, erlotinib, gefitinib, gemcitabine, nectinumumab, nivolumab, osimetrinib, pembrolizumab, pemetrexed, ramucirumab, topotecan hydrochloride |
| Lymphoma | $95 025 | $9074 | 1.02 | 1.4 | Bendamustine hydrochloride, bevacizumab, bortezomib, ibritumomab, ibrutinib, idelalisib, nivolumab, rituximab, tositumomab |
| Melanoma | $71 440 | $13 400 | 0.35 | 1.20 | Cobimetinib, dabrafenib, ipilimumab, nivolumab, pembrolizumab, trametinib, vemurafenib |
| Myeloma | $127 361 | $11 517 | 0.55 | 1.36 | Bortezomib, daratumumab, elotuzumab, ixazomib, panobinostat, pomalidomide |
| Other | $69 291 | $18 174 | 0.58 | 0.99 | Avelumab, dinutuximab, nivolumab, olaratumab, pembrolizumab, pemetrexed, polifeprosan with carmustine implant, sorafenib, temozolomide, trabectedin |
| Ovarian | $144 227 | $12 009 | 0.45 | 1.17 | Bevacizumab, gemcitabine, niraparib, olaparib |
| Pancreatic | $25 274 | $4222 | 0.25 | 0.58 | Erlotinib, everolimus, gemcitabine, irinotecan, sunitinib |
| Prostate | $57 870 | $7633 | 0.35 | 0.41 | Abiraterone acetate, cabazitaxel, docetaxel, enzalutamide, radium ra 223 dichloride, sipuleucel-t |
| Thyroid | $171 448 | $11 214 | 0.86 | 1.78 | Lenvatinib, sorafenib, vandetanib |
| All | $82 260 | $9902 | 0.56 | 0.91 | |

*Note.* Values are averaged across listed drugs. The "Other" category includes cancer types for which we have only a few drug approvals: brain, liver, Merkel cell carcinoma, mesothelioma, neuroblastoma, soft tissue carcinoma, and urothelial carcinoma.
LYG indicates life-years gained.

## Discussion

This study is the first to report trends in both price per median and mean LYG among newly approved cancer therapies launched in the United States between 1995 and 2017. We found the price per median LYG increased considerably more than the price per mean LYG among these drugs during the study period. These findings suggest different measures of a drug's clinical benefit may generate different implications for assessing value.

**Figure 2.** Fractional polynomial regression estimate.




Predictions are estimated from a fractional polynomial model that adjusts for indication and route of administration. We show trends in the predicted price per median LYG in thousands (navy) and the predicted price per mean LYG in thousands (maroon). LYG indicates life-years gained.

Our results on trends in the price per median LYG before 2013 are consistent with David Howard et al, who reported an annual increase of $8500 (in 2013 USD) in the price per median LYG.[10] Among first-approved indications, we found that the price per median LYG increased at $8942 (in 2017 USD) per year, and our estimate of a 10% annual increase in price per median LYG is consistent with the previous findings. Our study is the first to extend the Howard analysis to later years. We found that in recent years the growth in price per median LYG has halted, and this slowdown appears to be driven by larger gains in median survival relative to treatment-episode prices. Consequently, our results suggest that, on average, cancer drug prices have become more aligned with their clinical benefits.

The more stable trends in launch prices estimated for 2013 onwards may reflect the increasing prevalence of oral cancer drug launches.[54] From a pharmaceutical manufacturer's perspective, pricing incentives operate differently across formulations and payer benefit designs.[57] Non-oral infused and injected cancer drugs are typically reimbursed under a payer's medical benefit (Part B in fee for service Medicare), whereas oral cancer drugs are typically reimbursed under a payer's pharmacy benefit (Part D in fee for service Medicare).[58] Drugs covered under each benefit are subject to automatic 340B drug discounts if administered or dispensed by qualified providers and if not approved with an orphan designation.[59] Drug use qualifying for these discounts increased over the time period of our study.[60] In addition, branded pharmacy benefit–covered oral drugs are subject to rebates, which provide funds paid from manufacturers to pharmacy benefit managers and payers as a reward for high volume use and more favorable formulary tier placement.[57] Unlike 340B discounts, the presence of rebates feeds back to the setting of Medicare reimbursement for Part D–covered drugs,[10] and the ability of pharmacy benefit managers to extract rebates increases as more drugs become available to treat a specific cancer. In our analysis, sequential entry in oral cancer drugs was observed in numerous cancer indications and therapeutic classes, suggesting more innovation may have acted to help flatten out the actual prices Medicare paid for these therapies. The incremental effect of branded competition within therapeutic class and by disease indication on Medicare's reimbursement for Part D–covered drugs is an important area of future empirical study.

We also found cancer drugs launched after 2012 showed marked increases in both median and mean LYG compared with those launched previously. It is possible that this finding is related

**Table 2.** Trends in median LYG, mean LYG, and price.

| | Price per median LYG ($1000s) | Price per mean LYG ($1000s) | Median LYG | Mean LYG | Price ($1000s) |
|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) |
| A. All indications | | | | | |
| Time: | | | | | |
| 1995-2012 | 6.13 | 0.48 | −0.0047 | -0.00072 | 2.82 |
| | (4.15) | (3.25) | (0.011) | (0.019) | (1.94) |
| 2013-2017 | −10.49 | 0.41 | 0.12* | 0.15† | 15.27† |
| | (13.45) | (10.52) | (0.037) | (0.060) | (6.29) |
| Mean DV | 195.35 | 131.89 | 0.55 | 0.91 | 82.26 |
| No. Obs | 181 | 181 | 181 | 181 | 181 |
| B. First indications only | | | | | |
| Time: | | | | | |
| 1995-2012 | 8.94 | −2.86 | -0.021 | 0.0067 | 5.60‡ |
| | (8.27) | (6.28) | (0.020) | (0.034) | (3.15) |
| 2013-2017 | −32.87 | −9.17 | 0.24* | 0.15 | 12.85 |
| | (33.02) | (25.09) | (0.078) | (0.14) | (12.60) |
| Mean DV | 236.67 | 154.98 | 0.59 | 1.04 | 95.56 |
| No. Obs | 181 | 181 | 181 | 181 | 181 |

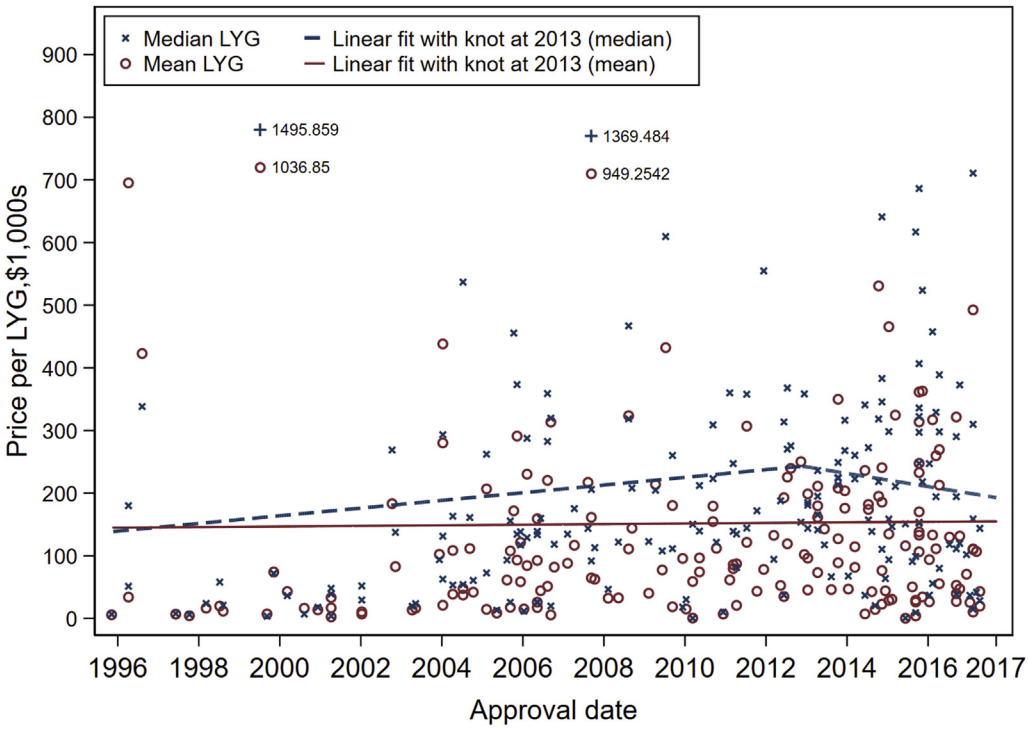
*Note*. Each column displays results from a separate linear spline regression, adjusted for indication and route of administration, with a knot at year 2013. Standard errors in parentheses *$P<.01$, †$P<.05$, ‡$P<.1$. Columns (1), (2), and (5) show changes in the price per year (in thousands) and columns (3) and (4) show changes in life-years gained. The mean of the dependent variables are shown.
DV indicates dependent variables; LYG, life-year gained; No. Obs, number of observations.

**Table 3.** Robustness checks with varying measures of price.

| Time: | A. Dropping outliers, price per | | B. Only trials with OS or PFS | | C. Ignoring 2012 Sequester | |
|---|---|---|---|---|---|---|
| | Median LYG (1) | Mean LYG (2) | Median LYG (3) | Mean LYG (4) | Median LYG (5) | Median LYG (6) |
| 1995-2012 | 9.780*** | 3.043 | 9.863*** | 1.906 | 6.187 | 0.518 |
| | (2.961) | (2.564) | (3.110) | (3.013) | (4.161) | (3.254) |
| 2013-2017 | −5.438 | 3.876 | −11.512 | −0.328 | −10.16 | 0.611 |
| | (9.523) | (8.246) | (10.293) | (9.972) | (13.48) | (10.55) |
| No. of Obs | 179 | 179 | 138 | 138 | 181 | 181 |
| | D. Log price per | | E. Monthly price per | | F. AWP per | |
| | Median LYG (3) | Mean LYG (4) | Median LYG (7) | Mean LYG (8) | Median LYG (9) | Mean LYG (10) |
| 1995-2012 | 0.104*** | 0.0884*** | 0.285 | −1.428* | 10.35** | 3.611 |
| | (0.0239) | (0.0260) | (0.824) | (0.800) | (4.520) | (3.451) |
| 2013-2017 | −0.160** | −0.116 | −4.600* | −0.600 | −13.64 | 0.0977 |
| | (0.0775) | (0.0842) | (2.672) | (2.593) | (14.65) | (11.18) |
| No. of Obs | 181 | 181 | 181 | 181 | 181 | 181 |

*Note.* Each column and panel displays results from a separate linear spline regression, adjusted for indication and route of administration, with a knot at year 2013. Standard errors in parentheses ***$P<.01$, **$P<.05$, *$P<.1$. In panel A, we dropped two outliers in the data with price per LYG more than $800 000 per LYG. The outliers corresponded to nilotinib for its treatment of leukemia and temozolomide for its treatment of brain cancer. In panel B, we considered only trials with overall or progression-free survival. In panel C, we examined prices as if the 2012 sequestration did not occur, so that Medicare prices for IV drugs from April 2013 onward were still reimbursed at 106% average sales price. In panel D, we considered the logged price per LYG. In panel E, we reported the monthly price (as opposed to the treatment episode price) per mean or median LYG. In panel F, we measured prices using the average wholesale price in the date closest to approval. AWP indicates average wholesale price; LYG, life-years gained; OS, overall survival; PFS, progression-free survival.

**Figure 3.** Trends in drug prices per median versus mean life-year gained.




Linear spline regressions are adjusted for indication and route of administration, with a knot at 2013. Slope estimates are shown in Table 2 (columns 1 and 2).

to the regulatory changes that Congress enacted coinciding with this time period. Since 2012, recommendations from the Institute of Medicine have emphasized the need to develop "high-value" drugs, which significantly extend survival or substantially improve quality of life.[2,29] Starting with the US Congress's July 2012 enactment of the FDA Safety and Innovation Act (FDASIA), the FDA has expedited the approval of drugs with evidence of substantial improvements.[31] FDASIA allowed the FDA to approve drugs based on surrogate or intermediate clinical endpoints that were clinically meaningful, defined as being "reasonably likely to predict clinical benefit." It also established a new drug review pathway for the drugs that meet specific endpoints in the Breakthrough Therapy Program.[31] 43% of the cancer drugs in our sample approved between 2012 and 2017 received the breakthrough therapy designation and had survival gains that were more than double that of non-breakthrough drugs (although the difference had limited statistical significance, $P = .11$).[61] Future research should empirically examine whether FDASIA's implementation contributed to survival gains among cancer drug approvals in recent years.[32-36,62,63]

### *Limitations*

Our analysis had a number of limitations. First, we used Medicare prices, as opposed to provider acquisition prices, to identify drug costs. Acquisition costs are not publicly reported in the US healthcare system and also do not accurately reflect the actual prices patients and their insurers pay for them.

Second, we were unable to capture mean LYG estimates for all drug-indication approvals. Because data availability is dependent on having a sufficient follow-up study post-FDA approval, it is not surprising we were missing mean LYG data for a larger share of drug-indication pairs in the more recent years (15 of the 26 dropped observations occurred in the 2013 to 2017 period).

Third, we did not assess the validity of extrapolations among mean LYG estimates, and it is possible that the accuracy of estimates improved over time as alternative survival modeling methods were adopted. Mean LYG estimates can be sensitive to model choice, and the fit of alternative models, sensitivity analyses, and levels of parameter uncertainty should be assessed.[12] Although such metrics existed in the majority of studies that we followed, the lack of standardization across metrics precluded us from analyzing how potential error in modeling may have affected our estimates. Nevertheless, it is important to note that our results regarding the slow-down in price per median LYG persisted and were robust to the inclusion of all drug-indication pairs for which we have median LYG data.

Fourth, we focused solely on the absolute survival gain and did not account for patient quality of life, work gains, or other elements of potential value entailed by these innovations. Many of these measures are neither routinely collected nor reported in clinical trials accepted by the FDA for new drug approval. Standardizing these elements' measurement and collection across cancer clinical trials and real-world outcome studies is an important future research goal, which could further many stakeholder aims including improved value assessments.[27,64-66]

## Conclusion

From 1995 to 2012, the price per mean LYG increased at a considerably slower rate than price per median LYG, which suggests that new cancer drugs have been more effective in increasing long-term survival. In recent years, benefit-adjusted launch prices have remained relatively stable, owing to price increases reflecting equally large gains in median and mean survival. In fact, from 2013 to 2017, the price per median LYG and price per mean LYG both fell, although the drop was only statistically significant for the price per median LYG.

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## Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.08.005.

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