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Spending on anticancer drugs among Medicare beneficiaries: Analyzing predictors of drug expenditures

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ABSTRACT

Objective: To evaluate the factors associated with Medicare spending on newly approved anticancer drugs in the US from 2012 through 2021.

Patient and methods: Using a cross-sectional analysis, we searched US FDA new oncology drug approvals (2012–2021). We analyzed clinical attributes and institutional factors influencing the annual cost of new anticancer drugs in the US. Annual treatment cost was calculated based on average spending per beneficiary from the Centers for Medicare and Medicaid Services, with product factors sourced from the FDA's annual New Drug Therapy Approval reports and drug package inserts at the time of approval.

Results: Over a ten-year period, 112 new anticancer drugs were approved, of which 97 met the study's criteria. A significant majority, 93 %, received expedited development designations from the FDA. At the time of approval, 40 % of these drugs had data on progression-free survival, and 19 % had data on overall survival; 29 % were first-in-class. The study found a significant relationship between the year of approval and factors associated with the size of the treatment population. No statistically significant relationship was found between the clinical value of a drug and its price.

Conclusions: Spending on anticancer drugs by Medicare are predominantly determined by reference pricing and the size of the anticipated treatment population, without an association with therapeutic value. The study advocates for reforms in reimbursement mechanisms for drugs lacking comparator arms and greater transparency for patients treated with these drugs.

1. Background

Spending on anticancer drugs in the U.S. escalated from $58 billion in 2018 to $88 billion in 2022[1], accounting for 45 % of worldwide spending on anticancer drugs [1].

The high cost of anticancer drugs is multifactorial. Proponents point to statistics showing the progress in cancer death rates, the rise of personalized medicines, and a development pipeline that invests in novel treatment approaches [2]. They argue anticancer prices are justified based on the value they represent and the development cost and risk necessary for innovation [2,3].

Critics of the industry cite findings showing an improvement in overall survival (OS) of a median of 2.1 months among novel drugs [4]. This modest improvement in anticancer drug efficacy is in stark contrast to perception among cancer patients that anticancer drugs cure cancer [5]. For approved anticancer drugs, the relationship between improvement in OS and drug prices is weak [6] Economists estimate that the prices of anticancer medication have been increasing after controlling for inflation and survival [7]. They point to a simple formula for explaining the increasingly higher prices: start with the price of the most recent approval and set your price within a 20-percent range [7]. The logical extension to this approach is ever increasing prices that bear little relationship to value [7].

Pricing decisions may not be based on clinical trial outcomes, but rather market perceptions and the desire to produce maximum value to the manufacturer [8,9]. Economists take this as a given that for-profit entities will pursue strategies that maximize profits [10]. To arrive at these profit maximizing prices, pricing strategies may integrate comparable prices of recently approved drugs with the disease characteristics of the particular indication the drug is approved to treat [8]. The disease characteristics most important from a pricing perspective are criticality (i.e., the urgency a doctor or patient feels to have a disease

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treated) and unmet need [8]. Based on these tenets, diseases with a high imperative for treatment should correspond to high prices.

Medicare, the U.S. federal health insurance program for individuals aged 65 and older and those with disabilities, diverges significantly from other countries in its approach to drug pricing. Unlike many nations that negotiate drug prices directly with pharmaceutical manufacturers, Medicare has traditionally accepted prices set by manufacturers, particularly for physician-administered drugs under Part B. Medicare has typically reimbursed these drugs based on the manufacturer's average sales price plus a 6 % premium, a system that affords manufacturers considerable latitude in pricing, with little incentive to align prices with value or affordability. This has resulted in U.S. prices for Medicare Part B drugs being, on average, 1.8 times higher than those in other OECD countries [11].

The economic incentives within the U.S. healthcare system further exacerbate this issue, favoring higher-priced drugs for both physician-administered therapies and patient-administered oral oncolytics, primarily due to the greater profitability they offer to providers and pharmacy benefit managers (PBMs) who serve private insurers.

Medicare's reimbursement model, particularly the average selling price plus 6 % (ASP+6) for physician-administered drugs, reimburses providers at 6 % above the average selling price of the drug, incentivizing the use of more expensive drugs since higher costs yield larger margins. For patient-administered drugs, the absence of a capitated payment model means payers often favor more expensive treatments that come with manufacturer rebates. These rebates, intended to reduce net costs, are frequently retained by PBMs and insurers to boost profits rather than being passed on to consumers [12]. This practice drives up drug prices, as PBMs are incentivized to select drugs with higher list prices that offer larger rebates, thereby contributing to rising healthcare costs and limiting patient access to affordable care [13].

Given this backdrop, we examined the launch prices of oncology drugs approved by the Food and Drug Administration (FDA) over a10-year period to identify the factors influencing the price of these drugs. We examined a number of factors– year of approval, novelty, development time, approval as a single agent, rare disease classification, and solid vs hematologic malignancy approval, among other factors– for their impact on pricing decisions.

2. Methods

2.1. Data sources

We comprehensively reviewed and included all US FDA anticancer drug approvals (2012–2021). We excluded anticancer drugs approved for supportive care, cellular and gene therapies, and drugs approved for pediatric indications only. Since the launch price is determined based on a drug's first indication, we confined our analysis to that indication.

Cost data were sourced from Medicare claims available on the Centers for Medicare and Medicaid Services (CMS) website, specifically from the "Medicare Spending by Drug" section for Parts B and D medications. To discern the economic impact on Medicare, we relied on the metric of average spending per beneficiary (ASPB) [14,15]. This metric indicates the mean annual outlay by Medicare for a single patient's treatment with the newly approved drug. All financial metrics were adjusted using the Consumer Price Index to reflect 2021 monetary values [16].

It is important to note that the ASPB is based on a calendar year. Therefore, beneficiaries initiating therapy in January are considered equivalent to those starting in December of the same year. Additionally, because these drugs are recently approved and are on an upward sales trajectory there are more patients initiating therapy during the second half of the year than the first half. Consequently, this methodology will lead to an underestimation of the true treatment costs over a 12-month period. To correct for this bias, we adjusted the ASPB to reflect a 12-month treatment period based on each individual drug's dosing parameters, according to the package insert. The CMS dataset costs were derived from the drug's wholesale acquisition cost. For Part D drugs, costs also included dispensing fees and taxes, whereas Part B expenses combined the average sales price with an additional 6 % payment [14,15]. Notably, both Part D and B figures exclude rebates or concessions.

We abstracted data from package inserts, including the drug's approved indications, mechanism of action, boxed safety warnings, and clinical trial information. The FDA's annual report, "New Drug Therapy Approvals," provided information on a drug's developmental trajectory, including its regulatory statuses such as regular approval, fast track, breakthrough, and priority, as well as the drug's designations regarding first-in-class status and orphan disease designation [17].

We also used data from ClinicalTrials.gov (study start and approval dates) and the National Institutes of Health's Surveillance, Epidemiology, and End Results (SEER) program (incidence and mortality statistics) [18]. To differentiate large pharmaceutical companies from smaller biopharmaceutical firms, we referred to an industry publication that ranked pharmaceutical companies by annual revenue [19].

2.2. Variable abstraction and coding

From the drug's package insert we obtained the following data: hazard ratios (HR) for OS and progression-free survival (PFS), the total number of subjects, and the average age of the subjects. Additionally based on the package insert we were able to classify drugs according to the following criteria: whether trials were randomized, included a boxed safety warning, were indicated as monotherapy, whether the drug required a biomarker test, whether the drug treats a solid or liquid tumor, and the earliest line of therapy for which the drug is approved. For OS HR and PFS HR metrics, if there were two phase 3 trials, the average of the two trials was used. If the drug was approved without OS or PFS information, their hazard ratios were set to 1.

For the respective year of drug sanctioning, using SEER data [18], we noted the annual mortality of the disease at the time of the drug's approval and whether the tumor was considered rare, defined as disease incidence less than 10,000. This threshold was chosen to provide a more stringent criterion for rarity, beyond the orphan designation, which applies to cancers affecting fewer than 200,000 people [20,21]. In our study, 72 % of the oncology drugs met the orphan criteria, while 10 % met our more stringent incidence-based criterion. It is generally accepted that rare diseases necessitate high prices to make drug development economically viable [21]. We then calculated a ratio of annual mortality to incidence. This ratio captures the lethality of the disease, the indirect lifetime cost of treatment for payers, and the economic attractiveness to manufacturers, as longer treatment durations are often seen as economically favorable by pharmaceutical companies [22,23].

Developmental timeframes (calculated by taking the difference in the time in months between the start of a phase 1 trial and the date of approval) and intensities (the number of phase 2 and phase 3 programs at the time of approval) were ascertained using ClinicalTrials.gov. Classification of Part B drugs was based on their primary reimbursement modality [24]. The complete list of variables collected, and their definitions are included in the supplementary documentation.

2.3. Statistical evaluation

ASPB descriptive statistics were summarized in frequencies and percentages or medians and interquartile ranges. We measured associations between ASPB and classification and continuous variables using Kruskal-Wallis and Spearman correlation analysis.

We developed 2 regression models with ASPB as the dependent variable. As part of model development, we used a regression subset selection package to limit the predictors to the most influential. This data-driven approach helped us avoid overfitting the model and minimize multicollinearity. In both models, we log transformed the dependent variable (ASPB) and the continuous independent variables to

address the skewed distribution.

We conducted comprehensive evaluations of the regression models to ascertain their adherence to key regression assumptions - linearity, homoscedasticity, independence, and normality of residuals - and to assess their robustness. These evaluations, detailed in the supplementary documentation, included a range of statistical tests, visualizations, and simulations. Based on these assessments, both models demonstrated satisfactory performance.

3. Results

From 2012–2021, 112 new anticancer drugs were approved. Of these, 97 were included in our statistical analysis. Thirteen agents were excluded due to lack of available ASPB information and two (larotrectinib and belzutifan) for uncertainties in incidence and mortality data for their initial indications. The regulatory characteristics of the approved anticancer therapies are reported in Table 1.

The median inflation adjusted ASPB rose from $121,000 in the early half of the decade to $204,000 in the latter half, alongside an increase in the prevalence of single-arm trials from 43 % to 60 %. This shift towards single-arm trials correlates with an increase in drugs approved via accelerated and breakthrough methods. Specifically, 94 % of drugs in the accelerated category and 73 % in the breakthrough category utilized this development approach. The rates of growth, in the second half of the 10-year period, for drugs approved through these pathways were 236 % for breakthrough and 94 % for accelerated approvals, markedly higher than the overall increase of 62 %. Fig. 1 illustrates the pricing trends across the study period, demonstrating that the real median ASPB escalated from $114,000 in 2012 to $256,000 in 2021, reflecting a compounded annual growth rate of 9.4 %.

Statistical analyses, including the Kruskal-Wallis test, identified significant differences in median ASPB across various groups, such as breakthrough status, orphan drug status, priority drug status, utilization of PFS as an outcome measure, single-arm trial design, and treatment of rare diseases. Spearman correlation further highlighted the relationship between ASPB and continuous drug attributes, notably the number of subjects in phase 3 clinical trials and the mortality-to-incidence ratio. These analyses are depicted in Figs. 2 and 3.

Through linear regression, insights into ASPB determinants were obtained. Model 1, with an adjusted R^2 of 0.29, suggested positive relationships with biomarkers, later lines of therapy, and rare disease classification, while indicating potential negative influences from larger phase 3 trial sizes and single-arm study configurations. These findings were statistically significant. The variables priority review status and the use of PFS outcomes were retained in the analysis based on our methodological criteria, despite their lack of statistical significance. The regression findings for model 1 are detailed in Table 2.

Compared to model 1, model 2 integrated the year of approval into its selection framework. In model 2, the adjusted R^2 was 0.63. Positive associations emerged with the year of approval, first-in-class designation, monotherapy, and the classification as a rare disease. In contrast, solid tumors and extended development periods were associated with negative effects. While biomarker presence and OS HR did not exhibit statistical significance, they were retained based on the selection guidelines. The regression findings for model 2 are detailed in Table 3. Notably, the drugs relugolix and tagraxofusp, with ASPB of $29,000 and $1000,000 respectively, were identified as statistical outliers and excluded from both regression models.

Table 1
Regulatory Characteristics of Approved Anticancer Therapies 2012–2021.

Characteristic	Percentage (N = 97)	Numerator	Denominator
Expedited process	92.8 %	90	97
Priority status	83.5 %	81	97
Orphan designation	72.2 %	70	97
First-in-Class	28.9 %	28	97
Single-Arm study	53.6 %	52	97
Included overall survival data	18.6 %	18	97
Included progression free survival data	40.2 %	39	97
Hematologic malignancy	37.1 %	36	97
Requires a biomarker test	45.4 %	44	97
Indicated for monotherapy	56.7 %	55	97
First line	37.1 %	36	97
Second line	43.3 %	42	97
Third line plus	16.5 %	16	97
Part B	30.9 %	30	97
Part D	69.1 %	67	97

The median phase 3 study size was 220 subjects.

4. Conclusion

In our univariate analysis, the association of ASPB with anticancer drug characteristics was consistent with prior findings [25–30]. Notably, ASPB did not demonstrate a relationship with value-related outcomes, such as improvements in OS or safety profiles. However, it was linked to factors like developmental pathways and disease-specific elements, including orphan status and mortality-to-incidence ratios. These findings suggest that institutional considerations might contribute to diminished constraints on pricing behavior by manufacturers.

After adjusting for multiple factors, our analysis found that neither OS nor PFS hazard ratios were significant predictors of drug pricing. Instead, factors related to the potential patient population size for the approved drug, such as the requirement for a biomarker test, approval for use in later lines of therapy, a smaller number of phase 3 study participants, and classification as a treatment for a rare disease, were associated with higher prices. This suggests that manufacturers set higher prices to offset limitations in market size, indicating that considerations of a drug's value to patients play a minor role, if any, in pricing decisions.

Including a drug's 'year of approval' resulted in a 34-point increase in the model's adjusted R^2. This finding supports the claim that new drug prices largely depend on the reference prices of existing treatments, with subsequent entrants progressively increasing these prices.

Collectively, our findings challenge the common industry assertion that drug prices reflect therapeutic value, suggesting a market-driven pricing strategy instead. This implies that manufacturers might set prices for therapies based on anticipated, yet unproven, clinical benefits. The potential use of FDA designations by the industry to construct a "value narrative" that supports high prices is concerning.

Absent robust clinical benefit evidence, such as incremental cost-effectiveness analysis, this narrative emphasizes factors like the relative prices of recently approved therapies, disease severity, uniqueness of mechanism of action, specific biomarkers, and more, which may not directly correlate with therapeutic efficacy. These factors could be tailored to influence emotional decision-making [31]. Manufacturers may exploit a "halo effect" associated with the "breakthrough" designation, where patients, providers, and payers might conflate this designation with actual breakthroughs in cancer care [32]. In 2021, six anticancer drugs with breakthrough designation were approved by the FDA. Of these, four manufacturers extended the term "breakthrough" beyond its regulatory context in their press releases [33–36]. From a "value narrative" perspective, the intent appears to be to frame such approvals as justifying their prices, thereby bypassing conventional value assessments. The substantial price escalation observed in the latter half of the study period, particularly alongside the rise in single-arm accelerated pathway studies, underscores how this narrative may be driving prices upward and highlights the need for closer scrutiny of these evolving practices.

5. Strengths and limitations

Our study has strengths and limitations. Ours is a large analysis,

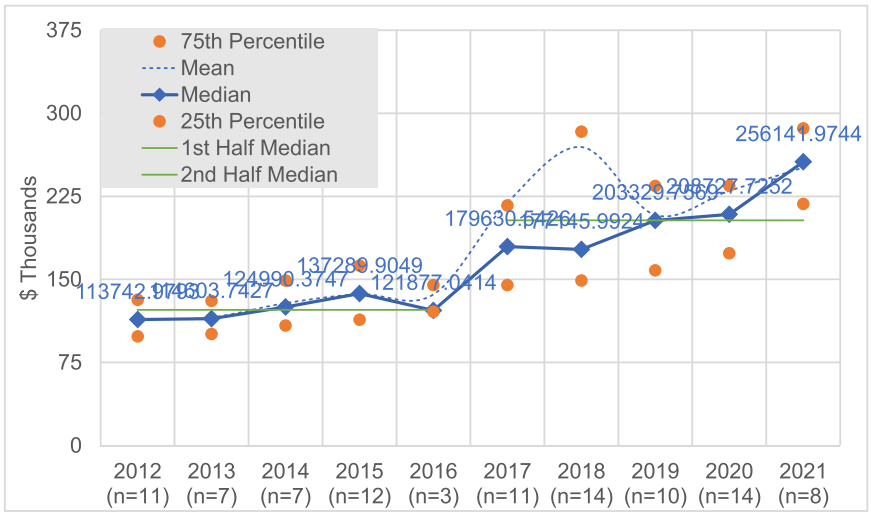

Fig. 1. Median Real Average Spending per Beneficiary (ASPB) for FDA-Approved Anticancer Drugs 2012–2021. The median values are reported above the diamonds, and the count of observations is detailed beneath each year. The aggregate number of observations is 97. The green lines display the average medians of the first and second half of the decade.

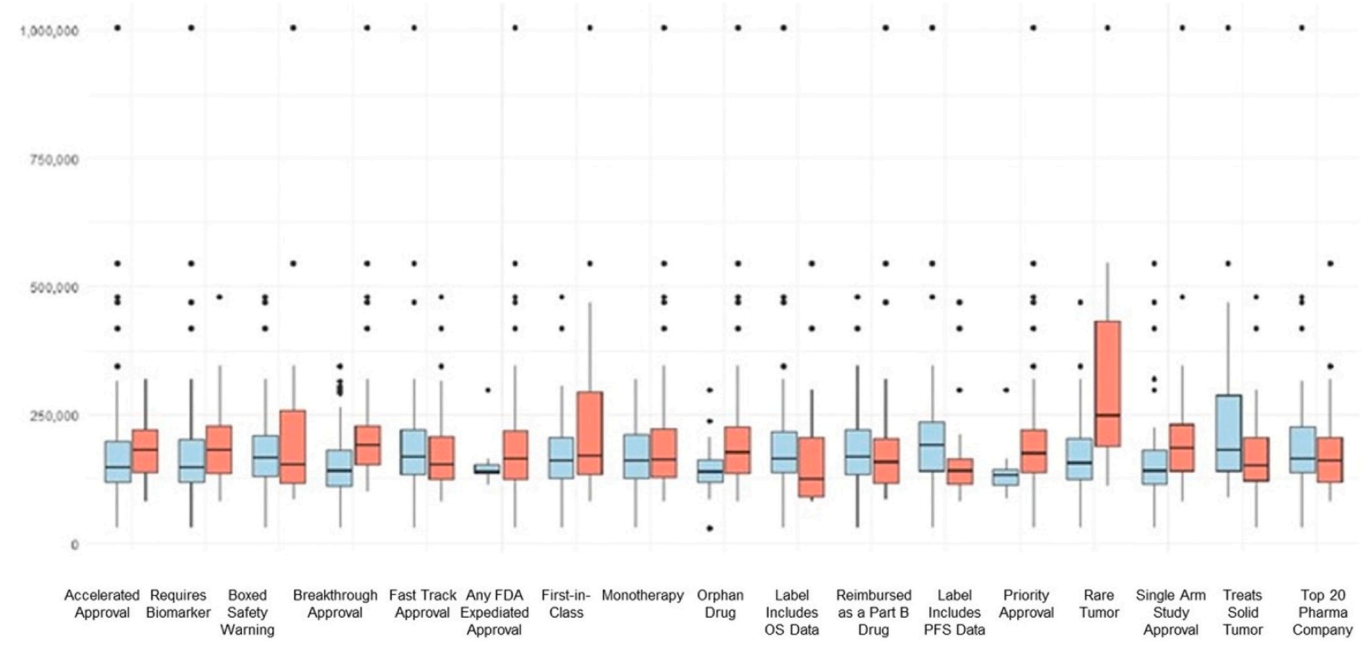

Fig. 2. A Univariate Comparison of Average Spending per Beneficiary (ASPB) Between 2012 and 2021 for Approved Anticancer Drugs. The pink box plots represent data for the group with the classification of interest. Conversely, the blue box plots correspond to the group without this classification. The dots represent individual observations beyond 1.5 times the interquartile range. The following classification variables had statistically significant ($p<0.05$) differences between groups: breakthrough approval, orphan drug designation, label which included PFS data, priority approval, rare tumor classification, and single arm trials. P values were determined using the Kruskal-Wallis test and adjusted for multiple comparisons with the Benjamini-Hochberg procedure.

considering many putative factors that may drive drug prices, using standardized spending from CMS, reflecting actual outlays for beneficiaries with cancer. As such, it has large implications for public spending on cancer drugs. In terms of limitations, it is a retrospective analysis of CMS Medicare payment data and information extracted from anticancer drug package inserts. We used ASPB as a proxy for price rather than the actual net prices manufacturers obtain from drug sales. While discounting on anticancer drugs is typically small compared to other indications, it is present in select situations due to legislatively mandated discounts such as Medicaid, 340B Hospital discounts, Veterans Administration/Department of Defense, and other instances [1,37]. In the case of discounts and rebates to private entities like insurance companies, specialty pharmacy providers, physician-owned clinics, hospitals, wholesalers, and distributors, it remains uncertain whether cost savings would occur, as these entities might absorb these discounts or rebates as additional revenue instead of passing the savings to patients in the form of reduced premiums or copays. Unfortunately, we are unable to identify all discounts and could not include them. Future data transparency may overcome this limitation.

6. Policy summary

Our study reveals a misalignment between drug pricing and the clinical benefits they offer. Cancer drug prices increase over time, and

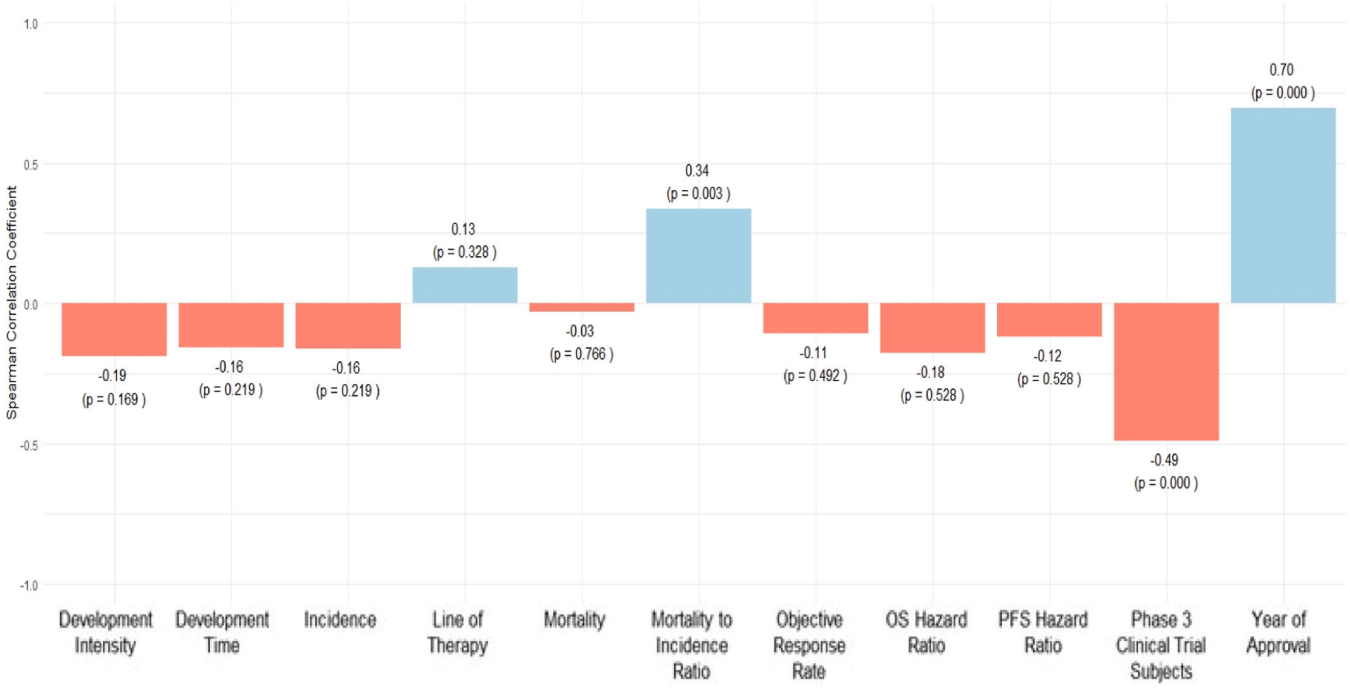

Fig. 3. Spearman Correlation Between Average Spending per Beneficiary (ASPB) Between 2012 and 2021 for Approved Anticancer Drugs. Mortality to incidence ratio, phase 3 clinical trial subjects, and year of approval were statistically significant. P values were adjusted for multiple comparisons using the Benjamini-Hochberg method.

Table 2
Regression Model 1 Coefficient Estimates, P-Values, and Confidence Intervals.

Regression Statistics					$ Impact (Thousands)		
Coefficients	Estimate	P-Value	Lower 95 % CI	Upper 95 % CI	Average	Lower 95 % CI	Upper 95 % CI
Intercept	12.76	**<0.0000**	11.92	13.60	155	31	779
Requires Biomarker	0.17	**0.03**	0.02	0.32	184	31	1076,
Priority Status Designation	0.19	**0.05**	−0.00	0.39	189	31	1156
Line of Therapy	0.09	**0.04**	0.01	0.19	170	31	938
Study Subjects	−0.16	**0.01**	−0.29	−0.04	146	28	768
PFS Reported	−0.25	0.09	−0.56	0.04	113	16	799
Rare Tumor Classification	0.26	**0.03**	0.03	0.49	190	29	1257
Single Arm Study	−0.31	**0.04**	−0.59	−0.03	107	15	748
Observations: 95							
Residual standard error: 0.35 on 87 degrees of freedom							
Multiple R-squared: 0.34, Adjusted R-squared: 0.29							
F-statistic: 6.49 on 7 and 87 DF, p-value: 3.648e−06							

Note the number of observations is 95. Relugolix and tagraxofusp, representing the highest and lowest priced drugs with average sales prices per beneficiary (ASPB) of $29,000 and $1000,000 respectively, were identified as statistical outliers. To maintain analytical rigor, these extremes were excluded from models 1 and 2. For a comprehensive understanding of the outlier detection methodology and analysis, refer to the supplementary documentation. Continuous variables are natural log adjusted.

this is the dominant factor in pricing considerations. A disconnect between metrics of clinical benefit and price may be particularly true with drugs approved via an accelerated pathway [38]. We underscore the influence of market dynamics, notably the trend of escalating reference prices to validate the costs of new drugs. This raises significant concerns about the alignment of drug prices with their therapeutic worth. Our findings should catalyze discussions aimed at enhancing drug approval and pricing processes to better represent the true value conferred to patients. Given these observations, the FDA may contemplate integrating a Risk Evaluation and Mitigation Strategies program for medications approved without a comparator group, ensuring informed consent for patients until robust randomized evidence emerges [39]. Similarly, Congress should deliberate on legislation addressing Medicare reimbursement and copay structures for drugs granted approval in the absence of proven efficacy, or empower CMS to do so.

CRediT authorship contribution statement

Ashley Nee: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Vinay Prasad:** Writing – review & editing, Methodology, Funding acquisition. **Alyson Haslam:** Writing – review & editing, Supervision, Methodology.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

Table 3
Regression Model 2 Coefficient Estimates, P-Values, and Confidence Intervals.

Regression Statistics					$ Impact (Thousands)		
Coefficients	Estimate	P-Value	Lower 95 % CI	Upper 95 % CI	Average	Lower 95 % CI	Upper 95 % CI
Intercept	12.26	**<0.0000**	11.58	12.94	149	75	294
Year of Approval	0.10	**<0.0000**	0.085	0.12	165	146	186
Requires Biomarker	0.09	0.13	−0.03	0.20	162	145	182
First-in-Class	0.14	**0.03**	0.02	0.25	170	151	191
Development Time	−0.13	**0.04**	−0.25	−0.01	146	85	251
Monotherapy	0.19	**0.001**	0.08	0.30	180	161	201
OS Hazard Ratio	−0.36	0.09	−0.78	0.06	178	144	219
Rare Tumor Classification	0.21	**0.02**	0.04	0.38	183	155	217
Solid Tumor Classification	−0.20	**0.002**	−0.33	−0.08	121	107	138
Observations: 95							
Residual standard error: 0.25 on 86 degrees of freedom							
Multiple R-squared: 0.66, Adjusted R-squared: 0.63							
F-statistic: 20.88 on 8 and 86 DF, p-value: < 2.2e−16							

Relugolix and tagraxofusp, were identified as statistical outliers and excluded from the analysis. The "Year of Approval" variable was coded numerically, beginning with 1 for the year 2011. Each subsequent year is represented by incrementally higher numbers (2 for 2012, 3 for 2013, and so forth). An estimated coefficient of 0.10 for this variable indicates that, for each additional year, there is an expected price increase of 10 %. Continuous variables are natural log adjusted.

the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jcpo.2024.100509.

References

[1] Aitken M., Kleinrock M., Connelly N., Pritchett J. GlobalOncology Trends 2023: Outlook To 2027. IQVIA Institute For Human Data Science 2023.
[2] PhRMA. CancerMedicines: Value in Context. PhRMA 2022.
[3] J.A. DiMasi, H.G. Grabowski, R.W. Hansen, Innovation in the pharmaceutical industry: new estimates of R&D costs, J. Health Econ. 47 (2016) 20–33, https://doi.org/10.1016/j.jhealeco.2016.01.012.
[4] Prasad V. Malignant:How Bad Policy and Bad Evidence Harm People with Cancer. Johns Hopkins University Press; 2020.
[5] J.C. Weeks, P.J. Catalano, A. Cronin, M.D. Finkelman, J.W. Mack, N.L. Keating, et al., Patients' expectations about effects of chemotherapy for advanced cancer, N. Engl. J. Med. 367 (2012) 1616–1625, https://doi.org/10.1056/NEJMoa1204410.
[6] S. Mailankody, V. Prasad, Five years of cancer drug approvals: innovation, efficacy, and costs, JAMA Oncol. 1 (2015) 539–540, https://doi.org/10.1001/jamaoncol.2015.0373.
[7] D.H. Howard, P.B. Bach, E.R. Berndt, R.M. Conti, Pricing in the market for anticancer drugs, J. Econ. Perspect. 29 (2015) 139–162, https://doi.org/10.1257/jep.29.1.139.
[8] Kolassa E.M. TheStrategic Pricing of Pharmaceuticals. The PondHouse Press.; 2009.
[9] F. Simon, G. Giovannetti, Managing Biotechnology FromScience to Market in the Digital Age, John Wiley & Sons, 2017.
[10] S. Morris, N. Devlin, D. Parkin, A. Spencer. Economic Analysis In Health Care, 2nd ed., John Wiley & Sons, 2012.
[11] US Department of Health and Human Services. Comparison of U.S. and InternationalPrices for Top Medicare Part B Drugsby Total Expenditures 2018.
[12] Sarnak D.O., Squires D., Bishop S. Paying for Prescription Drugs Around the World: Why Is the U.S. an Outlier? Commonweath Fund 2017.
[13] Sood N., Ribero R., Ryan M., Van Nuys K. New Evidence Shows Prescription Drug RebatesPlay a Role in Increasing List Prices. USC Schaeffer Center 2020.
[14] Centers for Medicare and Medicaid Services. Medicare Part B Spending by Drug Methodology 2023.
[15] Centers for Medicare & Medicaid Services Data. Medicare Part D Spending by Drug Methodology 2024.
[16] Consumer Price Index for All Urban Consumers: All Items in U.S. City Average. Federal Reserve Economic Data 2024. https://fred.stlouisfed.org/series/CPIAUCSL (accessed August 18, 2024).
[17] U.S. Food & Drug Administration. Novel Drug Approvals at FDA. FDA 2024. https://www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda (accessed August 19, 2024).
[18] Centers for Disease Control and Prevention. Download Data Tables | U.S. Cancer Statistics. US Cancer Statistics 2024. https://www.cdc.gov/united-states-cancer-statistics/dataviz/data-tables.html?CDC_AAref_Val=https://www.cdc.gov/cancer/uscs/dataviz/download_data.htm (accessed August 19, 2024).
[19] Dunleavy K. The top 20 pharma companies by 2021 revenue |. Fierce Pharma 2022. https://www.fiercepharma.com/special-reports/top-20-pharma-companies-2021-revenue (accessed August 19, 2024).
[20] U.S. Food & Drug Administration. Orphan Drug Act - Relevant Excerpts. FDA 2013. https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts (accessed August 19, 2024).
[21] Institute for Clinical and Economic Review. Modifications to the ICER value assessment frameworkfor treatments for ultra-rare diseases 2020.
[22] J.A. DiMasi, H.G. Grabowski, The cost of biopharmaceutical R&D: is biotech different? Manag. Decis. Econ. 28 (2007) 469–479, https://doi.org/10.1002/mde.1360.
[23] H. Kantarjian, D. Steensma, J. Rius Sanjuan, A. Elshaug, D. Light, High cancer drug prices in the United States: reasons and proposed solutions, J. Oncol. Pr. 10 (2014) e208–e211, https://doi.org/10.1200/JOP.2013.001351.
[24] The C for M and MS. Drug coverage under different parts of Medicare. Centers for Medicare and Medicaid Services; 2023.
[25] M.D. Miljkovic, J.E. Tuia, T. Olivier, A. Haslam, V. Prasad, Association between US drug price and measures of efficacy for oncology drugs approved by the US food and drug administration from 2015 to 2020, JAMA Intern. Med. 182 (2022) 1319–1320, https://doi.org/10.1001/jamainternmed.2022.4924.
[26] K.N. Vokinger, T.J. Hwang, T. Grischott, S. Reichert, A. Tibau, T. Rosemann, et al., Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis, Lancet Oncol. 21 (2020) 664–670, https://doi.org/10.1016/S1470-2045(20)30139-X.
[27] A.J. Chen, X. Hu, R.M. Conti, A.B. Jena, D.P. Goldman, Trends in the price per median and mean life-year gained among newly approved cancer therapies 1995 to 2017, Value Health 22 (2019) 1387–1395, https://doi.org/10.1016/j.jval.2019.08.005.
[28] C. Molto, T.J. Hwang, M. Borrell, M. Andres, I. Gich, A. Barnadas, et al., Clinical benefit and cost of breakthrough cancer drugs approved by the US food and drug administration, Cancer 126 (2020) 4390–4399, https://doi.org/10.1002/cncr.33095.
[29] V. Prasad, K. De Jesús, S. Mailankody, The high price of anticancer drugs: origins, implications, barriers, solutions, Nat. Rev. Clin. Oncol. 14 (2017) 381–390, https://doi.org/10.1038/nrclinonc.2017.31.
[30] J.C. Del Paggio, R. Sullivan, D. Schrag, W.M. Hopman, B. Azariah, C.S. Pramesh, et al., Delivery of meaningful cancer care: a retrospective cohort study assessing cost and benefit with the ASCO and ESMO frameworks, Lancet Oncol. 18 (2017) 887–894, https://doi.org/10.1016/S1470-2045(17)30415-1.
[31] E. Schoonveld. The Price of Global Health, 2nd ed, GowerPublishing, 2015.
[32] G. Goth, The eyes have it, Commun. ACM 53 (2010) 13, https://doi.org/10.1145/1859204.1859211.
[33] Amgen. F.D.A. Approves LUMAKRASTM (Sotorasib), The First And Only Targeted Treatment For Patients With KRAS G12C-Mutated Locally Advanced Or Metastatic Non-Small Cell Lung Cancer. Amgen 2021. https://www.amgen.com/newsroom/press-releases/2021/05/fda-approves-lumakras-sotorasib-the-first-and-only-targeted-treatment-for-patients-with-kras-g12cmutated-locally-advanced-or-metastatic-nonsmall-cell-lung-cancer (accessed August 19, 2024).
[34] G.S.K. Jemperli (dostarlimab) plus chemotherapy approved in the US as the first new frontline treatment option in decades for dMMR/MSI-H primary advanced or recurrent endometrial cancer. GSK 2023. https://www.gsk.com/en-gb/media/press-releases/jemperli-plus-chemotherapy-approved-in-us-for-new-indication/ (accessed August 19, 2024).
[35] Takeda's EXKIVITYTM (mobocertinib) Approved by U.S FDA as the First Oral Therapy Specifically Designed for Patients with EGFR Exon20 Insertion+ NSCLC. Taleda 2021. https://www.takeda.com/newsroom/newsreleases/2021/takeda-exkivity-mobocertinib-approved-by-us-fda/ (accessed August 19, 2024).
[36] Novartis. FDA approves Novartis Scemblix® (asciminib), with novel mechanism of action for the treatment of chronic myeloid leukemia. Novartis 2021. https://www.novartis.com/news/media-releases/fda-approves-novartis-scemblix-asciminib-novel-mechanism-action-treatment-chronic-myeloid-leukemia (accessed August 19, 2024).

[37] Blumenthal D., Squires D. Drug Price Control: How Some Government Programs Do It. Commonwealth Fund 2016. https://www.commonwealthfund.org/blog/2016/drug-price-control-how-some-government-programs-do-it (accessed August 19, 2024).

[38] B. Gyawali, A.S. Kesselheim, J.S. Ross, The accelerated approval program for cancer drugs - finding the right balance, 968–971, N. Engl. J. Med. 389 (2023), https://doi.org/10.1056/NEJMp2306872.

[39] U.S. Food & Drug Administration. Risk Evaluation and Mitigation Strategies | REMS. FDA 2023. https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (accessed August 19, 2024).