PharmacoEconomics (2025) 43:415–427
https://doi.org/10.1007/s40273-024-01448-x

ORIGINAL RESEARCH ARTICLE

Value-Based Indication-Specific Pricing and Weighted-Average Pricing: Estimated Price and Cost Savings for Cancer Drugs

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Accepted: 13 October 2024 / Published online: 30 December 2024

Abstract

Objectives For US Medicare and Medicaid, single drug prices do not reflect the value of supplemental indications. Value-based indication-specific and weighted-average pricing has been suggested for drugs with multiple indications. Under indication-specific pricing, a distinct price is assigned to the differential value a drug offers in each indication. Under weighted-average pricing, a single drug price is calculated that reflects the value and/or volume of each indication. This study estimates price reductions and cost savings for cancer drugs under value-based indication-specific pricing and weighted-average pricing.

Methods We collected data on US Food and Drug Administration (FDA)-approved cancer drugs and indications (2003–2020) from FDA labels, the Global Burden of Disease study, clinicaltrials.gov, and Medicare and Medicaid. A multivariable regression analysis, informed by characteristics of original indications, was used to predict value-based indication-specific prices for supplemental indications. These indication-specific prices were combined with each indication's prevalence data to estimate value-based weighted-average prices and potential cost savings under each policy.

Results We identified 123 cancer drugs with 308 indications. Medicare and Medicaid spent a total of $28.2 billion on these drugs in 2020. Adopting value-based indication-specific pricing would increase drug prices by an average of 3.9%, with cost savings of $3.0 billion (10.6%). However, 43.7% higher prices for ultra-rare diseases would increase spending by 16.8% ($44 million). Adopting value-based weighted-average pricing would reduce prices by an average of 4.6% and spending by $3.0 billion (10.6%). Under weighted-average pricing, prices for and spending on ultra-rare diseases would be reduced by 22.6% and $55 million, respectively.

Conclusions Value-based indication-specific and weighted-average pricing could help to align the value and price of new indications, thereby reducing expenditure on drugs with multiple indications.

1 Introduction

Cancer drugs are increasingly approved and used for multiple indications. Between 2000 and 2022, a total of 55% of cancer drugs received US Food and Drug Administration (FDA) approval for more than one indication, with an average of four indications per drug [1]. However, for the US public insurance schemes Medicare and Medicaid, a single (uniform) drug price is set based on the original indication's unmet needs and innovativeness [2]. This uniform drug price neglects the value of supplemental indications. This is particularly concerning for partial orphan drugs pursuing an "orphan-first" strategy—drugs that are initially approved for rare diseases and then extended for use in common diseases [3–8]. Under uniform prices, this strategy could unfairly boost revenues for drug sponsors by transferring high orphan prices to non-orphan indications [5]. Differential value-based pricing policies, such as indication-specific pricing

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Key Points for Decision Makers

For the US public insurance schemes Medicare and Medicaid, single drug prices do not reflect the value of supplemental indications.

Value-based indication-specific and weighted-average pricing were suggested for drugs with multiple indications. Under indication-specific pricing, a distinct price is assigned to the differential value a drug offers in each indication. Under weighted-average pricing, a single drug price is calculated that reflects the value and/or volume of each indication.

In this study of 123 cancer drugs with 308 indications, adopting weighted-average pricing would reduce drug prices by an average of 4.6%, with cost savings of $3.0 billion (10.6%). Similarly, adopting indication-specific pricing would reduce spending by $3.0 billion (10.6%).

Adopting value-based indication-specific pricing or weighted-average pricing for drugs with multiple indications could be associated with considerable cost savings for payers and patients in the USA.

(ISP) or weighted-average pricing, could help to better align prices with each indication's value and thereby resolve the current loopholes created under uniform drug pricing.

Systematic reviews have theoretically evaluated the merits of these differential pricing methods [9–11]. However, besides several theoretical articles [10–20] and four case studies [21–24], to date no study has analyzed the potential impacts of adopting these pricing systems in the USA. Therefore, we estimated prices and Medicare and Medicaid spending if ISP or weighted-average pricing were adopted in the USA for cancer drugs.

1.1 Value-Based Indication-Specific Pricing

ISP, also referred to as indication-based pricing or multi-indication pricing, is the most intuitive option to price drugs with multiple indications [21]. Under ISP, a distinct price is assigned to the differential value a drug offers in each indication ("one drug, multiple prices"). Thereby, higher prices are assigned to indications that offer substantial benefits (e.g. high quality-adjusted life-year gains) to patients with significant unmet needs, whereas a lower price is aligned to indications that only offer an incremental benefit (e.g. low quality-adjusted life-year gains). However, the implications of ISP on healthcare budgets, pharmaceutical competition, and patient access remain debated.

Bach [21] noted that ISP could rationalize drug pricing and thereby reduce healthcare expenditure. In contrast, Chandra and Garthwaite [12] argued that ISP "will result in higher prices for patients who benefit the most from a given drug, higher utilization by patients who benefit least, higher overall spending, and higher manufacturer profits." Although spending might increase under ISP, the greater healthcare budget would be allocated to high-value indications that provide substantial benefits to patients rather than wasting money on indications offering only marginal benefits [10]. ISP encourages pharmaceutical companies to engage in pharmaceutical R&D for both high-value low-prevalence and low-value high-prevalence indications if it is implemented alongside a value-based pricing mechanism. Thereby, ISP could not only increase the number of therapeutic options available to patients but also reduce incentives to delay or withhold indications (e.g. the sequencing of indication launches), resulting in quicker access to these novel indications [10, 19]. Towse et al. [10] argued that this greater number of available therapeutic alternatives would result in more competition that would dynamically reduce prices. Hitherto, evidence from a systematic review suggested that greater brand–brand competition did not lead to reduced prescription drug prices [25]. Ultimately, ISP could grant patient access to more therapeutic options and increase revenues and profits for pharmaceutical companies. In the short run, ISP would therefore result in increased spending on prescription drugs for insurers. However, in the long run, the increased competition at an indication level could drive down prices and spending for insurers [10, 26].

1.2 Value-Based Weighted-Average Pricing

Weighted-average pricing is an indirect differential pricing policy. Under this policy, a single drug price is calculated that reflects the value and/or volume of each indication. This system requires the ex ante estimation or ex post monitoring of patients receiving the drug for each indication [27]. As for all drug pricing considerations, the operationalization of "value" remains subject to the national drug coverage and reimbursement process. Therefore, this calculation or monitoring imposes an additional administrative burden on manufacturers and payers. Moreover, given that drug prices are still anchored to the initial indication, there remains an incentive for drug sponsors to sequence the development and launch of new indications. In particular, low-value high-prevalence indications, which may substantially reduce the weighted-average price for the entire drug, may not be launched [28]. Weighted-average pricing is currently applied in Germany, France, Spain, Australia, Austria, and Belgium [9, 11, 29], and weighted-average pricing was shown to be associated with declining list prices as new low-value

high-prevalence indications entered the pharmaceutical market [27].

2 Data and Methods

We collected data on all cancer drugs with FDA approval from 2003 to 2020. We used these data to calculate indication-specific and weighted-average prices. First, we conducted a regression analysis of prices for original approvals informed by each indication's innovativeness, R&D costs, disease incidence, disease severity, and the number of available treatment options. We then used this model to predict indication-specific prices for all supplemental indications. Based on these indication-specific prices, we calculated value- and population-weighted-average prices for each drug as new indications enter the market. Medicare and Medicaid drug spending was proportionally assigned to each indication based on disease prevalence rates published by the Global Burden of Disease study. The current uniform pricing policy was compared with ISP and weighted-average pricing regarding monthly treatment costs and total Medicare and Medicaid spending.

2.1 Data Collection

We systematically identified all cancer drugs that received FDA approval between 2003 and 2020 in the Drugs@FDA database. Then, we collected data from marketing authorization labels and clinicaltrials.gov on all anti-cancer drugs, including their original and supplemental indications, with FDA approval between 2003 and 2020. Epidemiologic data, including estimates for disease incidence, disability-adjusted life-years (DALYs), and number of available treatment options, were retrieved for all indications from the Global Burden of Disease study and the National Institutes of Health [30, 31].

Drug prices were collected from two distinct data sources coherent with a methodology employed in previous studies [32]. For drugs covered by Medicare Part B, prices were extracted from the Centers for Medicare & Medicaid Services files. For drugs covered by Medicare Part D, we obtained prices from Medicare's plan finder tool. To ensure comparability with prior studies [32], we collected Part D price data using the following steps. First, we searched the plan finder tool for each drug's name. For each indication, we selected the appropriate dosing regimen (see below) and then selected the lowest-cost pharmacy for patients living in New York City (ZIP code 10065). We chose the "Humana Basic Rx Plan (PDP)" and noted the "Full Cost of Drug", that is, the retail price. For drugs covered under both Medicare Part B and D, we used Part B prices. The collected treatment costs are an approximation of drug list prices. Patients' out-of-pocket expenses resulting from deductibles, premiums, co-payments, and coverage gaps may vary according to their health insurance plan.

For each indication, we calculated monthly treatment costs for an average adult with a body surface area of 1.7 m^2 weighing 70 kg with normal renal and hepatic function [32–34]. We then calculated the average monthly treatment costs for each indication based on indication-specific dosing schedules. Dosing schedules were obtained from each drug indication's FDA label. For regimens entailing different drug doses for initiation, consolidation, and/or maintenance treatment, we calculated the average monthly costs for the median treatment duration defined in the respective pivotal trial. For indications with multiple dosing schedules, we selected the dosing schedule resulting in the lowest treatment costs. Calculated treatment costs therefore only include a drug's price without any supportive treatment, doctor's fees, administrative costs, or delivery expenses. We have previously described details of the data collection methodology [1, 2].

2.2 Estimating Value-Based Indication-Specific Prices

US drug prices are set based on the characteristics of the original indication and then transferred to following supplemental indication approvals, regardless of their unmet needs, innovativeness, and R&D costs [2]. We sought to estimate value-based indication-specific prices for these supplemental indications based on the original indication's characteristics. First, we conducted a multivariable regression analysis of original indication prices informed by variables relevant to the value-based pricing of new cancer drugs/indications (selection of these value dimensions was informed by previous studies), as follows [2, 35, 36].

- Disease burden: Disease burden was measured by each disease's incidence rate per 100,000 US inhabitants in 2019 as published by the Global Burden of Disease study [31].
- Disease severity: Disease severity was estimated based on DALYs per patient as published by the Global Burden of Disease study [31]. DALYs are a composite measure of years of life lost and years lived with disability.
- Number of treatment alternatives: Besides disease rarity and burden, the number of treatment alternatives represents the last domain of unmet medical needs [37]. The number of available treatment options was obtained from the National Cancer Institute for each cancer entity [30].
- R&D costs: We used the number of patients enrolled in the pivotal trial supporting the new indication's FDA approval as a proxy for pharmaceutical companies' R&D costs. Although this proxy may be imperfect, R&D costs

were shown to be positively correlated with clinical trial size [38].

- Innovation/novelty: A drug's innovativeness/novelty may be judged from different aspects. The industry perspective has long focused on new drugs' biotechnological aspects: mechanism of action, target, and/or delivery method [35, 36, 39]. However, these biotechnological aspects may not be meaningful to patients and physicians. From a clinical perspective, innovativeness is better determined by combining the novelty of a drug's target as well as the medical novelty of the treated disease. Patients benefit from next-in-class drugs if they treat a novel disease. For instance, avelumab was not the first programmed death-ligand 1 (PD-L1) inhibitor to receive FDA approval, yet it is the first PD-L1 inhibitor to treat Merkel cell carcinoma. We consequently adopted the methodology of Lanthier et al. of determining the innovativeness of new drugs [39] and modified it for the classification of the innovativeness of new indications. We differentiated drugs for new indications (first in indication), drugs for known indications with a major benefit as exhibited by FDA priority review (advance in indication), and drugs for known indications without FDA priority review (addition to indication). Furthermore, this novel methodology of determining innovativeness fits the purpose of calculating indication-specific prices as it allows for varying levels of innovation across a drug's indications.

The results of the log-linear regression analysis with robust standard errors are presented in Table 1. This model was then used to predict prices for all supplemental indications, adjusting for smearing. These indication-specific prices were then used to calculate value-based weighted-average prices. Following the French and German examples, we estimated a single drug price weighted by the value and prevalence of each indication [9, 11]. This single drug price was then re-calculated as new indications were approved for the same drug [27]. We present prices as a percentage of the original indication's price, given that, under the current uniform pricing policy, the prices of drugs with two, three, or four indications vary.

Table 1 Multivariable regression analysis of selected variables on monthly treatment costs for original cancer indications

Variable	Log(treatment cost for first indication)		
	ß	95% CI	*P* value
Clinical innovativeness			
First in indication	0.00	Reference	
Advance in indication	0.08	− 0.40 to 0.55	*0.741*
Addition to indication	0.24	− 0.23 to 0.70	*0.315*
Log(enrolled patients)	− 0.23	− 0.47 to − 0.01	*0.045*
Log(disease incidence)[a]	− 0.36	− 0.73 to 0.01	*0.055*
Log(enrolled patients) × log(disease incidence)	0.05	− 0.02 to 0,12	*0.187*
DALYs per person[a]	0.03	0.01 to 0.05	*0.002*
No. of treatment options	− 0.00	− 0.01 to 0.01	*0.726*
Constant	10.98	9.58 to 12.38	*<0.001*
N	128		
F value	6.35		
R^2	37.8%		
Prob > *F*	< 0.001		

CI, confidence interval; DALYs, disability-adjusted life-years

[a]Disease incidence and DALYs for the US population in 2019

2.3 Estimating Medicare and Medicaid Spending

Finally, we combined drug spending data from the Centers for Medicare & Medicaid Services and our estimated prices to calculate the spending on and cost savings of adopting ISP and weighted-average pricing policies in the USA. For this purpose, we proportionally assigned drug usage to each indication based on the prevalence rate of the treated disease in the USA. Ideally, indication-specific usage would be tracked based on indication-specific monitoring of drug use, yet information technology systems with this capability have not yet been adopted across the entire nation [21]. Under the assumption that demand for anticancer drugs is inelastic to marginal changes in prices, we estimated spending under an ISP and weighted-average pricing policy by combining the previously calculated drug prices and drug usage.

2.4 Comparison Across Indications and Orphan Drugs

We examined where savings were realized under the aforementioned novel pharmaceutical policies by comparing subgroups of indications and drugs. First, we compared spending across original and supplemental indication approvals (first vs. second vs. third vs. fourth vs. fifth approved indications). Second, we compared drugs across their orphan designation status. We stratified drugs as full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications) [5]. Third, we compared indications across their orphan designation status. Orphan indications were stratified according to the number of affected US inhabitants as ultra-rare (< 6600), rare (6600–200,000), and common (> 200,000) [4].

Data were stored in Microsoft Excel and analyzed with Stata 14.2 (StataCorp LLC, College Station, TX, USA). Two-tailed *p*-values < 0.05 were considered significant.

This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline where applicable [40].

2.5 Sensitivity Analysis

We conducted various sensitivity analyses to check the robustness of our model and its input parameters. First, we re-calculated cost savings under different price elasticity of demand (PED) inputs given that the published estimates range from 0.10 to 0.74 [41–45]. Second, we re-calculated prices and associated cost savings using different input parameters for the multivariable regression model. For instance, we used the established definition of drug novelty rather than our novel definition of indication novelty and exchanged the number of available treatment options for the 5-year survival rates for each cancer as one of the pillars for unmet needs [37].

3 Results

A total of 123 cancer drugs with FDA approval for 308 indications between 2003 and 2020 were included in the analyses. Across all indications, monthly treatment costs amounted to a median of $16,013 (interquartile range 14,235–21,273) under the current uniform pricing policy. Medicare and Medicaid spent a total of $28.2 billion on these drugs in 2020. Descriptive statistics for the entire sample are included in Table 2.

Table 2 Descriptive statistics for the entire sample

Variable	Result
Innovativeness	
Addition to indication	40 (13)
Advance in indication	154 (50)
First in indication	114 (37)
Disease	
Solid	203 (66)
Hematologic	105 (34)
Orphan designation	
No	105 (34)
Yes	203 (66)
Trial phase	
I or II	131 (43)
III	177 (57)
No. of enrolled patients	307 (115–576)
Incidence per 100,000 US inhabitants	10 (5–68)
Prevalence per 100,000 US inhabitants	67 (17–155)
DALY per person	8 (6–16)
YLD per person	0.5 (0.3–0.7)
YLL per person	7 (5–16)
5-year survival rate, percentage (IQR)	72% (35–91)
Available treatment options	16 (12–38)
Total no. of indications	308 (100.0)

Data are presented as *n* (%) or median (interquartile range).

DALYs, disability-adjusted life-years; IQR, interquartile range; YLD, years lived with disability; YLL, years of life lost.

3.1 Value-Based ISP

Adopting a value-based ISP policy would result in an (average) increase of drug prices by 3.8% across all indications (Fig. 1 and Table 3). However, Medicare and Medicaid spending would reduce by a total of $3.0 billion or 10.6%. This is mainly a result of lower prices for non-orphan indications with a high prevalence, which offset higher prices for orphan indications with a low prevalence.

Prices for original indications would increase by 1.4%, and prices for the second (1.6%), third (1.7%), fourth (− 5.1%), and fifth or subsequent approvals (19.7%) would mostly increase. Spending on original indications would remain unchanged (0.2%), whereas spending would reduce on second (9.2%), third (16.5%), fourth (11.2%), and fifth or subsequent (19.2%) indications.

Spending would particularly reduce on full orphan drugs (16.3%), partial orphan drugs (7.6%), and non-orphan drugs (5.3%). Prices on orphan drugs for ultra-rare diseases would decline by 43.7%, for rare diseases by 7.8%, and for common diseases by 2.3%. Meanwhile, prices for non-orphan drugs would decline by 4.1%. Therefore, savings were particularly high for common diseases (17.7%), and lower savings would be realized for rare diseases (1.6%) and non-orphan diseases (5.8%). In contrast, 43.7% higher prices for ultra-rare diseases would increase spending by 36.3% ($80 million).

3.2 Value-Based Weighted-Average Pricing

Implementing a value-based weighted-average pricing policy would lower drug prices by a prevalence-weighted average of 4.6% across all indications. These price discounts would reduce Medicare and Medicaid spending by a total of $3.0 billion or 10.6%. Although the reduction in spending is similar between weighted-average and ISP, savings arose for different indications.

With the introduction of new indications, prices would decline by 1.1%, 4.0%, 7.1%, and 4.1% for second, third, fourth, and fifth or subsequent approvals, respectively. These price reductions would result in lower spending of 3.4%, 8.9%, 15.1%, 9.3%, and 17.2% for first, second, third, fourth, and fifth or subsequent approvals, respectively.

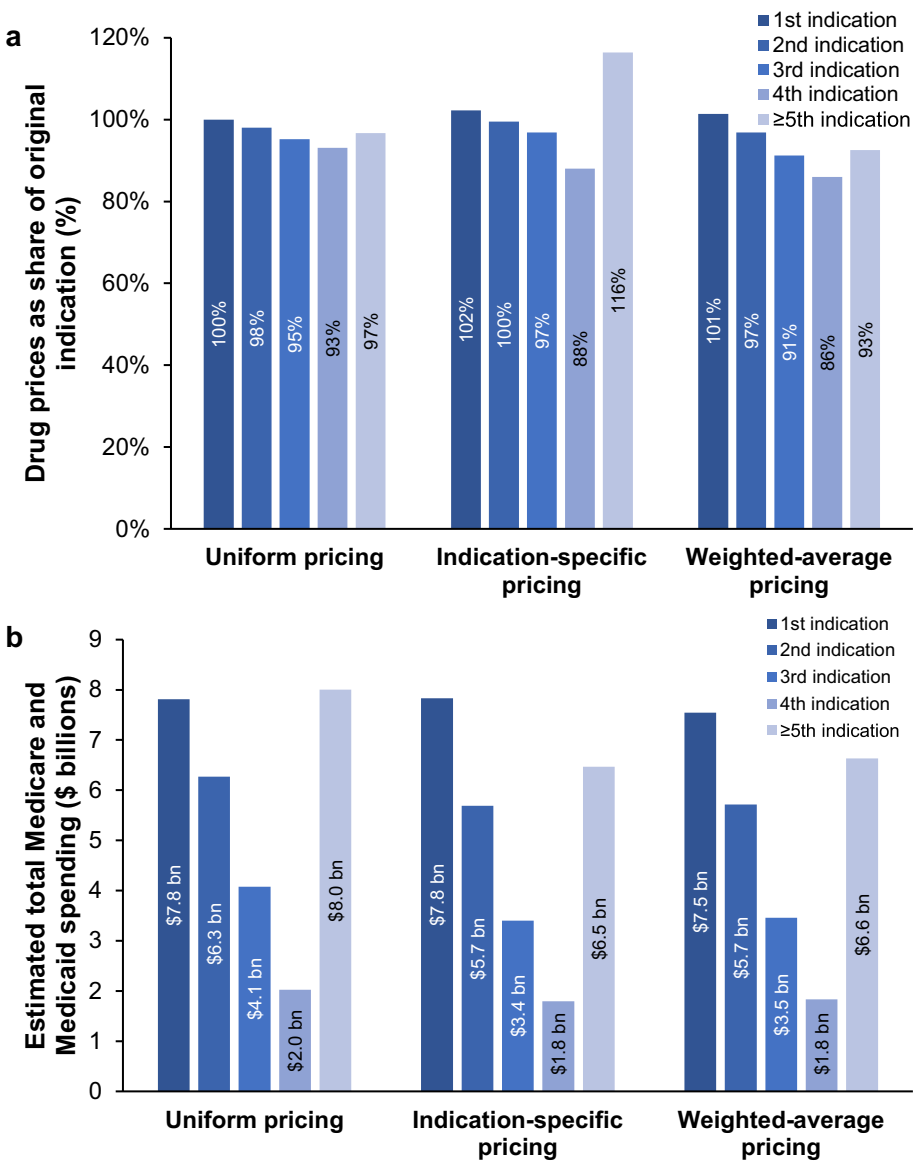

Fig. 1 Estimated cancer drug **a** prices and **b** spending under uniform pricing, value-based indication-specific pricing, and value-based weighted-average pricing. Uniform pricing represents the current policy under which a single price is assigned to drugs in the USA. We estimated prices and Medicare and Medicaid spending for our sample of anticancer drugs if a value-based indication-specific pricing or value-based weighted-average pricing policy were to be adopted in the USA. Drug prices are presented as a percentage of the original indication's cost. bn, billion

Spending on partial orphan drugs would decline by 7.6%, non-orphan drugs by 5.3%, and full orphan drugs by 16.2%. Prices on drugs for ultra-rare diseases would decline by 22.6%, for rare diseases by 12.1%, and for non-orphan diseases by 7.7%. Savings would be realized for non-orphan diseases (7.0%), rare orphan diseases (1.8%), and common orphan diseases (17.8%). In contrast to ISP, adopting weighted-average pricing would reduce spending on ultra-rare diseases by 25.0%.

3.3 Sensitivity Analysis

Results remained robust under sensitivity analyses with different input variables for the regression analysis and different PED (Table 4). Using drug instead of indication novelty would result in savings of 6.9% for value-based ISP and weighted-average pricing. Using the trial phase instead of the number of enrolled patients would result in savings of 12.8% for both policies. Results were marginally impacted by using prevalence instead of incidence rates, 5-year survival instead of number of available treatment options, or years of life lost instead of DALYs for the multivariable regression analysis.

In our base-case scenario, we assumed a PED of 0, indicating that drug usage is inelastic to price changes. However, the sensitivity analysis highlighted that elasticity inputs above 0 diminish expected cost savings as drug usage increases with lower prices. At a PED of 1, ISP would result in cost savings of 6.1% and weighted-average pricing in cost savings of 3.8%.

Table 3 Estimated Medicare and Medicaid spending and cost savings on cancer drugs under value-based indication-specific pricing and value-based weighted-average pricing in 2020, in millions ($US)

Variable	Uniform pricing	Indication-specific pricing			Weighted-average pricing		
	Total spending	Total spending	Δ spending (absolute)	Δ spending (%)	Total spending	Δ spending (absolute)	Δ spending (%)
Indication launch sequence							
1st indication	7815	7829	14	0.2	7547	−268	−3.4
2nd indication	6269	5693	−576	−9.2	5714	−555	−8.9
3rd indication	4076	3404	−672	−16.5	3459	−617	−15.1
4th indication	2023	1795	−227	−11.2	1835	−188	−9.3
≥ 5th indication	8006	6467	−1539	−19.2	6633	−1373	−17.2
Orphan drug type[a]							
Non-orphan drug	6970	6599	−370	−5.3	6599	−370	−5.3
Partial orphan drug	9490	8770	−720	−7.6	8764	−726	−7.6
Full orphan drug	11,729	9819	−1910	−16.3	9824	−1905	−16.2
Orphan disease type[b]							
Non-orphan disease	14,781	13,708	−1072	−7.3	13,746	−1034	−7.0
Common orphan disease	10,482	8630	−1851	−17.7	8618	−1863	−17.8
Rare orphan disease	2706	2550	−156	−5.8	2657	−49	−1.8
Ultra-rare orphan disease	221	301	80	*36.3*	166	−55	−25.0
Total	28,189	25,189	−3000	−10.6	25,187	−3001	−10.6

Uniform pricing represents the current base case scenario under which a single price is assigned to each drug in the US. We estimated Medicare and Medicaid spending on and cost savings for cancer drugs if a value-based indication-specific or weighted-average pricing policy was adopted in the US.

[a]Cancer drugs were stratified into full (only orphan indications), partial (orphan and non-orphan indications), and non-orphan (only non-orphan indications)

[b]Orphan indications were stratified according to the number of affected US inhabitants into common (> 200,000), rare (200,000-6600), or ultra-rare (< 6600)

4 Discussion

We estimate that Medicare and Medicaid could have realized cost savings of $3.0 billion (10.6%) with both value-based ISP or weighted-average pricing in 2020. These savings would be especially realized by reducing prices for low-value non-orphan follow-on indications for partial orphan drugs.

4.1 Value-Based Indication-Specific Pricing

We estimated that value-based ISP would reduce Medicare and Medicaid spending on supplemental indication approvals, particularly for non-orphan indications of partial orphan drugs. This is especially desirable given that supplemental indications were shown to be of lower value to patients and insurers [1, 27, 28]. Furthermore, partial orphan drugs were criticized for benefiting from high orphan drug prices for their non-orphan indications, resulting in substantial revenues and profit streams for manufacturers [3, 5, 7]. ISP could resolve these disputes. However, confirming Chandra and Garthwaite's theoretical expectations [12], ISP would also result in higher prices for patients who benefit most from new drugs, for example, patients with ultra-rare diseases. On the upside, pharmaceutical companies would be encouraged to especially develop high-value treatments for ultra-rare diseases. On the downside, this could lead to increased pharmaceutical expenditure in the long term. Moreover, the implementation of ISP remains challenging. It requires the tracking of drug usage across indications, which is currently not available across the entire USA. Given these technical challenges, alongside opposition from key stakeholders, scholars previously concluded that ISP is not feasible to implement (at least in the short term) [13].

4.2 Value-Based Weighted-Average Pricing

Similar to ISP, the adoption of value-based weighted-average pricing would reduce Medicare and Medicaid's expenditure on cancer drugs by 10.6%. These cost savings

Table 4 Sensitivity analysis, $US millions

Variable	Uniform pricing	Indication-specific pricing			Weighted-average pricing		
	Total spending	Total spending	Δ spending (absolute)	Δ spending (%)	Total spending	Δ spending (absolute)	Δ spending (%)
Regression input variables							
Base case	28,189	25,189	−3000	*−10.6*	25,187	−3001	*−10.6*
Drug instead of indication novelty	28,189	26,244	−1944	*−6.9*	26,237	−1951	*−6.9*
5-year survival instead of no. of available treatment options	28,189	25,089	−3100	*−11.0*	25,088	−3101	*−11.0*
YLL instead of DALYs	28,189	25,203	−2985	*−10.6*	25,202	−2987	*−10.6*
Trial phase instead of size	28,189	24,575	−3613	*−12.8*	24,575	−3614	*−12.8*
Prevalence instead of incidence	28,189	25,783	−2406	*−8.5*	25,780	−2408	*−8.5*
PED							
PED = 0.0 (base case)	28,189	25,189	−3000	*−10.6*	25,187	−3001	*−10.6*
PED = 0.1	28,189	25,316	−2873	*−10.2*	25,380	−2808	*−10.0*
PED = 0.2	28,189	25,443	−2746	*−9.7*	25,573	−2615	*−9.3*
PED = 0.3	28,189	25,569	−2619	*−9.3*	25,766	−2422	*−8.6*
PED = 0.4	28,189	25,696	−2492	*−8.8*	25,959	−2229	*−7.9*
PED = 0.5	28,189	25,823	−2366	*−8.4*	26,152	−2036	*−7.2*
PED = 0.6	28,189	25,950	−2239	*−7.9*	26,345	−1843	*−6.5*
PED = 0.7	28,189	26,077	−2112	*−7.5*	26,538	−1651	*−5.9*
PED = 0.8	28,189	26,203	−1985	*−7.0*	26,731	−1458	*−5.2*
PED = 0.9	28,189	26,330	−1858	*−6.6*	26,924	−1265	*−4.5*
PED = 1.0	28,189	26,457	−1732	*−6.1*	27,117	−1072	*−3.8*

Cost savings were re-calculated for scenarios with different input variables for the regression analysis and different PED values.

DALYs, disability-adjusted life-years; ISP, indication-specific pricing; PED, price elasticity of demand; YLL, years of life lost.

would be realized by sequentially lowering the drug's initial list price as new supplemental indications receive FDA approval. These results are consistent with a prior study that showed cancer drug prices declined with the introduction of each new indication in Germany and France (countries that employ weighted-average pricing) [27]. In contrast to ISP, the adoption of weighted-average pricing does not increase but reduces prices for drugs treating ultra-rare diseases. Thereby, weighted-average pricing could help to improve the financial sustainability of costly ultra-orphan drugs.

Medicare and Medicaid should, therefore, carefully examine the mechanisms of a weighted-average pricing system for its price negotiations as part of the Inflation Reduction Act of 2022 [46–48]. Given that the Secretary of Health and Human Services will be allowed to directly negotiate prices of the top-grossing drugs with manufacturers, weighted-average pricing considerations could support price proposition for top-selling drugs with multiple indications, especially partial orphans.

Nonetheless, there are several barriers to implementing weighted-average pricing across the entire USA [9, 11, 19, 20]. First, it requires an understanding that drug prices can be negotiated between insurers and manufacturers based on their value proposition for patients (value-based pricing). Second, value or benefit assessments must be conducted for each additional indication that receives FDA approval. Thereafter, payers and insurers must set or negotiate a price for each indication. These indication prices are then combined with the anticipated or monitored indication usage to calculate a single drug price. Given that drugs are still sold for a single price under weighted-average pricing, it is more feasible than ISP to implement in the current US healthcare system. However, similar to ISP, politicians must propose changes to the current US drug price system and overcome opposition from pharmaceutical benefit managers, pharmaceutical companies, and other stakeholders that stand to lose with a new pricing policy.

4.3 Short- and Long-Term Effects of Value-Based Indication-Specific Pricing

In this study, we estimated static short-term price and cost savings for value-based ISP and weighted-average pricing.

However, economists previously debated that the dynamic long-term economic effects of ISP on social welfare, consumer surplus, and producer surplus may differ (Fig. 2) [12, 21, 26, 49]. Bach [21], who assumed that US prices are set based on the first high-value indication (single-highest price), argued that ISP would increase patient access to new treatments, reduce prices for low-value indications, and, thereby, increase social welfare, payers' spending and producer surplus (Fig. 2a). In contrast, Chandra and Garthwaite [12], who assumed that US prices are set based on the lowest-value indication (single-lowest price), argued that (overall) ISP would increase drug prices for high-value indications, increase payers' spending, and transfer consumer surplus to producers while social welfare would remain constant (Fig. 2b). Similarly, a recent simulation study highlighted that ISP would reduce consumer surplus and thereby patient welfare relative to a single weighted-average pricing policy [50].

Under a single drug price system, the adoption of value-based ISP encourages pharmaceutical companies to launch new low-value indications (Fig. 2c). Theoretically, with a single drug price, companies would be incentivized to withhold these indications as they would deteriorate this single price [27–29]. Similarly, insurers would be reluctant to reimburse indications for a price exceeding the indication's incremental value. These additional new indication launches would increase patient access to new therapeutic options. This expanded access would, of course, increase consumer surplus and producer surplus and thereby maximize social welfare. In the short term, the additional approval of new indications would also increase payers' spending. Nonetheless, this additional spending would increase enrollees' health benefits, if ISP were to be adopted as part of a formal health technology assessment (HTA) process that uses value-based pricing. In a system with a formal HTA process, payers only reimburse new cost-effective indications, for example, indications with an incremental cost-effectiveness ratio below the nation's willingness-to-pay threshold. A formal HTA process essentially ensures that pharmaceutical companies are only incentivized to develop new indications that are worthwhile for patients and the health system.

The long-term effects of ISP are more complex (Fig. 2d). As previously explained, pharmaceutical companies are incentivized to research, develop, and launch more indications under ISP. The increased number of new indications would likely intensify competition at the indication level. Economic theory suggests that the market entry of new competitors drives down prices, even below the national willingness-to-pay threshold [26]. These dynamic competitive effects of ISP could, thereby, increase consumer surplus, while reducing producer surplus and payers' spending. However, previous studies analyzing brand–brand competition in the pharmaceutical market could not confirm that the entry of new competitors would result in a reduction in drug prices [25, 51]. Furthermore, our sensitivity analysis highlighted that the estimated cost savings are subject to consumers' underlying PED. As a consequence, price reductions for low-value indications could increase consumer demand and thereby increase payers' overall spending in the long term. On the other hand, a positive PED also implies that higher prices for high-value indications could pose a barrier for consumers to purchase drugs that deliver substantial value to them and, therefore, reduce spending (especially in the USA). Our analysis suggests that, because low-value indications are typically for diseases with a higher prevalence and high-value indications are typically for diseases with a lower prevalence, the effects of a positive PED would likely diminish the estimated cost-saving potential.

4.4 Limitations

There are several limitations inherent to our analysis. First, our model did not capture the upfront investments and ongoing administrative costs of introducing ISP or weighted-average pricing. Presumably, the cost of introducing weighted-average pricing would be lower than that for ISP, given that the latter requires the introduction of new information technology and prescription systems across healthcare providers in the USA, whereas the former only entails a novel way to calculate, negotiate, and assign single drug prices. Furthermore, we only calculated cost savings for cancer drugs. Adopting a new pricing policy would, of course, also reduce costs for drugs of other therapeutic areas. This would also mean that upfront investments in introducing these novel pricing systems could be shared (and likely be easily covered by the savings realized) across all therapeutic areas. Second, we conducted a retrospective analysis. Cost savings that Medicare and Medicaid may realize in the future may differ. Nonetheless, our model highlights the mechanism of ISP and weighted-average pricing policies, particularly underlining their implications for partial orphan drugs and indications for ultra-rare diseases. Third, other pricing mechanisms, such as indication-specific discounts on drug prices, single-lowest drug prices, or indication-specific managed entry agreements, are currently employed in countries but not included in our analysis [9, 11]. Although these policies impact drug spending and usage, they do not affect list prices—the underlying main variable of our model. Fourth, our analysis was based on list prices without considering closely guarded confidential rebates/discounts. Results may therefore vary for net prices and patient out-of-pocket spending, although rebates and discounts are small for anticancer drugs [35]. Further, price and spending data were evaluated for Medicare and Medicaid. Within the heterogeneous US healthcare market, drug prices may substantially vary across insurers, states, and insurance schemes.

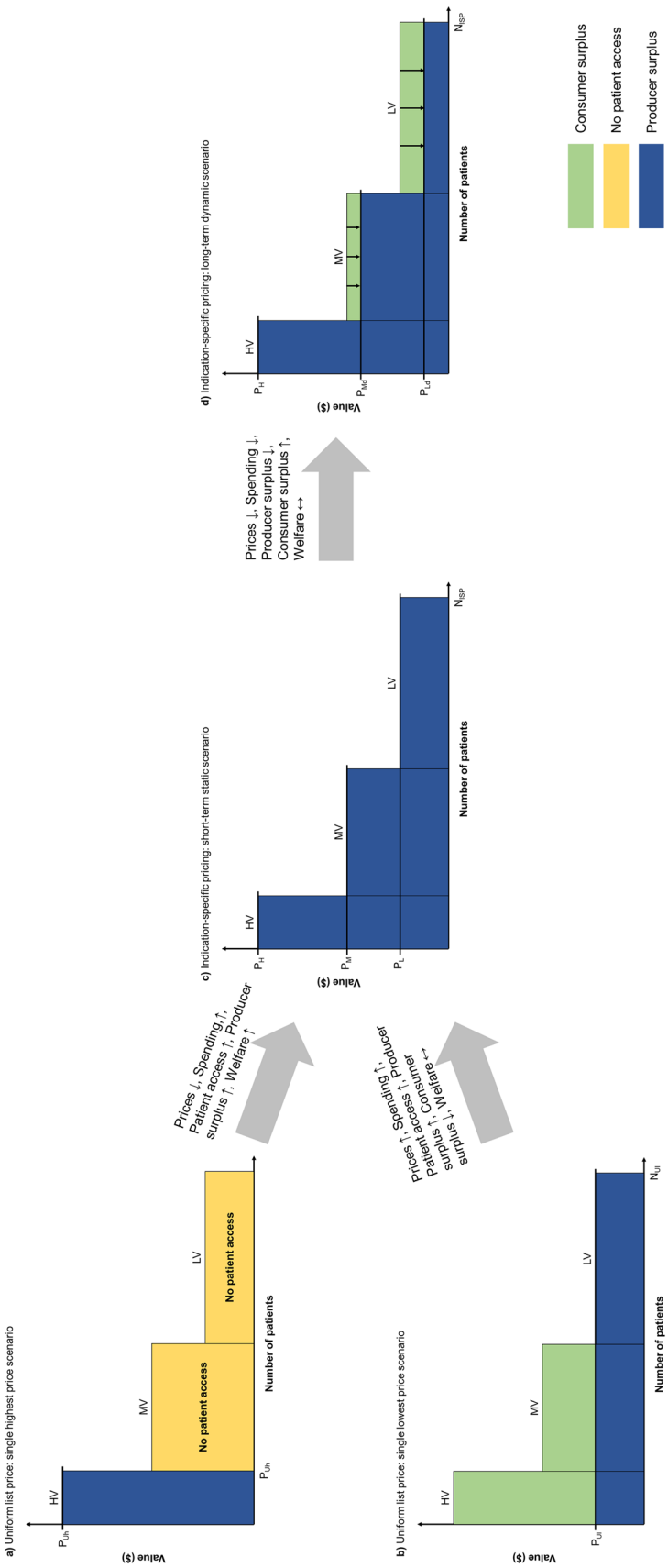

Fig. 2 Short- and long-term effects of value-based indication-specific pricing on consumer surplus, producer surplus, prices, spending, and social welfare. Under a single-highest list price scenario, producers only sell their drug at price P_{Uh} for the HV indication to N_{Uh} patients. Patients in the MV and LV indication may not have access to the drug because insurers are reluctant to reimburse drugs for a price exceeding the indication's incremental value. In the short term, adopting indication-specific pricing would reduce prices, increase spending, increase patient access, increase producer surplus, and thereby increase welfare. Under a single-lowest list price scenario, producers sell their drug at price P_{Ul} to N_{Ul} patients with indications HV, MV, and LV. Adopting ISP would increase prices, increase spending, increase producer surplus, and increase welfare, and patient access would remain unchanged. In the long term, ISP encourages the development of new MV and LV indications. The dynamic market entry of new indications under this scenario, with fierce competition between these new indications, would lower prices for the MV and LV indications to P_{MVd} and P_{LVd}. Graphs adapted from Towse (2018) [26]. HV, high value; LV, low value; MV, medium value

5 Conclusion

In this study, we estimated that Medicare and Medicaid could reduce expenditure on new cancer drugs with FDA approval by 10.6% by adopting value-based ISP or value-based weighted-average pricing. However, prices for ultra-rare orphan drugs would increase under ISP. Furthermore, there are several barriers to adopting ISP in the USA. In contrast, weighted-average pricing would also reduce prices for ultra-rare orphan drugs and be more compatible with the current US pricing system. In conclusion, value-based ISP and weighted-average pricing could help limit the growing burden of rising cancer drug prices on the US healthcare system by aligning the value and price of drugs with multiple indications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40273-024-01448-x.

Acknowledgements The authors thank Prof. Dr. Hendrik Jürges, University of Wuppertal, for his comments on an early draft of the manuscript. None of the additional contributors received any compensation.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Author contributions D.T.M. and T.M. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: All authors. Administrative, technical, or material support: All authors. Study supervision: All authors.

Conflict of interest The authors declare that they have no conflicts of interest.

Data sharing statement All data used in this study were in the public domain. All data relevant to the study are included in the article or uploaded as supplementary information.

Patient consent for publication Not applicable.

Ethics approval None needed.

Data availability All data used in this study were in the public domain. All data relevant to the study are included in the article or uploaded as supplementary information.

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