



Relationship between costs and clinical benefits of new cancer medicines in Australia, France, the UK, and the US

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ABSTRACT

As cancer drug prices rise, it remains unclear whether the cost of new interventions is related to their beneficial impact for patients at a societal-level. Using data for 2003–2015 from the IQVIA MIDAS® dataset, the relationship between cancer drug costs and drug clinical benefits was studied in four countries with different approaches to drug pricing. Summary measures of drug clinical effects on overall survival, quality of life, and safety were obtained from a review of health technology assessments. Mean total drug costs for a full course of treatment were estimated using standard posology for each medicine and in each country. Regression analysis was used to test whether, at a societal-level, the cost of recently licensed drugs is related to their beneficial impact for patients. Across all eligible medicines, average treatment costs were lowest in France and Australia and highest in the UK and US. Compared with Australia, France, and the UK, cancer medicines were on average between 1.2 and 1.9 times more expensive in the US, where the average total per patient cost for treatment was \$68,255.17. Costs for new cancer medicines are high and, at best, only weakly associated with drug clinical benefits. The strength of this relationship nevertheless varied across countries. Some new cancer drugs—particularly in the US—may be neither affordable nor clinically beneficial over existing treatments. While all countries can benefit from strategies that more robustly align price with therapeutic benefit in cancer drugs, the US stands out in its opportunity to improve both affordability and value in cancer drug treatment.

1. Introduction

Prices have risen faster for cancer drugs than those associated with most other diseases (Bach, 2009; Savage et al., 2017; Vogler et al., 2016). These trends have led to concerns that escalating costs may cause health insurers and payers to restrict access to high-cost treatments (Goldman et al., 2007), and make it difficult for patients to afford, or remain adherent with, life-extending medicines, ultimately impacting patient care (Bestvina et al., 2014; Experts in Chronic Myeloid Leukemia, 2013; Weaver et al., 2010).

Notwithstanding important questions about the affordability of new drugs (World Health Organization, 2018), some have suggested that high prices for new cancer drugs may be justified if they offer equally large clinical benefits (Mailankody and Prasad, 2015). The concept of healthcare value as health outcomes achieved per dollar spent underpins many of the conceptual frameworks have been proposed to assess the value of new cancer drugs in relation to existing treatments (Chandra et al., 2016; Frakt, 2016; Maervoet et al., 2016; Neumann and

Cohen, 2015; Porter, 2010; Schnipper et al., 2016, 2015). Their goals and methods nevertheless often differ (Leopold et al., 2018; Neumann and Cohen, 2015), raising questions on how to reliably compare the clinical impact and cost of new drugs in medical oncology and whether the cost of interventions is related to their beneficial impact for patients at a societal-level (Schnipper et al., 2015).

In the United States and other developed countries, different combinations of governmental interventions and market-based strategies are used to reign in on the cost-benefit relationship in prescription drug markets. These may manifest as generic competition, price discounts and freezes, profit controls, reference pricing, and health technology assessment (HTA) in price setting (Carone et al., 2012; US Department of Commerce, 2004).

For instance, France has traditionally negotiated drug prices directly with manufacturers on the basis of HTA, including comparative clinical efficacy data, after they have been licensed for use. Drugs that are deemed to provide little to no added clinical benefit over existing treatments are only publicly listed if they come at a lower price or

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induce cost savings (Haute Autorité de Santé, 2014; Rodwin, 2019). While the United Kingdom generally permits free drug pricing for licensed medicines, a national rate-of-return regulation scheme includes mechanisms for price cuts and profit controls. Cost-effectiveness analysis is also used as a key criterion in drug reimbursement, which may indirectly pressure manufacturers to lower drug prices when cost-effectiveness is not realized (Schoonveld, 2015). The impact from this policy may be particularly strong in oncology, as all newly licensed cancer drugs are now referred to the national HTA agency for recommendations on whether they should be made available for routine commissioning throughout the National Health System (NHS) (NHS England Cancer Drugs Fund Team, 2016). Historically a model for governments seeking to contain drug expenditures (Doran and Alexander Henry, 2008), Australian drug prices have generally been characterized as low to comparable with those observed elsewhere (Australian Government Productivity Commission, 2001; Kanavos et al., 2013; Medbelle, 2019; Vogler et al., 2016). Australian authorities use internal reference pricing for drugs that are deemed to be clinically comparable to existing treatments, and recommendations for public coverage may be based on pharmacoeconomic evaluations and cost-minimization assessments (Verghese et al., 2019; Vitry et al., 2015). Single- or multi-source medicines that are deemed to be reimbursable may also be subject to price negotiations, rebates, mandatory price reductions, and statutory price disclosure (Paris and Belloni, 2014; Vitry et al., 2015). Managed Entry Agreements (MEAs) may be used to optimize cost-effective commissioning of drugs when their clinical benefits or financial impact are uncertain. When, how, and for what purpose these contractual agreements are used nevertheless varies across countries (Pauwels et al., 2017; Robinson et al., 2018; Verghese et al., 2019). In contrast, drug pricing policies in the United States are fragmented (Blumenthal and Squires, 2016) and do not generally focus on enhancing the cost-effective use of medicines. In all settings, the use and impact of market-regulating strategies may also be influenced by assessments of health prospects, treatment intent, unmet health needs, and availability of alternative treatments (Dolan et al., 2005; Simoens, 2011; Tordrup et al., 2014; Wellman-Labadie et al., 2010), with disease type and rarity potentially influencing cancer drug pricing (Chicoye and Chhabra, 2009; Drummond et al., 2007; Simoens, 2011; Turkstra et al., 2015).

The extent to which strategies currently used in different countries ultimately deliver value to patients remains an important question. In the United States, some have reported a positive correlation between the episode treatment price of new medicines—defined as each drug's monthly cost to the Medicare program—and incremental survival benefits (Howard et al., 2015). Important issues nevertheless remain unexplored. First, the lack of international comparisons in these studies leaves readers unable to judge the strength of correlation estimates in any single country. Second, treatment duration varies across cancer medicines, making month-denominated drug costs an imprecise measure of the total financial impact from treatment and biasing drug cost and value comparisons. The use of annualized costing estimates in other settings is equally susceptible to this bias (Mailankody and Prasad, 2015) and reflects the lack of a standard approach for estimating cancer drug treatment costs from unit prices. Finally, regression-based studies of this sort should consider measures of efficacy, as well as other clinical outcome measures that matter to patients, including quality of life and safety (Schnipper et al., 2015).

In addressing these gaps, this study tests the value-based proposition that the cost of cancer medicines newly approved between 2003 and 2013 does indeed bear a relationship to their beneficial impact to patients in four countries that take different approaches to the regulation of drug pricing: Australia, France, the United Kingdom and the United States (World Health Organization, 2015).

2. Methods

2.1. Sample selection

All New Molecular Entities approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) between 2003 and 2013 with an initial, primary anti-cancer indication were eligible for inclusion. This time period was chosen to coincide with previous research on the clinical risks and benefits associated with cancer medicines (Salas-Vega et al., 2016). Supplemental applications, new non-active treatments, licensing supplements, labeling revisions, and new or modified indications were not considered, as the benefits from new drugs for non-initial indications may be unknown at the time of launch, and thus may be difficult to incorporate into pricing decisions (Howard et al., 2015). To reconcile across available data sources, cancer drugs were also excluded if they had been approved to treat multiple disease conditions ($n = 9$), or if consumer list pricing data were not available from the IQVIA Multinational Integrated Analysis System (MIDAS®) dataset ($n = 5$).

2.2. Data sources

Average annual pricing data for cancer drugs marketed in Australia, France, the United Kingdom, and the United States was obtained from the IQVIA MIDAS® dataset. MIDAS® gathers international drug sales and pricing data via periodic audits corresponding to all domestic channels of distribution and has previously been used in comparative pricing and expenditure studies (Danzon and Furukawa, 2006; Divino et al., 2016; Kanavos et al., 2013). Our MIDAS® extract provided cancer medicine list prices—set by manufacturers with or without input from national regulators—collected at the point-of-sale from both hospital and retail pharmacy settings for each year between 2003 and 2015. Cancer drugs were defined by IQVIA as any molecule with an L01 or L02 Anatomical Therapeutic Chemical (ATC) classification. Adjuvant therapies and products with other ATC codes were excluded from this analysis. Due to data licensing restrictions, this study does not publish any list pricing data from MIDAS®.

Summary measures of the comparative effect on overall survival (OS), quality of life (QoL), and safety from the cancer drugs included in our sample were adopted from previous publications (Salas-Vega et al., 2016). Drug-related effects on OS were coded as a continuous variable, while QoL and safety effects were coded as overall improvement, reduction, mixed evidence, or no difference relative to existing standards of care. In all cases, summary measures of clinical benefit were based on a review of English-language HTA agency technology evaluations from Australia, France, and the United Kingdom that were published between 2003 and May 2015. This time period was chosen to allow for potential delays between initial drug licensing and publication of HTA evaluations (Jaksa et al., 2017). The US is a major producer of HTA evidence, with for instance the United States Centers for Medicare & Medicaid Services (CMS) and private insurers commissioning HTA reports on new medical technologies to inform coverage decisions at national and local levels, the Veterans Health Administration (VHA) performing pharmaceutical HTA through its Pharmacy Benefits Management Strategic Healthcare Group, and the Institute for Clinical and Economic Review (ICER) evaluating the clinical and economic value of new health technologies. However, there is still no national HTA agency in the US that provides guidance on coverage, pricing, or reimbursement decisions. Nevertheless, unlike licensing authorities such as the FDA, HTA agencies may have the authority to require submission of all applicable clinical data, published and unpublished; their assessments may include any clinical evidence comparing the clinical performance of new medicines against that of the therapies that would most likely be replaced by the new intervention (Haute Autorité de Santé, 2009; National Institute for Health and Care Excellence, 2016; Panteli et al., 2016; Pharmaceutical Benefits Advisory Committee, 2014); and they

systematically assess clinical efficacy, quality of life, and safety when evaluating new medicines, with the former often defined in terms of patient survival and length of life (Australian Government Department of Health, 2016; Haute Autorité de Santé, 2012; NICE, 2013). HTA agency recommendations on drug coverage, pricing, or reimbursement were not incorporated into this study.

FDA approved primary indications, date of initial FDA approval, and date of first FDA-approved new or modified indication (target), new dosing regimen, or modified patient population through Jan 1, 2016 were obtained from FDA prescription drug labels and associated medical and statistical reviews. For the EMA, these data were obtained from European public assessment reports (EPARs), and by reviewing documents from the EMA's drug assessment history. For Australia, they were obtained by conducting a search of Australian Register of Therapeutic Goods (ARTG) registrations, Australian Public Assessment Reports (AusPARs), Therapeutic Goods Administration (TGA) Product Information documents, the search engine of the TGA website, the TGA's Orphan Drugs registry, the Pharmaceutical Benefits Scheme (PBS) A-Z drug list, and Adis Insight (Springer) drug profiles. Data from each country was linked to the corresponding drug-indication.

Pre-defined recommendations on treatment dose and duration were extracted from FDA and EMA prescription drug labels that corresponded to initial drug licensure. In some instances, licensing authorities may recommend that treatment continue until clinical benefits cease, progressive disease occurs, or unacceptable toxicity develops, [e.g. (European Medicines Agency, 2010; US Food and Drug Administration, 2007, 2012, 2013)] and clinical trials may also be designed for to discontinue treatment or allow for patient cross-over once symptoms deteriorate, toxicity develops, or progression occurs. Estimates of the treatment duration required to achieve the reported clinical benefits observed in approval trials were therefore sought from FDA reviews and prescription drug labels if end-of-therapy recommendations were instead based on symptom assessment.

Latest available anthropometric reference data were obtained for Australia (2014–2015) by querying the Australian Health Survey; (Australian Bureau of Statistics, 2015) for France (2006–2007), by contacting the authors of Castetbon et al., (2009); for the United Kingdom (2010), by querying the Health Survey for England 2010 (NHS Digital, 2011); and for the United States (2007–2010), by querying the Anthropometric Reference Data for Children and Adults: United States, 2007–2010 dataset from the United States Centers for Disease Control and Prevention (Fryar et al., 2012).

Orphan drug status in the United States and European Union and Anatomical Therapeutic Chemical (ATC) classifications for approved indications were obtained from FDA and EMA registries of orphan drug designations and the World Health Organization Collaborating Centre for Drug Statistics Methodology ATC/Defined Daily Doses (DDD) index. Australian orphan drug status was obtained from the TGA's orphan drug registry. A clinical expert also used approved primary indications to classify all newly licensed cancer medicines by their therapeutic target, which included malignant ascites, as well as thyroid, gastrointestinal (GI), lung, hematological, prostate, skin, renal, and breast malignancies.

3. Analysis

3.1. Cancer drug costs

Standard posology was used to estimate the total per patient cost for drug acquisition over the expected period of treatment with each included medicine in Australia, France, the United Kingdom, and the United States (DrugAbacus, 2017; Goldstein et al., 2017; Herold and Hieke, 2003; Iyengar et al., 2016; Osterlund et al., 2016; Ray et al., 2010). Country-specific anthropometric reference data were used to adjust for international differences in the weight/body surface area (BSA) of treatment populations, and were stratified by age and sex to

account for age- (adult/pediatric) and sex-specific drug indications. MIDAS® euro pricing for all countries included in our analysis was converted to US dollar equivalents using period average euro-USD exchange rates for Q4 2015, the delivery quarter of the QuintilesIMS dataset, and nominal pricing was converted to constant 2015 terms by using consumer price inflation indices from the World Bank. Costing estimates were calculated over the first three years following market launch, and were censored once new or modified indications, dosing regimens, or modifications to the approved patient population were approved for the drugs in our sample. Cost analysis was used to describe mean estimates of the total, per patient cost borne by payers for drug treatment.

3.2. Cancer drug costs versus clinical benefits

Simple and multiple linear regression analysis was used to test the value-based proposition that the cost of cancer drugs is associated with their beneficial impact to patients. Models were designed in accordance with the American Society for Clinical Oncology's (ASCO) Value Framework, which recommends that value be assessed by comparing the cost of cancer regimens with their clinical efficacy (overall survival, when possible), and effects on toxicity and quality of life (Schnipper et al., 2016, 2015), implicitly defining value by the strength of positive associations between measures of drug clinical benefits and cost. The relationship between measures of drug clinical benefits and cancer drug spending may vary by country; interaction effects were therefore considered. Regression analysis used robust standard errors, square root transformed drug cost estimates in the first year of their marketing, and modeled OS as a continuous variable and QoL and safety as categorical variables. As they independently influence cancer drug pricing (Chicoye and Chhabra, 2009; Drummond et al., 2007; Simoons, 2011; Turkstra et al., 2015), and may affect assessments of the relative clinical impact of new medicines, drug indication and orphan status were adjusted for in regression analyses. Ethical approval was not required for this study as human subjects were in no way involved and no patient-level data was used. For more information on study methods, please refer to the Online Supplementary.

4. Results

62 cancer molecules were approved by the United States (FDA) and European Union (EMA) between 2003 and 2013 with a primary indication for oncology. Of those, treatment duration and recommended dosing information was unavailable for 6 drugs. Another 9 were approved for multiple primary indications or disease conditions, and pricing data was not available from IQVIA for 5 drugs. The remaining 42 drugs were included in costing analyses (Table 1). Of those, 36 were assessed for OS by at least one of the three HTA agencies through May 2015 and were therefore included in subsequent analyses examining the link between drug costs and clinical benefits.

4.1. Cancer drug costs

For all cancer drugs approved between 2003 and 2013 for which data was available, drug costs were on average lowest in France and Australia and highest in the United Kingdom and United States (Fig. 1). The average per patient cost for treatment in these settings equaled \$35,114.98, \$35,499.50, \$55,616.63, and \$68,255.17 respectively, meaning that cancer drugs were on average between 1.2 and 1.9 times more expensive in the United States compared with Australia, France, and the United Kingdom in the first year of drug marketing. This finding persisted after limiting the sample to drugs that were available in all four countries. Per patient drug costs for treatment also remained lowest in Australia (\$38,621.04) and France (\$42,888.09) in the third year of drug marketing and highest in the United Kingdom (\$56,959.31) and the United States (\$76,888.09).

Table 1
Cancer drug sample.

Active ingredient	Indication ¹	Comparator(s)	Total Expected Drug Cost per Patient for Treatment ²			
			Australia	France	UK	US
Ascites						
catumaxomab	Ascites (EMA)	paracentesis	.	.	\$10,001-\$30,000	.
Breast						
trastuzumab emtansine	Breast cancer	lapatinib + capecitabine	\$30,001-\$50,000	\$50,001-\$70,000	\$90,001-\$110,000	> \$110,000
eribulin	Breast cancer	TPC	\$10,001-\$30,000	\$10,001-\$30,000	\$30,001-\$50,000	\$50,001-\$70,000
ixabepilone	Breast cancer	n/a	.	.	.	\$50,001-\$70,000
lapatinib	Breast cancer	capecitabine monotherapy	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000
pertuzumab	Breast cancer	trastuzumab + docetaxel	\$50,001-\$70,000	\$50,001-\$70,000	\$90,001-\$110,000	> \$110,000
bevacizumab	Colorectal carcinoma	IFL/5-FU/LV	\$30,001-\$50,000	\$10,001-\$30,000	\$30,001-\$50,000	\$50,001-\$70,000
cetuximab	Colorectal carcinoma	BSC	\$30,001-\$50,000	\$30,001-\$50,000	\$30,001-\$50,000	\$90,001-\$110,000
panitumumab	Colorectal carcinoma	BSC/cetuximab (safety)	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000	\$30,001-\$50,000
regorafenib	Colorectal cancer	placebo	> \$110,000	\$10,001-\$30,000	\$10,001-\$30,000	\$30,001-\$50,000
ziv-aflibercept	Colorectal cancer	placebo	.	\$10,001-\$30,000	\$10,001-\$30,000	\$50,001-\$70,000
azacitidine	MDS	conventional care	< \$10,001	\$70,001-\$90,000	> \$110,000	\$90,001-\$110,000
bendamustine	Lymphocytic leukemia	chlorambucil	.	< \$10,001	\$10,001-\$30,000	\$50,001-\$70,000
bortezomib	Multiple myeloma	high-dose dexamethasone	< \$10,001	\$30,001-\$50,000	\$30,001-\$50,000	\$30,001-\$50,000
carfilzomib	Multiple myeloma	n/a	.	.	\$90,001-\$110,000	\$90,001-\$110,000
clofarabine	ALL	non-comparative	\$70,001-\$90,000	\$90,001-\$110,000	> \$110,000	> \$110,000
decitabine	MDS	n/a	.	\$30,001-\$50,000	\$50,001-\$70,000	\$30,001-\$50,000
ibrutinib	MCL	n/a	\$90,001-\$110,000	\$70,001-\$90,000	> \$110,000	> \$110,000
nelarabine	ALL/LL	non-comparative	.	\$10,001-\$30,000	\$30,001-\$50,000	\$30,001-\$50,000
obinutuzumab	CLL	chlorambucil	\$30,001-\$50,000	.	\$50,001-\$70,000	\$50,001-\$70,000
ofatumumab	CLL	chlorambucil	\$50,001-\$70,000	\$50,001-\$70,000	\$70,001-\$90,000	> \$110,000
romidepsin	Cutaneous lymphoma	n/a	.	.	.	> \$110,000
roxolitinib	Myelofibrosis	BSC	\$30,001-\$50,000	\$30,001-\$50,000	\$70,001-\$90,000	\$50,001-\$70,000
tositumomab	NHL	n/a	.	.	.	< \$10,001
vorinostat	Cutaneous lymphoma	BSC	.	.	.	\$50,001-\$70,000
Lung						
afatinib	NSCLC	erlotinib/gefitinib	\$30,001-\$50,000	\$30,001-\$50,000	\$50,001-\$70,000	\$90,001-\$110,000
crizotinib	NSCLC	pemetrexed	< \$10,001	\$50,001-\$70,000	\$70,001-\$90,000	\$70,001-\$90,000
erlotinib	NSCLC	placebo/BSC	\$10,001-\$30,000	< \$10,001	\$10,001-\$30,000	\$10,001-\$30,000
gefitinib	NSCLC	paclitaxel + carboplatin	< \$10,001	.	\$10,001-\$30,000	< \$10,001
Prostate						
abiraterone acetate	Prostate cancer	BSC (prednisolone)	\$10,001-\$30,000	\$10,001-\$30,000	\$30,001-\$50,000	\$30,001-\$50,000
cabazitaxel	Prostate cancer	mitoxantrone	\$30,001-\$50,000	\$50,001-\$70,000	\$70,001-\$90,000	\$90,001-\$110,000
degarelix	Prostate cancer	leuprorelin + LHRH agonists	< \$10,001	< \$10,001	< \$10,001	< \$10,001
enzalutamide	Prostate cancer	placebo	\$10,001-\$30,000	\$30,001-\$50,000	\$50,001-\$70,000	\$70,001-\$90,000
Renal						
axitinib	RCC	BSC	\$30,001-\$50,000	\$30,001-\$50,000	\$50,001-\$70,000	\$70,001-\$90,000
everolimus	RCC	BSC	.	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000
pazopanib	Advanced RCC	BSC/interferon-alfa	\$10,001-\$30,000	\$10,001-\$30,000	\$30,001-\$50,000	\$50,001-\$70,000
sorafenib	RCC	BSC	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000	\$10,001-\$30,000
temsirolimus	RCC	interferon-alfa	.	< \$10,001	\$10,001-\$30,000	.
Skin						
dabrafenib	Melanoma	dacarbazine/vemurafenib (safety)	\$30,001-\$50,000	\$30,001-\$50,000	\$50,001-\$70,000	\$30,001-\$50,000
ipilimumab	Melanoma	dacarbazine	.	.	> \$110,000	> \$110,000
trametinib	Melanoma	dabrafenib	\$10,001-\$30,000	.	\$30,001-\$50,000	\$30,001-\$50,000
Thyroid						
cabozantinib	Medullary thyroid cancer	placebo	.	.	> \$110,000	.

¹ EMA indication used in instances where FDA approval was not available. MDS = myelodysplastic syndromes; ALL = acute lymphoblastic leukemia; CLL = Chronic lymphocytic leukemia; LL = lymphoblastic lymphoma; MCL = Mantle cell lymphoma; NHL = Non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma. ² Drug costs were not estimated if drug pricing information was unavailable for countries within our period of analysis, e.g. if medicines were not licensed for sale. Medicine costing bins are defined in terms of 2015 USD. Drug sample selection and parameters, as described in Methods section.

The total expected per patient cost of cancer drugs over a typical duration of treatment varied widely. Among the 25 drugs for which data was available from all four countries, sorafenib was associated with the smallest cost difference between the least and most expensive country (27%) in its first year of marketing. Another 4 were associated with a cost difference of between 33% (degarelix, lapatinib) and 88% (pazopanib); 7 of between 102% (dabrafenib) and 138% (sorafenib); 5 of between 158% (pertuzumab) and 197% (crizotinib); and 5 of greater than or equal to 213% (abiraterone, enzalutamide, trastuzumab emtansine, bortezomib, and azacitidine), all of which cost the least in Australia.

4.2. Cancer drug costs versus clinical benefits

Overall survival benefits were, in general, positively associated with the total expected per patient drug cost for a typical course of treatment (Fig. 2). However, the magnitude of that association varied across the four countries that were considered. Simple linear regression showed that gains in overall survival significantly predicted total per patient drug costs for a typical course of treatment in the United Kingdom in the first year that drugs were marketed ($b = 9.86$, $p = 0.04$), with overall survival benefits alone accounting for 12% of the variability in drug costs. A positive, albeit weaker, relationship was also observed in France ($b = 7.15$, $p = 0.07$). Correlation coefficients were not significantly different from zero in the United States ($b = 7.07$, $p = 0.17$) or Australia ($b = -1.69$, $p = 0.79$). Similar results were observed in

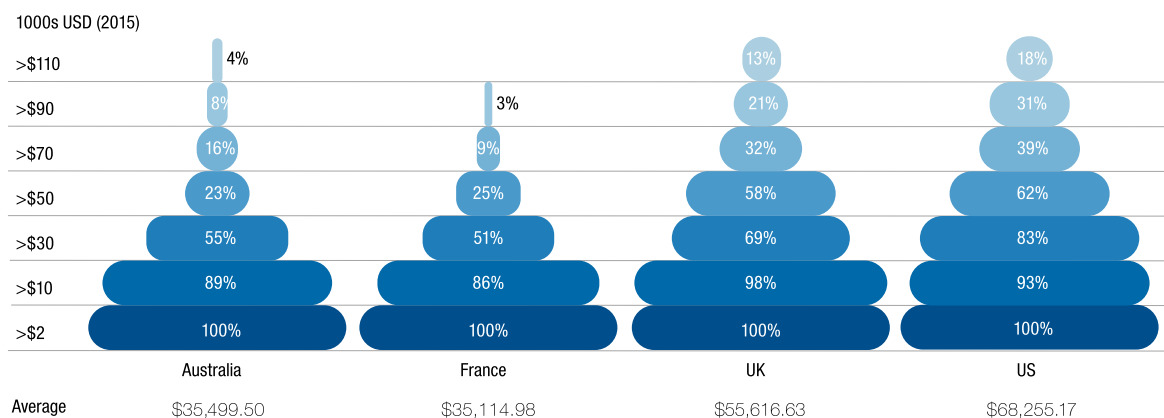


Fig. 1. Total expected cost of cancer medicines over a typical duration of treatment in the first year of their marketing (percentage share of all eligible cancer medicines in each country). Bins are defined in terms of thousand 2015 USD. Authors' analysis of data, as described in Methods section.

subsequent years of drug marketing: overall survival benefits were positively associated with drug costs corresponding to the second year of drug marketing in France ($b = 8.85$, $p = 0.02$) and both the second ($b = 10.96$, $p = 0.03$) and third ($b = 10.53$, $p = 0.04$) years of drug marketing in the United Kingdom. Drug costs tended to rise with improvements in quality of life in France and the United Kingdom, but did not increase with improvements in safety in any setting (Fig. 2).

Including drug-related effects on OS, QoL, and safety in multiple regression analysis increased the predictive power of the regression model (Table 2), suggesting that these measures of drug clinical benefit can help explain drug costs more than treatment descriptors alone. Nevertheless, a majority of the model's explanatory power came from accounting for drug-related effects on OS and quality of life. Breast, GI, hematological, prostate, skin, and thyroid indications, for example, were associated with significantly higher drug costs than the reference malignant ascites indication. The association between orphan status and higher drug costs under model (3)—preferred based on the adjusted R^2 statistic—also approached statistical significance ($p = 0.06$).

Compared to Australia, interactions between country and OS benefits on cancer drug costs were positive and significant in the United Kingdom and France under the preferred model (3), and their magnitudes varied between countries. Interaction terms between there being no drug-related QoL effect and both the United Kingdom and France were also significant and negative under alternative model specifications (4, 6). These findings suggest that while drug clinical benefits are, in general, weakly associated with costs for treatment, it is also possible for that relationship to be mediated by domestic policy.

5. Discussion

In part because of the impact of drug costs on healthcare expenditures, medication adherence, and, ultimately, patient outcomes, the importance of critically assessing the added value of new cancer drugs has increasingly become apparent to providers, payers, and policymakers. To better understand the value from spending on new cancer treatments, this study took a novel approach to examine cancer drug treatment costs in Australia, France, the United Kingdom, and the United States, and the relationship between cancer drug costs and their clinical benefits.

Just as cancer drug prices vary widely across countries (Savage et al., 2017), so too do their costs corresponding to a typical duration of treatment. We find that payers in Australia and France generally bear lower costs for cancer drugs than those in the United Kingdom or United States. This remains true through to the third year of drug marketing and even when only considering the drugs that are available in all four countries. Cancer drug costs are particularly high in the United States, where treatment with cancer drugs in their first year of

marketing is on average between 1.2 and 1.9 times more expensive than in Australia, France, and the United Kingdom.

Notwithstanding important questions over affordability, patient access, and adherence to treatment, high cancer drug costs may be justified if new medicines offer equally large clinical benefits to patients. This study finds some evidence to suggest that the clinical benefits from cancer drugs may be associated with their cost for treatment. However, the strength of this relationship is weak at best, varies across countries, and is not significantly different from zero in some settings. Overall survival benefits were predictive of cancer drug costs in France and the United Kingdom. In both settings, drug costs also tended to rise with quality of life benefits. Under no circumstance, however, was the relationship between overall survival, quality of life, or safety benefits and drug costs significant in Australia or the US.

Why should we care whether the cost of new cancer medicines is related to their beneficial impact to patients? Consider how the value, affordability, innovation, and patient choice objectives intertwine. Lowering drug prices can improve treatment affordability and broaden access to medicines, two necessary objectives in healthcare decision-making. Yet, some have suggested that doing so may stifle innovation and patient choice (Parker-Lue et al., 2015). Accounting for value in this process can further refine the drive to make drugs more affordable—it can help identify drugs whose prices are not justified by their benefits, and thus whose prices may be most subject to review and negotiation. In a world of limited resources, such efforts may help to rationalize drug expenditures, maximize health outcomes at a societal level, and incentivize drug development that is truly clinically meaningful (Claxton, 2007; Howard et al., 2015; Kyle, 2018).

Do we therefore pay for what we get with cancer drugs? This study offers evidence to refute the notion that cancer drug costs are necessarily related to their therapeutic benefits (Schnipper et al., 2015). This is particularly true for the US, where a subset of new cancer medicines may be both expensive and no better for patients compared to existing alternatives. Yet, we also find that countries appear capable of altering the relationship between drug costs and clinical benefits. That US cancer drug costs are both high and unrelated to therapeutic benefits suggests that governmental intervention—as utilized by France and the United Kingdom—may play an appropriate economic role in the pricing of cancer medicines.

Governments may for instance use cost and clinical efficacy data within the context of HTA to inform mechanisms that help to ensure value for money, including price negotiations, arbitrations, and terms of drug reimbursement. Such an approach may be particularly useful when there are questions about the cost and health benefits of new treatments (Sorenson et al., 2008). In the US, CMS is prohibited from negotiating prices or taking costs into consideration during the drug reimbursement decision-making process; that process also often does

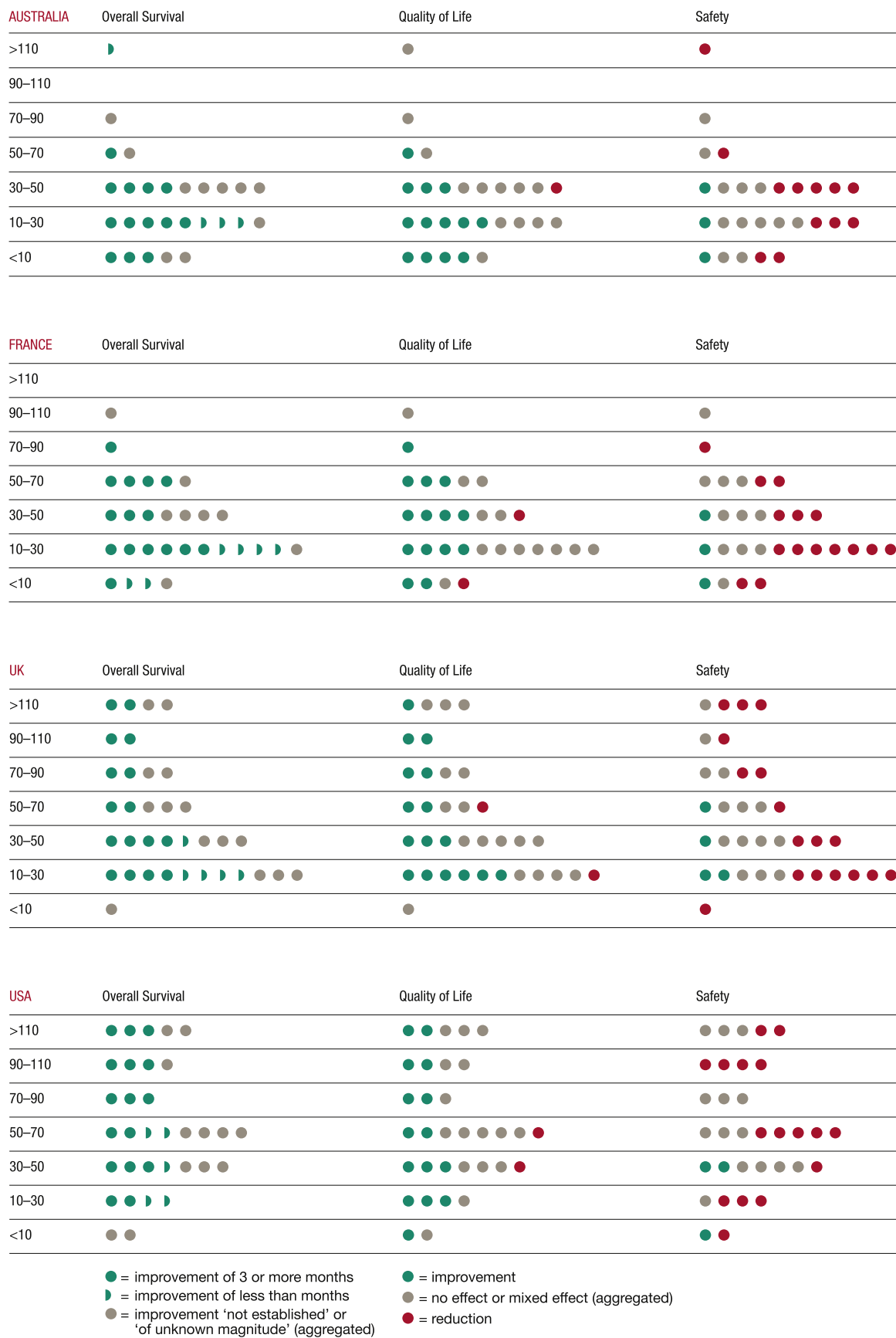


Fig. 2. Cost of cancer medicines approved between 2003 and 2013 versus their impact on overall survival, quality of life, and safety (first year of marketing, mean measure of cost, 2015 USD). Authors' analysis of data, as described in Methods section.

Table 2

Regression analysis.

Source: Authors' analysis of data, as described Methods section.

Variable ¹	Model ²					
	(1)	(2)	(3)	(4)	(5)	(6)
Dep. Var.	sqrt_TcP	sqrt_TcP	sqrt_TcP	sqrt_TcP	sqrt_TcP	sqrt_TcP
orphan	-0.14 [19.80]	7.67 [24.87]	44.99 [23.74]	51.19 [26.99]	23.79 [29.75]	77.46* [35.18]
breast	65.56* [25.16]	73.87* [34.71]	105.8* [42.46]	109.6* [43.57]	124.5* [60.22]	149.6* [63.14]
gi	50.96* [24.94]	62.42 [34.15]	97.71* [38.33]	97.50* [41.01]	112.20 [56.40]	139.9* [62.99]
hematological	98.67*** [14.54]	89.76*** [24.97]	95.20** [32.46]	102.2** [35.55]	115.1* [48.04]	115.6* [53.08]
lung	25.81 [26.52]	37.37 [42.84]	64.44 [43.92]	74.27 [47.06]	80.20 [58.25]	111.50 [63.22]
prostate	32.59 [30.20]	73.82 [43.46]	109.9* [49.66]	113.3* [49.94]	123.90 [63.25]	153.5* [66.74]
renal	23.81* [11.61]	8.91 [31.55]	5.01 [34.41]	-5.42 [36.19]	36.66 [50.77]	11.78 [53.54]
skin	90.83** [30.11]	252.0*** [34.68]	249.3*** [40.45]	273.8*** [42.12]	280.6*** [60.08]	316.6*** [63.83]
thyroid	192.5*** [19.80]	237.4*** [29.07]	274.0*** [28.32]	276.8*** [28.73]	289.5*** [57.64]	342.1*** [63.33]
OS		3.51 [3.456]	-6.66 [6.141]	3.63 [3.044]	4.37 [2.938]	-0.54 [7.243]
QoL		-13.91 [11.18]	-13.54 [9.269]		-13.19 [9.939]	
safety		37.13** [12.17]	36.36** [11.02]	32.97** [11.76]		
FR			-30.47 [36.62]	78.45* [36.64]	19.12 [13.09]	0.06 [29.90]
UK			3.89 [38.23]	125.3** [37.10]	60.61** [19.13]	38.68 [26.61]
US			44.26 [39.36]	140.1** [43.20]	33.92 [34.81]	26.12 [45.27]
FR # OS			13.49* [6.319]			7.42 [7.764]
UK # OS			15.61* [6.533]			9.51 [7.828]
US # OS			11.43 [6.999]			3.67 [8.436]
QoL_reduce				-52.88 [38.29]		-70.72 [54.07]
QoL_NE				57.37 [60.49]		96.59 [72.04]
QoL_reduce # FR				-47.44 [39.77]		27.53 [84.19]
QoL_reduce # UK				-63.19 [41.10]		21.46 [84.42]
QoL_NE # FR				-115.8* [57.72]		-142.70 [74.42]
QoL_NE # UK				-129.9* [59.56]		-154.2* [75.09]
QoL_NE # US				-111.00 [65.54]		-176.2* [80.97]
safety_ME					-12.33 [44.16]	-28.15 [51.42]
safety_reduce					60.66 [47.34]	-32.10 [66.22]
safety_NE					91.11 [61.35]	-25.21 [76.99]
safety_ME # FR					35.80 [54.46]	55.68 [62.13]
safety_ME # UK					38.68 [60.99]	50.36 [66.89]
safety_ME # US					80.17 [68.61]	98.18 [80.26]
safety_reduce # FR					-30.37 [51.14]	69.10 [68.27]
safety_reduce # UK					-32.43 [54.07]	67.68 [73.65]
safety_reduce # US					31.49 [63.38]	153.40 [90.69]
safety_NE # FR					13.28 [66.62]	126.40 [79.79]
safety_NE # UK					10.24 [73.23]	132.80 [85.44]
safety_NE # US					74.49 [75.52]	207.9* [95.69]
Constant	146.1*** [19.80]	45.33 [57.44]	5.76 [68.63]	-90.00 [69.11]	12.92 [63.77]	-20.23 [66.79]
Observations	136	94	94	94	94	94
R ²	0.149	0.295	0.463	0.482	0.444	0.539
Adj R ²	0.088	0.19	0.334	0.33	0.228	0.26

¹OS = overall survival; QoL = quality of life; improve = overall improvement; reduce = overall reduction; ME = mixed evidence; NE = no established difference in outcome measure relative to best alternative treatment. ²Square root transformation of the dependent variable, total cost per patient per full expected course of treatment (TCp) in the first year of marketing. ³Reference categories: ascites; AU; QoL: improve; safety: improve. ⁴Standard errors (SE) are provided in brackets. ***: p ≤ 0.01, **: p ≤ 0.05, *: p ≤ 0.10.

not consider the clinical evidence supporting drug use (Bach and Pearson, 2015; Barnieh et al., 2014). CMS may also be required to cover all or substantially all medicines that fall within six protected classes, including anti-neoplastics and immunosuppressants (Bach and Pearson, 2015). As healthcare costs rise, Congress has introduced initiatives to better control drug spending, including by empowering the federal government to negotiate drug prices (Morten and Kapczynski, 2019) and recent efforts by CMS help to promote the use of lower-cost alternative therapies (Centers for Medicare and Medicaid Services, 2019). While the US and other countries should consider such initiatives to improve the affordability of new treatments, their focus on drug costs raises questions about how they may specifically impact the relationship with drug clinical benefits and value from spending. Additional research should consider replicating our analysis to include new cancer medicines to address this question. In the meantime, innovative policies meant to rationalize drug costs could also be designed to consider drug clinical benefits.

As it stands, among the countries considered in this study, France

appears to be particularly adept at ensuring that recently licensed cancer drugs are both affordable and that their costs reflect their beneficial impact to patients. The US stands at the opposite end of this spectrum: US payers and patients consistently pay more for recently licensed cancer drugs than those in other countries, yet do so without it necessarily leading to any greater health benefit. While all countries share in the opportunity to improve value-for-money in cancer drug spending, the US may benefit the most from a re-imagined approach to drug pricing. As the country seeks to contain drug costs while also improving patient outcomes, other countries may offer lessons on how to better ensure affordability and value-for-money in oncology.

5.1. Limitations

Our study has several limitations that should be considered. First, the drug pricing data used in our analysis reflects the list price rather than the transaction price; confidential discounts and rebates are not built in (Vogler et al., 2012). Various approaches have been used to try

to address this issue, with one, for instance, using disclosed rebate offers from CMS to assume a constant price reduction on the published price for purchasers of two specialty medicines for Hepatitis C in multiple countries (Iyengar et al., 2016). Assuming a fixed discount to published drug prices in our study would have led to drug cost estimates that were proportionally discounted. There is however little reason to justify one price discount level over another across multiple products (Mattingly et al., 2018), or across countries. Moreover, any fixed price reduction would not have impacted our findings regarding international cost trends or their relationship with drug clinical benefits. We agree with arguments that net prices should be used instead. However, without information on confidential discounts and rebates, net prices would have to be calculated from aggregated sales data, raising questions over how and to what extent they would accurately reflect the transactional price incurred by any single payer. Despite the challenges inherent to their use, list prices are set by manufacturers with or without the input of national regulators. In theory, they may reflect transactional prices when rebates and discounts are not applied (e.g. the uninsured, private patients), meaning that our results provide accurate, international costing estimates in this scenario. Future studies should nevertheless repeat our analysis as information on transactional prices become available. We see progress in this regard, with survey-based methods encompassing a limited number of cancer centers starting to offer data on the actual cost of some new cancer medicines (van Harten et al., 2016), and recent bipartisan policy initiatives that would require CMS to publish drug discounts and rebates (Spanberger, 2019).

Next, 42 drugs were eligible for inclusion in this study. Although this sample encompasses all New Molecular Entities that had been approved by either the FDA or EMA with a single, primary anti-cancer indication over the 10-year period 2003–2013, and which could be reconciled with the longest longitudinal dataset that is available from IQVIA, this remains a relatively small sample. Future studies should build on this analysis by extending it to other countries, or by re-running it to include additional cancer drugs that have been approved in the intervening period.

This study is in part based on a review of HTA agency assessments of the added clinical benefits associated with cancer medicines. To do so, these agencies evaluate the primary clinical data to perform technology appraisals. It is well known that clinical research may be subject to various forms of bias, which may impact the reliability of technology appraisals by licensing and regulatory authorities. The summary measures of drug clinical benefits used in this study were based on a review of technology appraisals from three HTA agencies. The bodies also may require submission of all relevant information, published and unpublished, including RCTs necessary to complete their appraisal, and they base their assessments on systematic reviews and expert evaluations of the evidence. This approach not only helps to mitigate any impact from bias present in the primary clinical evidence, it is also less subject to interpretation bias and provides a more representative assessment of the clinical impact from new cancer medicines (Salas-Vega and Mossialos, 2017).

Finally, this study focuses on drug-related effects on OS, QoL, and safety. This approach is designed to reflect recommendations from ASCO's Value Framework, which is specific to cancer; was designed through a deliberative consensus process; is rules-based; weights clinical measures according to their perceived value to patients; explicitly synthesizes clinical benefits; and incorporates direct costs from treatment (Schnipper et al., 2016, 2015). This study did not consider surrogate measures of efficacy, including progression-free survival and response rates. If it is accepted that surrogate efficacy markers represent unique dimensions to the clinical benefits from treatment, then their absence would mean that our analysis may be prone to bias. However, ASCO's Value Framework recommends that these variables only be used to assess efficacy if data on overall survival is not available. For its part, the FDA states that while surrogate markers of efficacy may be

predictive of clinical benefits, they are “not themselves a measure of clinical benefit” (US Food and Drug Administration, 2016). Furthermore, there is evidence to suggest that any difference between OS and PFS is often negligible (Howard et al., 2015).

Declarations of interest

None.

Authorship contributions

SSV: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Supervision. ES: Formal analysis, Writing - original draft, Writing - review & editing, Visualization. EM: Writing - review & editing, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.socscimed.2020.113042>.

References

- Australian Bureau of Statistics, 2015. National Health Survey, 2014-15. Retrieved from <http://www.abs.gov.au/ausstats/abs@.nsf/mf/4364.0.55.001>.
- Australian Government Department of Health, 2016. PBAC Outcomes. Australian Government Department of Health Retrieved from <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes>.
- Australian Government Productivity Commission, 2001. International Pharmaceutical Price Differences. Retrieved from <https://www.pc.gov.au/inquiries/completed/pharmaceutical-prices/report>.
- Bach, P.B., 2009. Limits on medicare's ability to control rising spending on cancer drugs. *N. Engl. J. Med.* 360 (6), 626–633. <https://doi.org/10.1056/NEJMhpr0807774>.
- Bach, P.B., Pearson, S.D., 2015. Payer and policy maker steps to support value-based pricing for drugs. *J. Am. Med. Assoc.* 314 (23), 2503. <https://doi.org/10.1001/jama.2015.16843>.
- Barnieh, L., Manns, B., Harris, A., Blom, M., Donaldson, C., Klarenbach, S., ... Clement, F., 2014. A synthesis of drug reimbursement decision-making processes in organisation for economic Co-operation and development countries. *Value Health* 17 (1), 98–108. <https://doi.org/10.1016/j.jval.2013.10.008>.
- Bestvina, C.M., Zullig, L.L., Yousuf Zafar, S., 2014. The implications of out-of-pocket cost of cancer treatment in the USA: a critical appraisal of the literature. *Future Oncol.* 10 (14), 2189–2199. <https://doi.org/10.2217/fon.14.130>.
- Blumenthal, D., Squires, D., 2016. Drug Price Control: How Some Government Programs Do it. Retrieved from https://www.commonwealthfund.org/blog/2016/drug-price-control-how-some-government-programs-do-it?redirect_source=/publications/blog/2016/may/drug-price-control-how-some-government-programs-do-it.
- Carone, G., Schwierz, C., Xavier, A., 2012. European Economy: Cost-Containment Policies in Public Pharmaceutical Spending in the (EU).
- Castetbon, K., Vernay, M., Malon, A., Salanave, B., Deschamps, V., Roudier, C., ... Herberg, S., 2009. Dietary intake, physical activity and nutritional status in adults: the French nutrition and health survey (ENNS, 2006–2007). *Br. J. Nutr.* 102 (5), 733. <https://doi.org/10.1017/S0007114509274745>.
- Centers for Medicare & Medicaid Services, 2019. Medicare Advantage and Part D Drug Pricing Final Rule. Retrieved from <https://www.cms.gov/newsroom/fact-sheets/medicare-advantage-and-part-d-drug-pricing-final-rule-cms-4180-f>.
- Chandra, A., Shafirin, J., Dhawan, R., 2016. Utility of cancer value frameworks for patients, payers, and physicians. *J. Am. Med. Assoc.* 315 (19), 2069–2070. <https://doi.org/10.1001/jama.2016.4915>.
- Chicoye, A., Chhabra, A., 2009. France - Pharmaceuticals. Retrieved from <https://www.ispor.org/HTARoadMaps/France.asp>.
- Claxton, K., 2007. OFT, VBP: QED? *Health Econ.* 16 (6), 545–558. <https://doi.org/10.1002/hec.1249>.
- Danzon, P.M., Furukawa, M.F., 2006. Prices and availability of biopharmaceuticals: an international comparison. *Health Aff.* 25 (5), 1353–1362. <https://doi.org/10.1377/hlthaff.25.5.1353>.
- Divino, V., DeKoven, M., Kleinrock, M., Wade, R.L., Kaura, S., 2016. Orphan drug expenditures in the United States: a historical and prospective analysis, 2007–18.

- Health Aff. 35 (9), 1588–1594. <https://doi.org/10.1377/hlthaff.2016.0030>.
- Dolan, P., Shaw, R., Tsuchiya, A., Williams, A., 2005. QALY maximisation and people's preferences: a methodological review of the literature. *Health Econ.* 14 (2), 197–208. <https://doi.org/10.1002/hec.924>.
- Doran, E., Alexander Henry, D., 2008. Australian pharmaceutical policy: price control, equity, and drug innovation in Australia. *J. Publ. Health Pol.* 29 (1), 106–120. <https://doi.org/10.1057/palgrave.jph.3200170>.
- DrugAbacus. 2017. DrugAbacus Methods: FAQs. Retrieved from. <https://drugpricinglab.org/tools/drug-abacus/methods/#faqs>.
- Drummond, M.F., Wilson, D.A., Kanavos, P., Ubel, P., Rovira, J., 2007. Assessing the economic challenges posed by orphan drugs. *Int. J. Technol. Assess. Health Care* 23 (1), 36–42. <https://doi.org/10.1017/S0266462307051550>.
- European Medicines Agency, 2010. Annex I: Summary of Product Characteristics (Cetuximab). Retrieved from. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000558/WC500029119.pdf.
- Experts in Chronic Myeloid Leukemia, 2013. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. *Blood* 121 (22), 4439–4442. <https://doi.org/10.1182/blood-2013-03-490003>.
- Frakt, A.B., 2016. Determining value and price in health care. *J. Am. Med. Assoc.* 316 (10), 1033. <https://doi.org/10.1001/jama.2016.10922>.
- Fryar, C., Gu, Q., Ogden, C., 2012. Anthropometric reference data for children and adults: United States, 2007–2010. *Vital Health Statistics* 11 (252).
- Goldman, D.P., Joyce, G.F., Zheng, Y., 2007. Prescription drug cost sharing. *J. Am. Med. Assoc.* 298 (1), 61. <https://doi.org/10.1001/jama.298.1.61>.
- Goldstein, D.A., Gordon, N., Davidescu, M., Leshno, M., Steuer, C.E., Patel, N., ... Zer, A., 2017. A pharmacoeconomic analysis of personalized dosing vs fixed dosing of pembrolizumab in first-line PD-L1-positive non-small cell lung cancer. *J. Natl. Cancer Inst.* 109 (11), dxj063. <https://doi.org/10.1093/jnci/djx063>.
- Haute Autorité de Santé, 2009. Medical Device Assessment in France: Guidebook. Retrieved from. http://www.has-sante.fr/portail/upload/docs/application/pdf/2010-03/guide_dm_gb_050310.pdf.
- Haute Autorité de Santé, 2012. Choices in Methods for Economic Evaluation.
- Haute Autorité de Santé, 2014. Pricing & Reimbursement of Drugs and HTA Policies in France. Retrieved from. https://www.has-sante.fr/portail/upload/docs/application/pdf/2014-03/pricing_reimbursement_of_drugs_and_hta_policies_in_france.pdf.
- Herold, M., Hieke, K., 2003. Costs of drug delivery for CHOP, COP/CVP, and fludarabine: an international assessment. *Value Health* 6 (2), 167–174. <https://doi.org/10.1046/j.1524-4733.2003.00227.x>.
- Howard, D.H., Bach, P.B., Berndt, E.R., Conti, R.M., 2015. Pricing in the market for anticancer drugs. *J. Econ. Perspect.* 29 (1), 139–162. <https://doi.org/10.1257/jep.29.1.139>.
- Iyengar, S., Tay-Teo, K., Vogler, S., Beyer, P., Wiktor, S., de Joncheere, K., Hill, S., 2016. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. *PLoS Med.* 13 (5), e1002032. <https://doi.org/10.1371/journal.pmed.1002032>.
- Jaksa, A., Pontynen, A., Bastian, A., 2017. Exploring the time delay between regulatory approval and health technology assessments (HTAs) of oncology therapies in France, Germany, England, Scotland, Canada, and Australia. *J. Clin. Oncol.* 35 (15, Suppl. D). https://doi.org/10.1200/jco.2017.35.15_suppl.6545. 6545–6545.
- Kanavos, P., Ferrario, A., Vadoros, S., Anderson, G.F., 2013. Higher US branded drug prices and spending compared to other countries may stem partly from quick uptake of new drugs. *Health Aff.* 32 (4), 753–761. <https://doi.org/10.1377/hlthaff.2012.0920>.
- Kyle, M.K., 2018. Are important innovations rewarded? Evidence from pharmaceutical markets. *Rev. Ind. Organ.* 53 (1), 211–234. <https://doi.org/10.1007/s11151-018-9639-7>.
- Leopold, C., Peppercorn, J.M., Zafar, S.Y., Wagner, A.K., 2018. Defining Value of Cancer Therapeutics-A Health System Perspective. *Journal of the National Cancer Institute. Oxford University Press*<https://doi.org/10.1093/jnci/djy079>.
- Maervoet, J., Moise, P., Naidoo, S., 2016. Overview and comparison of frameworks for the valuation of oncology drugs. *Value Health* 19 (3), A168. <https://doi.org/10.1016/j.jval.2016.03.1527>.
- Mailankody, S., Prasad, V., 2015. Five years of cancer drug approvals: innovation, efficacy, and costs. *JAMA Oncology* 1 (4), 539–540. <https://doi.org/10.1001/jamaoncol.2015.0373>.
- Mattingly, T.J., Levy, J.F., Slejko, J.F., Onwudiwe, N.C., Peretto, E.M., 2018. Estimating drug costs: how do manufacturer net prices compare with other common US price references? *Pharmacoeconomics* 36 (9), 1093–1099. <https://doi.org/10.1007/s40273-018-0667-9>.
- Medbelle, 2019. 2019 Medicine Price Index. Retrieved from. <https://www.medbelle.com/medicine-price-index-usa>.
- Morten, C.J., Kapczynski, A., 2019, November. Assessing Drug Pricing Reform Proposals: the Real Leverage and Benefits of Competitive Licensing. *Health Affairs Blog*.
- National Institute for Health and Care Excellence, 2016. NICE Technology Appraisal Guidance. Retrieved from. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance>.
- Neumann, P.J., Cohen, J.T., 2015. Measuring the value of prescription drugs. *N. Engl. J. Med.* 373 (27), 2595–2597. <https://doi.org/10.1056/NEJMp1512009>.
- NHS Digital, 2011. *Health Survey for England - 2010*.
- NHS England Cancer Drugs Fund Team, 2016. Appraisal and Funding of Cancer Drugs from July 2016 (Including the New Cancer Drugs Fund). Retrieved from. <https://www.england.nhs.uk/wp-content/uploads/2013/04/cdf-sop.pdf>.
- NICE, 2013. Guide to the Methods of Technology Appraisal 2013. Retrieved from. <http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9>.
- Osterlund, P., Sorbye, H., Pfeiffer, P., Johnsson, A., Rodrigues, F., Furneri, G., 2016. Drug costs and benefits of medical treatments in high-unmet need solid tumours in the Nordic countries. *Journal of Cancer Policy* 7, 12–22. <https://doi.org/10.1016/j.jcpo.2015.12.003>.
- Panteli, D., Nolting, A., Eckhardt, H., Kulig, M., Busse, R., 2016. Published and unpublished evidence in coverage decision-making for pharmaceuticals in Europe: existing approaches and way forward. *Health Res. Pol. Syst.* 14, 6. <https://doi.org/10.1186/s12961-016-0080-9>.
- Paris, V., Belloni, A., 2014. Value in Pharmaceutical Pricing Country Profile: Australia. Retrieved from. <https://www.oecd.org/health/Value-in-Pharmaceutical-Pricing-Australia.pdf>.
- Parker-Lue, S., Santoro, M., Koski, G., 2015. The ethics and economics of pharmaceutical pricing. *Annu. Rev. Pharmacol. Toxicol.* 55 (1), 191–206. <https://doi.org/10.1146/annurev-pharmtox-010814-124649>.
- Pauwels, K., Huys, I., Vogler, S., Casteels, M., Simoens, S., 2017. Managed Entry agreements for oncology drugs: lessons from the European experience to inform the future. *Front. Pharmacol.* 8, 171. <https://doi.org/10.3389/fphar.2017.00171>.
- Pharmaceutical Benefits Advisory Committee, 2014. About the Guidelines. Retrieved from. <https://pbac.pbs.gov.au/information/about-the-guidelines.html>.
- Porter, M.E., 2010. What is value in health care? *N. Engl. J. Med.* 363, 2477–2481. Retrieved from. <http://www.nejm.org/doi/full/10.1056/NEJMp1011024>.
- Ray, J.A., Carr, E., Lewis, G., Marcus, R., 2010. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-hodgkin's lymphoma in the UK. *Value Health* 13, 346–357. <https://doi.org/10.1111/j.1524-4733.2009.00676.x>.
- Robinson, M.F., Mihalopoulos, C., Merlin, T., Roughead, E., 2018. Characteristics of managed entry agreements in Australia. *Int. J. Technol. Assess. Health Care* 34 (1), 46–55. <https://doi.org/10.1017/S0266462317001106>.
- Rodwin, M., 2019, November. What Can the United States Learn from Pharmaceutical Spending Controls in France? *Issue Brief*. Retrieved from. https://www.commonwealthfund.org/sites/default/files/2019-11/Rodwin_pharma_cost_control_France_ib_v2.pdf.
- Salas-Vega, S., Iliopoulos, O., Mossialos, E., 2016. Assessment of overall survival, quality of life, and safety benefits associated with new cancer medicines. *JAMA Oncology* 116 (14), 3493–3504. <https://doi.org/10.1001/jamaoncol.2016.4166>.
- Salas-Vega, S., Mossialos, E., 2017, December 1. Overestimating the Benefit of Cancer Drugs-Reply. *JAMA Oncology. American Medical Association*<https://doi.org/10.1001/jamaoncol.2017.1976>.
- Savage, P., Mahmood, S., Patel, Y., Kantarjian, H., 2017. Cancer drugs: an international comparison of postlicensing price inflation. *Journal of Oncology Practice* 13 (6), e538–e542. <https://doi.org/10.1200/JOP.2016.014431>.
- Schnipper, L.E., Davidson, N.E., Wollins, D.S., Blayney, D.W., Dicker, A.P., Ganz, P.A., ... Schilsky, R.L., 2016. Updating the American society of clinical oncology value framework: revisions and reflections in response to comments received. *J. Clin. Oncol.: Official Journal of the American Society of Clinical Oncology* 34 (24), 2925–2934. <https://doi.org/10.1200/JCO.2016.68.2518>.
- Schnipper, L.E., Davidson, N.E., Wollins, D.S., Tyne, C., Blayney, D.W., Blum, D., et al., 2015. American society of clinical oncology statement: a conceptual framework to assess the value of cancer treatment options. *J. Clin. Oncol.: Official Journal of the American Society of Clinical Oncology* 33 (23), 2563–2577. <https://doi.org/10.1200/JCO.2015.61.6706>.
- Schoonveld, E., 2015. *The Price of Global Health: Drug Pricing Strategies to Balance Patient Access and the Funding of Innovation*, second ed. Routledge, Milton Park.
- Simoens, S., 2011. Pricing and reimbursement of orphan drugs: the need for more transparency. *Orphanet J. Rare Dis.* 6 (1), 42. <https://doi.org/10.1186/1750-1172-6-42>.
- Sorenson, C., Drummond, M., Kristensen, F.B., Busse, R., 2008. *How Can the Impact of Health Technology Assessments Be Enhanced?* (Policy Brief).
- Spanberger, A.D., 2019. Public Disclosure of Drug Discounts and Real-Time Beneficiary Drug Cost Act. 116th Congress, pp. 2019–2020.
- Tordrup, D., Tzouma, V., Kanavos, P., 2014. Orphan drug considerations in Health Technology Assessment in eight European countries. *Rare Diseases and Orphan Drugs: Int. J. Publ. Health* 1 (3), 86–97.
- Turkstra, E., Comans, T., Gordan, L., Scuffham, P., 2015. Australia - Pharmaceuticals. Retrieved from. https://www.ispor.org/HTARoadMaps/Australia_Pharm.asp#5.
- US Department of Commerce, 2004. *Pharmaceutical Price Controls in OECD Countries Implications for U.S. Consumers, Pricing, Research and Development, and Innovation*. Washington, DC, DC. Retrieved from. <http://trade.gov/td/health/DrugPricingStudy.pdf>.
- US Food and Drug Administration, 2007. Highlights of Prescribing Information - Lapatinib. Retrieved from. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/0220591bl.pdf.
- US Food and Drug Administration, 2012. Highlights of Prescribing Information - Ziv-Aflibercept. Retrieved from. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125418s0001bl.pdf.
- US Food and Drug Administration, 2013. Highlights of Prescribing Information - Ado-Trastuzumab Emtansine. Retrieved from. http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/1254271bl.pdf.
- US Food and Drug Administration, 2016. Information for Healthcare Professionals (Drugs) - Accelerated Approval Program. Center for Drug Evaluation and Research. Retrieved from. <http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm313768.htm>.
- van Harten, W.H., Wind, A., de Paoli, P., Saghatchian, M., Oberst, S., 2016. Actual costs of cancer drugs in 15 European countries. *Lancet Oncol.* 17 (1), 18–20. [https://doi.org/10.1016/S1470-2045\(15\)00486-6](https://doi.org/10.1016/S1470-2045(15)00486-6).

- Verghese, N.R., Barrenetxea, J., Bhargava, Y., Agrawal, S., Finkelstein, E.A., 2019. Government pharmaceutical pricing strategies in the Asia-Pacific region: an overview. *Journal of Market Access & Health Policy* 7 (1), 1601060. <https://doi.org/10.1080/20016689.2019.1601060>.
- Vitry, A.I., Thai, L., Roughead, E.E., 2015. Pharmaceutical pricing policies in Australia. In: Babar, Z.-U.-D. (Ed.), *Pharmaceutical Prices in the 21st Century*. Springer International Publishing, Cham, pp. 1–23. https://doi.org/10.1007/978-3-319-12169-7_1.
- Vogler, S., Vitry, A., Babar, Z.-U.-D., 2016. Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study. *Lancet Oncol.* 17 (1), 39–47. [https://doi.org/10.1016/S1470-2045\(15\)00449-0](https://doi.org/10.1016/S1470-2045(15)00449-0).
- Vogler, S., Zimmermann, N., Habl, C., Piessnegger, J., Bucsics, A., 2012. Discounts and rebates granted to public payers for medicines in European countries. *Southern Medical Journal* 105 (1), 38–46. Retrieved from. <http://www.ncbi.nlm.nih.gov/pubmed/23093898>.
- Weaver, K.E., Rowland, J.H., Bellizzi, K.M., Aziz, N.M., 2010. Forgoing medical care because of cost. *Cancer* 116 (14), 3493–3504. <https://doi.org/10.1002/cncr.25209>.
- Wellman-Labadie, O., Zhou, Y., Schuurman, A., Simoens, S., Rovira, J., McCabe, C., ... Morris, M., 2010. The US Orphan Drug Act: rare disease research stimulator or commercial opportunity? *Health Pol.* 95 (2–3), 216–228. <https://doi.org/10.1016/j.healthpol.2009.12.001>.
- World Health Organization, 2015. WHO Guideline on Country Pharmaceutical Pricing Policies. Retrieved from. <http://apps.who.int/medicinedocs/documents/s21016en/s21016en.pdf>.
- World Health Organization, 2018. *Technical Report: Pricing of Cancer Medicines and its Impacts*.