How Well Has Cost-Effectiveness Predicted Drug Market Success?
Evidence of Omitted Value

Cohen JT, Lin CH, Ghule P, Lin PJ

INTRODUCTION

For most goods and services, conventional competitive market forces – supply and demand – determine the equilibrium price, as no single buyer or seller has the power to significantly influence the price. In the absence of "market failures", the result is an optimal allocation of societal resources.

The pharmaceutical market does not mirror competitive markets. On the demand side, individuals mostly purchase private or public insurance plans to access care. The ultimate consumers (patients) typically lack sovereignty: i.e., they do not have the necessary knowledge to evaluate options, and their agents with competing interests (e.g., clinicians and payers) often dominate decision-making. On the supply side, a patent-protected reward system incentivizes risky and costly pharmaceutical R&D efforts. The market can be distorted by monopolistic behavior, patent protections, and other barriers that limit competition, allowing manufacturers to set prices above what would emerge in a truly competitive market.[1]

In place of the market, centralized or decentralized negotiations between payers and manufacturers determine prices for pharmaceuticals. To inform such negotiations, researchers and policymakers have developed and used health technology assessment to estimate the price that aligns with value.[2] Cost-effectiveness analysis (CEA) has become the primary technocratic tool for measuring the value of pharmaceuticals, ostensibly filling the gap left by market mechanisms.[3,4]

CEA critics argue that CEA serves as a poor substitute for market-derived prices. Some have made a "bottom-up" case, arguing that traditional CEA (TCEA) does not account for the full range of benefits that drugs confer, particularly those that address unmet needs for patients, caregivers, and society.[5]

Incorporating "novel value elements" into CEA represents an effort to address these criticisms.[6] Examples include the additional value of addressing severe health conditions, reducing disease transmission, reducing caregiver impacts, and accounting for future price reductions attending loss of exclusivity that most published CEAs overlook.[7,8] Studies have shown that incorporating novel value elements into a conventional CEA could change cost-effectiveness conclusions.[9-11]

This paper investigates the potential disconnect between traditional CEA and societal value by examining discrepancies between post-launch market performance and CEA value estimates at launch. Under the assumption that market prices of widely used medicines better represent their "true" value to patients and society and taking into account factors such as the real-world clinical effectiveness and a broader set of value elements that consumers deem important, a gap between market performance and CEA-estimated value constitutes prima facie evidence that traditional CEA conducted at launch is incomplete.

Our "top-down" approach investigates the discrepancy between CEA and aggregate value as revealed by real-world market sales and contrasts with the "bottom-up" approach described above that compares cost-effectiveness estimated using traditional value elements to cost-

effectiveness computed using the more comprehensive set of value elements that CEA purportedly should include. By addressing this question from a different direction, our findings provide perspective on the robustness of competing positions on the completeness of traditional CEA.

Our investigation has three parts:

- First, we describe CE ratios estimated using traditional CEA for drugs that subsequently demonstrated market success after launch. A finding for this "top-down" analysis of unfavorable CE ratios for these drugs suggests the possibility that the underlying assessments have omitted value elements that suggest true benefits are higher or actual costs are lower than in those CEAs.
- Second, among drugs that are successful in the market, we examine characteristics associated with unfavorable CE ratio estimates. Identifying these characteristics can shed light on when traditional CEA may undervalue medicines relative to how the market values them.
- Finally, we conduct a series of "bottom-up" analysis case studies that investigate the potential CE ratio impact of including missing "novel" value elements. Substantial differences provide insight into the potential importance of including these broader value elements.

METHODS

Our analysis examined (1) the proportion of commercially successful drugs with unfavorable cost-effectiveness (CE) ratios to assess alignment between value measurement (via cost-effectiveness analysis, or "CEA") and market success; (2) the association between drug characteristics and unfavorable cost-effectiveness; and (3) how much omission of novel value elements may influence estimated cost-effectiveness.

1. Proportion of commercially successful drugs with unfavorable CE ratios

- **Sample**: We included drugs that met three conditions: (1) we could estimate their cost-effectiveness from studies meeting our inclusion criteria (see "Outcome", below), (2) they achieved strong market success, defined as global annual sales exceeding $1 billion within 7 years of U.S. launch (based on GlobalData Market Data & Insights), and (3) they received approval by the FDA between January 1, 2010, and December 31, 2024 (based on the Drugs@FDA database).
- **Outcome**: We estimated the proportion of drugs in our sample with an unfavorable cost-effectiveness ratio. We designated a drug as having unfavorable cost-effectiveness if its ratio exceeds $150,000 per QALY,[12] or if it increases cost without improving health. We estimated a drug's cost-effectiveness as the median of the included, published values from either (1) studies catalogued in the Tufts CEA Registry (www.cearegistry.org) or (2) final evidence reports published by the Institute for Clinical and Economic Review (ICER). We included ratios from studies meeting the following criteria: (1) reports in a U.S.-based study published within 3 years of product launch; (2) reports in "base-case" analyses that compare the drug to recognized standard of care; (3) represents a societal perspective (we accepted health care payer perspective if a societal perspective estimate

was unavailable); and (4) represents the earliest approved indication when ratios addressing multiple indications were available.

2. Association between drug characteristics and unfavorable cost-effectiveness

- **Analysis**: We used Fisher's exact test to assess associations between cost-effectiveness favorability and drug characteristics.
- **Sample and cost-effectiveness outcome**: We used the same sample of drugs, cost-effectiveness estimates, and definition of cost-effectiveness favorability as in the first analysis.
- **Characteristics** included accelerated approval (based on the FDA Accelerated Approval list), which applies to drugs addressing serious conditions with unmet medical needs, and disease category (based on the International Classification of Diseases [ICD]) for the first approved indication.

3. How much omission of novel value elements may influence estimated cost-effectiveness

We conducted five case studies that compared traditional cost-effectiveness ratios to ratios estimated with the inclusion of novel value elements.

- **Case study drugs**: Our case studies investigated five commercially successful drugs with unfavorable CE ratios: Trikafta (elexacaftor / tezacaftor / ivacaftor), Xtandi (enzalutamide), Vyndaqel (tafamidis meglumine), Ibrance (palbociclib), and Eylea (aflibercept). We selected these case studies based on their peak sales and because they represent different therapeutic areas and types of technologies (e.g., small molecules vs. biologics).
- **Novel value elements considered**: For each drug, we first identified a subset of novel value elements that might have a substantial impact on estimated cost-effectiveness, selected based on disease characteristics, treatment context, and two rounds of qualitative interviews with investors, innovators, and patients. We then selected two of these value elements for each drug for further investigation, balancing the potential impacts with the desire to explore a broad range of value drivers. For example, dynamic pricing has the potential to materially affect pricing for a broad range of products, but we included it for only two drugs so that we could explore the potential impact of additional, distinct novel value elements. Our exploration estimated the impact of incorporating the selected novel elements for each drug, both individually and at the same time. As our appendices describe, we referenced various sources to identify appropriate assumptions for the scenarios we evaluated.
- **Discount rates:** We conducted assessments using both the conventional 3% discount rate recommended by the 2016 Second Panel on Cost-Effectiveness in Health and Medicine,[13] and a 2% discount rate suggested by a more recent review.[14]
- **Estimation of novel value element impact:** We characterized the impact of each novel value element scenario as the ratio of the revised CE ratio, reflecting the incorporation of one or more novel value elements, to the baseline TCEA ratio. To calculate the TCEA ratios, we first established baseline values using assumptions from the published analyses (Appendix A), including annual drug costs, non-drug costs, accrued QALYs, treatment

duration, and life years. Because published CEA models are typically unavailable, we relied on two calculators to estimate the revised ratios. First, we used the online "GCEA calculator" developed by No Patient Left Behind (NPLB) (https://www.nopatientleftbehind.org/gcea-calculator), which quantifies the societal value of new medicines and health innovations. Second, we conducted our own calculations ("Tufts calculator") in Microsoft Excel 365 (version 2506). For the revised ratios, we updated the baseline assumptions using data from the literature (Appendix B) to reflect the impact of incorporating novel value elements.

- **Exploratory analysis:** We identified the most influential novel value element and then estimated its impact on all five drugs when incorporated into the CEA individually.

3a. Trikafta

- Published traditional CE ratio: $1,050,000 per QALY[15]
- Novel elements
  - Dynamic pricing: We estimated drug cost reductions following patent expiration by modeling 30 patient cohorts and a 14-year exclusivity period using IQVIA post-loss of exclusivity pricing trend data. (Appendix B1.1)
  - Productivity: We included productivity improvements from better disease management, addressing the burden of uncontrolled respiratory symptoms that limited patient work capacity. This analysis used the total productivity cost difference reported by ICER ($83,000). (Appendix B1.2)

3b. Xtandi

- Published traditional CE ratio: $437,623 per QALY[16]
- Novel elements
  - Dynamic pricing: We modeled drug cost reductions after patent expiration for both Xtandi (14-year exclusivity) and its comparator abiraterone (13-year exclusivity), by modeling 30 patient cohorts using IQVIA post-loss of exclusivity pricing trend data. (Appendix B2.1)
  - Real option value (ROV): We incorporated potential benefits from future prostate cancer therapies in the evolving oncology drug landscape. We estimated total cost and QALY changes by using percentage changes in a published ROV case study of cancer drugs. (Appendix B2.2)

3c. Vyndaqel

- Published traditional CE ratio: $880,000 per QALY[17]
- Novel elements
  - Family and caregiver burden: We quantified productivity losses for caregivers managing untreated patients, who spend approximately 17.5 hours per week providing care. We assumed that caregivers dedicate half of their work to caregiving and multiplied this duration by average weekly wages ($936). (Appendix B3.1)
  - Disease severity: We adjusted the willingness-to-pay threshold based on disease severity. We applied a 1.5-fold higher willingness-to-pay threshold ($225K/QALY vs.

$150K/QALY) following established methodology for severity-adjusted valuations. (Appendix B3.2)

3d. Ibrance

- Published traditional CE ratio: $918,166 per QALY[18]
- Novel elements
  - Real option value: We incorporated potential benefits from future breast cancer therapies in the evolving oncology drug landscape. We estimated total cost and QALY changes by using percentage changes reported in a published real option value case study of cancer drugs. (Appendix B4.1)
  - Productivity: We calculated productivity improvements from survival benefits by multiplying total annual productivity losses from breast cancer ($1,407 work-related plus $368 home-related per capita) by survival time. We assumed that Ibrance reduced annual productivity losses by 42%, corresponding to its hazard ratio for progression-free survival. (Appendix B4.2)

3e. Eylea

- Published traditional CE ratio: $1,147,293 per QALY[19]
- Novel elements
  - Productivity: We calculated productivity improvements from reduced injection frequency (25.6 fewer injections over 11 years). We multiplied the time saved by average daily wages for the relevant age group (≥65 years). (Appendix B5.1)
  - Family and caregiver burden: We estimated caregiver productivity improvements from reduced time accompanying patients to clinics and injections. Assuming equivalent time commitment as patients, we multiplied saved time by daily wages for the typical caregiver population (age ≥25 years). (Appendix B5.2)

RESULTS

1. Proportion of commercially successful drugs with unfavorable CE ratios

Of the 111 drugs that achieved global annual sales exceeding $1 billion within seven years of their U.S. launch, 56 had CE ratios meeting our inclusion criteria (Appendix C Table 1). Of these 56 drugs, 28 (50%) had unfavorable CE ratios exceeding the conventional $150,000/QALY value benchmark. Figure 1 illustrates the distribution of CE ratios. The median was $161,000/QALY and the interquartile range was $72,000 – $404,000/QALY.

2. Association between drug characteristics and unfavorable cost-effectiveness

Accelerated approval: Six of the nine drugs in our sample (67%) that received accelerated approval had unfavorable CE ratios (Table 1). For the 47 drugs that did not receive accelerated approval, 22 (47%) had unfavorable ratios.

Disease groups: No drugs indicated for diseases of the circulatory system (n=4) had unfavorable CE ratios. For drugs indicated for certain infectious and parasitic diseases (n=10), 20% had unfavorable CE ratios. For other indications, at least half of the drugs had unfavorable CE ratios: neoplasms (56%), diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (50%), endocrine, nutritional and metabolic diseases (62%), diseases of the nervous system (71%), diseases of the eye and adnexa (100%), diseases of the respiratory system (75%), and diseases of the skin and subcutaneous tissue (50%).

3. How much omission of novel value elements may influence estimated cost-effectiveness

Tables 2a and 2b report case study results for discount rates of 3% and 2%, respectively. The results showed that dynamic pricing appears to be the most influential novel value element among all the case studies examined, resulting in a reduction of at least 72% for Trikafta and at least 31% for Xtandi. Our exploratory analysis extended investigation of its impact to the remaining case study drugs. Table 3 reports the results. The findings further confirm that dynamic pricing had the most substantial impacts across all the case studies (range: 28% – 91%).

DISCUSSION

Our findings support the hypothesis that traditional CEA does not incorporate all value elements that could contribute to value recognized by the market.

Our **first analysis** found that half of commercially successful drugs in our sample had unfavorable published CE ratios, with some ratios exceeding the common benchmark of $150,000 per QALY by more than an order of magnitude. As these drugs are commercially successful, these markedly unfavorable ratios raise the possibility that conventional CEAs can omit important value elements that markets recognize. While CEA does not explicitly affect pricing in the US, it does in some countries.[20] Because price controls can delay a drug's introduction,[21] it follows that if CEA omits value elements, it might deny patient access to treatments that confer favorable value.

We note, however, that other factors may explain the apparent inconsistency between unfavorable cost-effectiveness and marketplace success: **(1)** some CEAs use list prices rather than the actual net prices after discounts and rebates paid in the marketplace; **(2)** a drug's unfavorable cost-effectiveness may reflect its initial indication (on which our cost-effectiveness literature review focused), while its market success may reflect subsequent indications; **(3)** initial CEA projection may reflect a drug's initial formulation or mode of administration, attributes that can affect tolerability and convenience. Later market success may result from improvements in these attributes; and **(4)** a drug with an unfavorable ratio from U.S.-based CEAs (to which we limited attention) might have achieved marketplace success outside of the U.S. where its price was lower and its cost-effectiveness was favorable; in that scenario, there would be no actual inconsistency between marketplace success (outside the U.S.) and unfavorable cost-effectiveness (reflecting pricing inside the U.S.).

We also note that these CEAs reflect only information available at launch and might not fully reflect the real-world effectiveness of these therapies that subsequent price negotiations would have had an opportunity to account for. A closer look at the attributes for drugs we identified as marketplace successes having unfavorable cost-effectiveness would shed light on how often

these factors play a role. Finally, whether "market success" is an accurate indicator of value is contestable given the possible market failures we identified in this paper's introduction. That is, it is possible that the market is "overpaying" for many drugs, reimbursing at amounts exceeding true value. On the other hand, evidence from bottom-up analyses,[22] including our third analysis, discussed below, supports the overall conclusion that conventional CEA may omit important value elements.

Our **second analysis** investigated but did not find evidence that CEA underestimation of value for commercially successful drugs was associated with whether they were approved on an accelerated basis (Table 1). Given our small sample of 9 drugs with accelerated approval (out of 56 drugs in total), it is possible that we did not have sufficient statistical power to detect a possible association.

Our **third analysis** – the case studies – suggests that incorporating novel elements can yield more favorable CE ratios, although impacts varied substantially across drugs (Tables 2a and 2b). We found that dynamic pricing drives the most substantial CE ratio improvements, achieving 72 – 91% reductions for Trikafta and 31-38% for Xtandi – changes often far exceeding the impact of other novel elements. The exploratory analysis found dynamic pricing to be influential across all case study drugs (Table 3).

While not as substantial, some of the other novel elements produced notable CE ratio improvements for at least one drug. These improvements included the productivity element's 22% reduction of the CE ratio for Eylea, the caregiver element's 20% reduction (also for Eylea), and the disease severity element's 33% reduction for Vyndaqel. The real option value element produced either a small CE ratio reduction (Tufts calculation for Ibrance and both calculations for Xtandi) or an increase (GCEA calculation for Ibrance), suggesting that incorporation of the real option value element can make the CE ratio (slightly) less favorable. This result seems to reflect added costs attending the extended life expectancy that the real option value scenario recognizes.

For most novel value elements, lowering the discount rate from 3% to 2% affects both the numerator and denominator of the CE ratio proportionally, so the ratio itself does not change. In contrast, the price dynamics element is sensitive to the discount rate because the cost savings from loss of exclusivity occur in the future. Even so, reducing the rate from 3% to 2% only modestly increased the impact of this element in the Trikafta and Xtandi case studies (see Tables 2a and 2b).

Our analysis has several limitations.

First, we relied on approximations to the models used to produce published CE ratio estimates because authors typically do not provide sufficient detail to reconstruct the original CEA models.[23] Because our calculations are approximate, we restricted our case studies to exploring the order-of-magnitude and directional impact of incorporating novel value elements rather than quantifying their total combined effects or producing precise CE estimates. This exercise allowed us to assess which novel elements may have the greatest potential to influence cost-effectiveness conclusions and how these impacts might vary across different therapeutic contexts.

Second, because of the scope of this effort, we did not necessarily examine all relevant novel elements of value for each case study. Instead, we made judgment calls to identify novel elements to include based on available evidence, stakeholder feedback, and the desire to explore

a broad range of novel elements of value. Other value elements might have also had an impact on estimated cost-effectiveness.

Third, limited empirical data for novel value elements posed substantial challenges. Many inputs required assumptions drawn from sparse literature and expert judgment rather than validated, real-world data. Some have argued that our assumptions are conservative. For example, to estimate the impact of price dynamics, we modeled 30 additional future cohorts. Others recommend a longer horizon (e.g., 70 cohorts) to reflect that, once discovered, medicines can benefit successive patient generations at very low marginal cost.[24] Future studies should develop more robust empirical evidence, particularly for the dynamic pricing and ROV elements. We also note that while the exploratory analysis extended assessment of dynamic pricing to all case study drugs, prior research indicates that long-term pricing patterns can depend on a drug's characteristics, such as post-loss of exclusivity competition intensity[25-27] (which could in turn depend on factors like market size and ease of manufacturing) and formulation (e.g., oral vs. injectable),[28] which we could not account for here. In addition, the Inflation Reduction Act will influence prices for affected drugs. Accordingly, the results of the exploratory analysis should be interpreted as illustrative of the potential impact of dynamic pricing rather than as predictions for these particular drugs.

Finally, although incorporating novel value elements in our case studies seems to reduce CE ratio estimates (making them more favorable), we have not accounted for incorporation of these value elements into assessments for other, non-pharmacological interventions that may compete with drugs for health care resources. Incorporating novel value elements into assessments for these alternative opportunities to ensure consistency may make these other interventions also appear to be more favorably cost-effective, thus diminishing the case for greater spending on drugs that look more valuable because of the incorporation of novel value elements into their value assessments.[29] Indeed, assuming fixed resources for competing priorities implies a more stringent value benchmark (i.e., a lower cost-per-QALY "threshold").[29] As a practical matter, this issue arises only insofar as CEA informs investment and adoption decisions for non-pharmaceutical interventions. Key health technology assessment organizations – such as the National Institute for Health and Care Excellence (NICE) in the UK[30] and the Institute for Clinical and Economic Review (ICER)[31] in the US – focus largely on pharmaceuticals.

Incorporating relevant novel elements into non-health care interventions is also warranted, however. For example, climate change may adversely affect productivity, suggesting that assessments of investments to mitigate climate change should incorporate the productivity value element.[32] If the resources available to spend on competing priorities remain unchanged, the value benchmark must be more stringent.

Incorporating novel elements into drug assessments is most likely to suggest more investment in drugs when they are uniquely applicable to these interventions. Price dynamics (reduced future prices attending loss of market exclusivity) is not unique to drugs, as many technologies have likewise experienced substantial price reductions. But for many interventions, especially those that depend on labor (e.g., hospital care and education), incorporation of price dynamics will not have the same beneficial impact on value estimates.

CONCLUSION

Our analyses lend plausibility to the argument that traditional CEA conducted at launch does not reflect all quantifiable aspects of value subsequently recognized by the market. For some value elements – including price dynamics in particular – these omissions may have a substantial impact on cost-effectiveness findings.

More broadly, when incorporating additional value elements, it is important to consider how consistently applying such methodological changes would affect evaluations of other types of interventions. Extending novel value elements across a wider range of domains could imply a more stringent value benchmark and, consequently, a smaller relative increase in drug value than the "first-order" effects described here. Nevertheless, because pharmaceuticals have uniquely low long-term marginal costs, incorporating price dynamics would likely continue to exert a substantial influence on value assessments for many therapies.

Incorporating novel elements of value into CEAs at product launch may be infeasible because of limited data availability. Nonetheless, the finding that market value can frequently exceed the value implied by traditional CEA – and the possibility that it may better align with societal preferences – is important. It suggests that modelers and assessors should explore, in sensitivity analyses, additional value elements that might contribute to these differences.

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Table 1
Successful drug characteristics, stratified by CE ratio favorability

	Favorable CE ratio (n=28)	**Unfavorable CE ratio** (n=28)
Accelerated approval (p = 0.17)		
Yes	3 (33%)	6 (67%)
No	25 (53%)	22 (47%)
Disease category (p = 0.14)		
Certain infectious and parasitic diseases (A00-B99)	8 (80%)	2 (20%)
Neoplasms (C00-D48)	7 (44%)	9 (56 %)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)	1 (50%)	1 (50%)
Endocrine, nutritional, and metabolic diseases (E00-E90)	3 (38 %)	5 (62%)
Diseases of the nervous system (G00-G99)	2 (29%)	5 (71%)
Diseases of the eye and adnexa (H00-H59)	0 (0 %)	1 (100%)
Diseases of the circulatory system (I00-I99)	4 (100%)	0 (0%)
Diseases of the respiratory system (J00-J99)	1 (25%)	3 (75 %)
Diseases of the skin and subcutaneous tissue (L00-L99)	2 (50%)	2 (50 %)

Table 2a
Novel element impact on traditional CE ratio (percent reduction): 3% discount rate[(a)(b)]

	Trikafta		Xtandi		Vyndaqel		Ibrance		Eylea	
	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts
TCEA ratio ($'000 / QALY)	1,547	1,186	481	438	1,082	926	1,826	786	994	994
Single elements										
• PD	72%	90%	35%	31%						
• Prod	1%	1%					1%	1%	22%	22%
• ROV			2%	2%			↑3%	2%		
• CG					7%	7%			20%	20%
• Severity					33%	33%				
Multiple elements										
• PD & Prod	73%	91%								
• PD & ROV			37%	34%						
• CG & Severity					38%	38%				
• Prod & ROV							↑2%	4%		
• Prod & CG									42%	42%

Abbreviations: CG: Caregiver, PD: Price dynamics, Prod: Productivity, ROV: Real option value.

Notes:

(a) An "up arrow" ("↑") indicates that incorporation of the novel value element increased the value of the cost-effectiveness ratio, making it *less* favorable.

(b) We have highlighted in green results for individual novel value elements that exceed 15%.

Table 2b
Novel element impact on traditional CE ratio (percent reduction): 2% discount rate[(a)]

	Trikafta		Xtandi		Vyndaqel		Ibrance		Eylea	
	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts
TCEA ratio ($'000 / QALY)	1,436	1,074	479	437	1,043	913	1,800	774	994	994
Single elements										
• PD	78%	91%	38%	35%						
• Prod	1%	1%					1%	1%	22%	22%
• ROV			2%	2%			↑3%	2%		
• CG					7%	7%			20%	20%
• Severity					33%	33%				
Multiple elements										
• PD & Prod	79%	93%								
• PD & ROV			41%	38%						
• CG & Severity					38%	38%				
• Prod & ROV							↑2%	4%		
• Prod & CG									42%	42%

Abbreviations: CG: Caregiver, PD: Price dynamics, Prod: Productivity, ROV: Real option value.

Notes: Same as Table 2a.

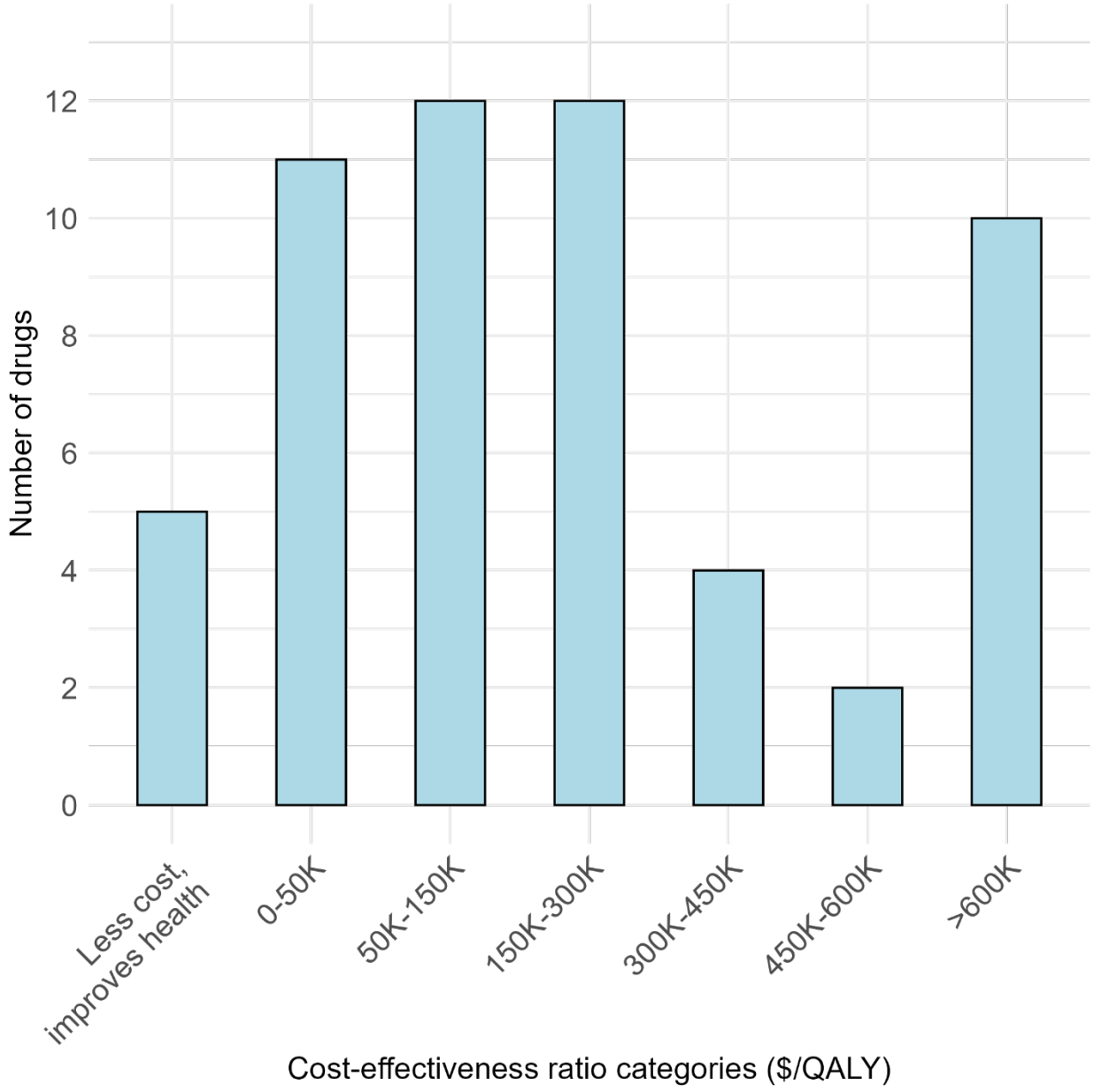
Table 3
Exploratory analysis: Price dynamic impact on traditional CE ratio (percent reduction) [(a)]

	Trikafta		Xtandi		Vyndaqel		Ibrance		Eylea	
	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts	GCEA	Tufts
3% discount rate										
TCEA ratio ($'000 / QALY)	1,547	1,186	481	438	1,082	926	1,826	786	994	994
Price dynamics	72%	90%	35%	31%	41%	38%	37%	32%	28%	49%
2% discount rate										
TCEA ratio ($'000 / QALY)	1,436	1,074	479	437	1,043	913	1,800	774	994	994
Price dynamics	78%	91%	38%	35%	44%	40%	40%	35%	31%	52%

Notes:

(a) Results for Trikafta and Xtandi come from the core analysis (results in Tables 2a and 2b). Results for Vyndaqel, Ibrance, and Eylea are part of the exploratory analysis. See Discussion for commentary.

Figure 1: Histogram of median cost-effectiveness ratios (n=56 drugs)



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ENDNOTES

Endnote#1

The market can be distorted by monopolistic behavior, patent protections, and other barriers that limit competition, allowing manufacturers to set prices above what would emerge in a truly competitive market.[1]

> **(Ref #1)** Neumann et al. 2021 see Chapter 2, page 16: "As Nobel- Prize winning economist Kenneth Arrow observed in a seminal 1963 paper; healthcare markets deviate from "normal" competitive markets in their "adaptations to the existence of uncertainty in the incidence of disease and in the efficacy of treatments." Economists also characterize the market as having "information asymmetry," meaning that buyers have much less information than sellers and thus cannot appropriately value products." See also Chapter 2, page 28 "Patents and market exclusivity confer a powerful incentive, restricting competition and providing drug developers considerable pricing power."

Endnote #2

To inform such negotiations, researchers and policymakers have developed and used health technology assessment to estimate the price that aligns with value.[2]

> **(Ref#2)** Neumann et al. 2021 see Chapter 4, page 62: "For prescription drugs, the market distortions described in Chapter 2 of this volume mean that prices do not reasonably represent value. As a consequence, economists have developed value assessment techniques for medications."

Endnote #3

Cost-effectiveness analysis (CEA) has become the primary technocratic tool for measuring the value of pharmaceuticals. [3,4] ostensibly filling the gap left by market mechanisms.

> **(Ref #3)** Neumann et al. 2018, see page 119-120: "Concerns about rising spending on prescription drug prices and in other areas of health care have led to multiple initiatives in the United States designed to measure and communicate the value of pharmaceuticals and other health care technologies for decision making. Some rely on conventional cost-effectiveness analysis (CEA) that uses the outcomes metric of the quality-adjusted life-year (QALY), whereas others rely on multiple attributes or criteria to reach a decision."
>
> **(Ref #4)** Kim DD et al. 2021, see page 640: "However, a growing concern about inefficient health care spending has led to the incorporation of value (typically measured by ICERs using QALY as the measure of health gain) into organizations' health care decisions and practice guidelines. For example, the Institute for Clinical and Economic Review (ironically, with the moniker ICER), a US-based nonprofit organization, applies systematic and evidence-based approaches—including CEAs—to assess the value of various health technologies."

Endnote # 4

CEA critics argue that CEA serves as a poor substitute for market-derived prices. Some have made a "bottom-up" case, arguing that traditional CEA (TCEA) does not account for the full range of benefits that drugs confer, particularly those that address unmet needs for patients, caregivers, and society.[5]

> **(Ref #5)** Lakdawalla et al. 2018, see page 137-138: "Nevertheless, some additional elements that may reflect value but are not normally captured in CEA with the QALY should be considered as well, depending on the perspective of the analysis. Productivity gains, net of consumption, should be included for societal-level perspectives in the incremental cost calculations for CEA. Augmenting CEA to consider these additional elements would result in a more comprehensive CEA in line with the Second Panel's Impact Inventory."

Endnote # 5

Incorporating "novel value elements" into CEA represents an effort to address these complaints.[6]

> **(Ref#6)** Shafrin et al. 2021, see page 651: "Several recent studies and consensus panels agree that wider individual and societal benefits should be accounted for in CEAs and have enumerated broader elements of value that the traditional health care sector perspective may neglect". See also p. 651: "ISPOR organizes elements of value used in CEA into core elements (quality-adjusted life-years [QALYs] and net costs), commonly but inconsistently used elements (productivity and adherence-improving factors), and novel elements that may be considered when conducting CEA from a societal perspective."

Endnote # 6

Examples include the additional value of addressing severe health conditions, reducing disease transmission, reducing caregiver impacts, and accounting for future generic pricing that most published CEAs overlook. [7,8]

> **(Ref#7)** Neumann et al. 2021, see page 62 and Table 4: "Most published (95%) CEAs did not include assumptions about future genericization (Table 4). Only 5% included assumptions about future generic prices for intervention drugs and even fewer (2%) included such assumptions about comparator drugs."
>
> **(Ref#8)** Leech et al. 2023, see page 2: "For example, we reviewed oncology CEAs that used a societal perspective (published 2012–17; n = 102) and found that family spillover effects had largely been omitted from analyses, despite the large family impact often observed from cancer. Only 22% of CEAs incorporated family costs and no studies included family health effects."

Endnote #7

Studies have shown that incorporating novel value elements into a conventional CEA could change cost-effectiveness conclusions. [9-11]

> **(Ref#9)** Ma et al. 2022, see page 1339: "The ICER for HPV vaccines from the original published article, which assumed a healthcare sector perspective, was $38 334 per DALY averted. The ICER became more favorable after incorporating 3 additional value elements (ie, patient time, unpaid caregiver time, costs of lost productivity because of illness). Adding lost productivity because of illness substantially changed the cost-effectiveness ratio, from its base-case value of $36 725 per DALY averted to cost saving. Including all of these elements yielded results indicating that the HPV vaccine was cost-saving (ie, less costs and more DALYs averted compared with no vaccination)."
>
> **(Ref#10)** Rubin et al. 2022, see page 787: "Allowing drug prices to be reduced after the loss of exclusivity decreased the incremental costs of ELX/TEZ/IVA from $4,416,000 to $2,435,000, thereby reducing the ICER by approximately 45% to $266,000."
>
> **(Ref#11)** McQueen et al. 2023, see page 324 and Table 2: "Base-case ICERs were $327,000, $102,000, $700,000, and $102,000 for allergic asthma, endometriosis, PPMS, and AD, respectively (Table 2). In scenario 1, with genericization, the range of ICER changes was from a 14% increase (ocrelizumab for PPMS) to a 31% increase (dupilumab for AD). In scenario 2, with a static net price increase until patent expiration and genericization, the range of ICER changes was from − 4% (ocrelizumab for PPMS) to − 37% (omalizumab for allergic asthma). In scenario 3, with a 4.5% increase until patent expiration and no genericization, the range of ICER changes was from a 22% increase (ocrelizumab for PPMS) to a 232% increase (omalizumab for allergic asthma). Finally, in scenario 4, with drug specific net pricing changes and genericization, the range of ICER changes was from − 5% (ocrelizumab for PPMS) to − 56% (elagolix for endometriosis)."

Endnote #8

We estimated the proportion of drugs in our sample with an unfavorable cost-effectiveness ratio. We designated a drug as having unfavorable cost-effectiveness if its ratio exceeds $150,000 per QALY[12]

(Ref #12) Neumann et al. 2023, see page 1313: "US-based authors increasingly referenced $100 000 per QALY—19 of 209 (9.1%) in 1990-1999, 199 of 861 (23.1%) in 2000-2009, 691 of 1761 (39.2%) in 2010-2019, and 209 of 445 (47.0%) in 2020-2021)—or $150 000 per QALY—13 of 861 (1.5%) in 2000-2009, 158 of 1761 (9.0%) in 2010-2019, and 105 of 445 (23.6%) in 2020-2021"

Endnote #9

We conducted assessments using both the conventional 3% discount rate recommended by the 2016 Second Panel on Cost Effectiveness in Health and Medicine,[13] and a 2% discount rate suggested by a more recent review. [14]

(Ref#13) Sanders et al. 2016, see page 1098: "Costs and health effects should be discounted at the same rate in cost-effectiveness analyses. Furthermore, given available data on real economic growth and corresponding estimates of the real consumption rate of interest and to promote comparability across studies, 3% is the most appropriate real discount rate for cost-effectiveness analyses."

(Ref#14) Cohen JT 2024, see page 582: "This review finds that although the health economics literature recommends 2 well-accepted approaches to inform appropriate discount rates, there is no firm basis for determining this value.HTA guidance for most countries recommends a rate without providing a basis. Even among economists who study the discount rate, opinions regarding the Ramsey Equation's parameters span a wide range. Nor is there consensus regarding what interest rate should inform the discount rate's value. This article addresses these challenges by taking past discount rate recommendations as an acceptable starting point (thus assuming an annual rate of 3% for 2010). It then focuses on the subsequent decline in both per capita consumption growth and real interest rates. Those declines imply a reduction in the annual discount rate to approximately 1.5% to a bit more than 2%. A continued decline in consumption growth, real interest rates, or both suggests possible further discount rate reductions."

Endnote #10

Trikafta: Published traditional CE ratio: $1,050,000 per QALY[15]

(Ref#15) Tice et al. 2021, see page 278 and Table 1: "Table 1 summarizes the cost-effectiveness results for each of the drugs compared with best supportive care in each of the populations for which the drug has an FDA indication. In all cases, the cost per QALY gained is greater than $1 million, which is substantially higher than cost-effectiveness thresholds in the United States and the rest of the world"

Endnote #11

Xtandi: Published traditional CE ratio: $437,623 per QALY[16]

(Ref#16) Wilson et al. 2014, see page 423 and Table 5: "The ICER for enzalutamide when compared to the next lowest treatment, abiraterone, is $437.6 K/QALY."

Endnote #12

Vyndaqel: Published traditional CE ratio: $880,000 per QALY[17]

(Ref#17) Kazi et al. 2020, see page 1219 and Table 2: "Compared with usual care, treatment with tafamidis over the lifetime horizon was projected to generate 1.29 (95% UI, 0.60–1.89) additional QALYs at an incremental cost of $1 135 000 (95% UI, 872 000–1 377 000), resulting in an ICER of $880 000 (95% UI, 697 000–1 553 000) per QALY gained."

Endnote #13

Ibrance: Published traditional CE ratio: $918,166 per QALY[18]

(Ref#18) Mamiya et al. 2017, see page 1828 and Table 2: "Under the usual care (FUL), the quality-adjusted life expectancy in patients with prior endocrine therapy was 1.34 QALYs, with a lifetime cost of $154 961 (Table 2). PAL + FUL was estimated to provide higher quality-adjusted life expectancy (1.46 QALYs) at greater costs ($269 551), resulting in an incremental cost-effectiveness ratio of $918 166 per QALY gained."

Endnote #14

Eylea: Published traditional CE ratio: $1,147,293 per QALY[19]

(Ref#19) Brown et al. 2020, see page 234 and Table 7: "The 11-year model ophthalmic cost perspective and societal cost perspective, incremental CURs comparing aflibercept to bevacizumab were both $1,147,273/QALY."

Endnote #15

While CEA does not explicitly affect pricing in the US, it does in some countries.[20]

(Ref#20) Neumann et al. 2021, page 98. "A 2017 report found that of the 20 western/southern European or Scandinavian members of the European Union or European Economic Area, 17 have at least one HTA organization with a national mandate to inform drug coverage, pricing, and/or reimbursement."

Endnote #16

Because price controls can delay a drug's introduction,[21] it follows that if CEA omits value elements, it might deny patient access to treatments that confer favorable value.

(Ref #21) Cockburn et al. "… countries that adopt strong pharmaceutical price controls experience significantly longer launch lags for new drugs. We estimate that introducing price controls increases launch lags by about 25 percent, and with instrumental variables the estimate rises to more than 80 percent."

Endnote #17

On the other hand, evidence from bottom-up analyses,[22] including our third analysis, discussed below, supports the overall conclusion that conventional CEA may omit important value elements.

(**Ref #22**) The abstract states, "The static cost-effectiveness estimate was less favorable than the dynamic estimate for a chronically administered drug by between 82% (case 1) and 62% (case 2), and for a 1-time drug by between 34% (case 3) and 27% (case 4)."

Endnote #18

First, we relied on approximations to the models used to produce published CE ratio estimates because authors typically do not provide sufficient detail to reconstruct the original CEA models.[23]

(Ref #23) Cohen et al. 2017, see page 912: "Health economics in particular raises credibility questions because it typically relies on computer simulation models that can combine multiple sources of data, including randomized trials and observational studies, to characterize treatment efficacy, effectiveness, harm, quality of life, and cost. Hlatky noted that many of these models "lack transparency, are difficult to understand and evaluate, and have too many hidden assumptions." Their credibility can suffer because of what the New England Journal of Medicine referred to as "the discretionary nature of model building and data selection in these analyses."

Endnote #19

Others recommend a longer horizon (e.g., 70 cohorts) to reflect that, once discovered, medicines can benefit successive patient generations at very low marginal cost.[24]

(**Ref #24**) Shafrin et al., 2024. "… in practice we highly recommend using additional cohorts (e.g., 70 cohorts if the model extends 70 years since patients will forever benefit from the upgrade to outcomes that a novel drug offers, even if it's later displaced by better treatments)…"

Endnote #20

… prior research indicates that long-term pricing patterns can depend on a drug's characteristics, such as post-loss of exclusivity competition intensity[25-27] (which could in turn depend on factors like market size and ease of manufacturing) and formulation (e.g., oral vs. injectable),[28]…

> **(Ref #25)** Conrad and Lutter, 2019. "We find that for products with a single generic producer, the generic AMP is 39% lower than the brand AMP before generic competition, compared to a 31% reduction using invoice prices. With two competitors, AMP data show that generic prices are 54% lower than the brand drug price before generic competition, compared to 44% when calculated using invoice-based drug prices. With four competitors, AMP data show that the generic prices are 79% less than the brand drug price before generic entry, compared to 73% when calculated using invoice-based drug prices. With six or more competitors, generic prices using both AMP and invoice prices show price reductions of more than 95% compared to brand prices."
>
> **(Ref #26)** Dickson and Kent, 2021. "…when outliers were excluded from the average marginal effects, 1 generic competitor was associated with a mean price decrease of 17.0%, 2 competitors with a 39.5% price decrease, 3 competitors with a 52.5% price decrease, and 4 or more competitors with a 70.2% price decrease"
>
> **(Ref#27)** Nguyen et al., 2022. "Prices decline by 20% in markets with about three competitors (the expected price ratio of current generic to pre-generic entry brand average prices is 80%). Prices continue to decline by 80% relative to the pre-generic entry price in markets of ten or more competitors (the expected price ratio is about 30% following 2 years after entry, dropping to 20% following 3 years after entry)."
>
> **(Ref#28)** IMS Institute, 2016. Page 3: "Price reductions occur faster for oral medicines than for injectable drugs, which often attract fewer generic competitors."

Endnote #21

…thus diminishing the case for greater spending on drugs that look more valuable because of the incorporation of novel value elements into their value assessments.[29]

> **(Ref #29)** Neumann et al. 2024: "More generally, drug values may not seem as favorable after analyses also apply adjustments to other health interventions, which can compete with drugs for health care resources. For example, analyses of effective nonpharmacological intervention - for example, cognitive behavioral therapy to address anxiety-should also account for spillover effects, such as favorable impacts on patients' family members. Lower discount rates should also apply to public health programs with long-term benefits. Because these adjustments can make non-drug interventions also appear more valuable, their universal application might diminish the case for diverting limited resources to pharmaceuticals. Applying these adjustments only to drugs amounts to a thumb on the scale."

Endnote #22

Indeed, assuming fixed resources for competing priorities implies a more stringent value benchmark (i.e., a lower cost-per-QALY "threshold").[29]

> **(Ref #29)** Neumann et al. 2024: "Incorporating these factors also implies that the benchmarks used to identify value (that is, the thresholds at which a drug or intervention is deemed to be cost-effective) should be lower (more restrictive) or that overall health spending should increase."

Endnote #23

Key health technology assessment organizations – such as the National Institute for Health and Care Excellence (NICE) in the UK[30] and the Institute for Clinical and Economic Review (ICER)[31] in the US – focus largely on pharmaceuticals.

> **(Ref #30)** Osipenko et al. 2024 states, "Technology appraisals (TA) is the core HTA programme that has been conducting multiple TAs (MTAs) since the inception of NICE… TAs predominantly focus on

pharmaceuticals." Of the 539 unique TAs listed in sheets 3-10 of the supplement data (https://zenodo.org/record/5236080), 490 (91%) focused on pharmaceuticals.

(Ref #31) Neumann et al. 2024: "The Institute for Clinical and Economic Review (ICER), a value assessment organization in the US, focuses almost exclusively on pharmaceuticals."

Endnote #24

For example, climate change may adversely affect productivity, suggesting that assessments of investments to mitigate climate change should incorporate the productivity value element.[32]

(Ref#32) Marinaccio et al. 2025, see page 1: "A decrease in productivity of about 6.5% was estimated for workers engaged in physical activities requiring high metabolic rates for every unit degree increase in temperature between 19.6 C° and 31.8 C°"