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WHITE PAPER

GETTING THE MATH RIGHT WHEN MEASURING THE **VALUE OF NEW MEDICINES**

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ABSTRACT:

Cost-effectiveness analysis (CEA) is commonly used to inform the assessment of value from new healthcare technologies. However, traditional CEA methods often fail to capture important components of social value for biopharmaceutical and other innovations. Two examples are the failure of traditional CEA to account for diminishing returns to health improvement and its failure to account for declines in price as products lose market exclusivity, both of which would appear in "generalized cost-effectiveness analyses" (GCEA).

We investigated the effect of these two elements of social value on traditional CEA value assessments, using a sample of 20 traditional CEA health technology assessments conducted by the Institute of Clinical and Economic Review. We accounted for diminishing returns using Generalized Risk-Adjusted Cost-Effectiveness (GRACE), and we accounted for changes in the price after the loss of market exclusivity—sometimes referred to as "dynamic pricing" effects. We determined the effect on "value for money" and on the share of societal value estimated to accrue to innovators versus the rest of society.

In traditional CEA, 8 of the 20 medicines produced value for money. However, accounting for diminishing returns and dynamic pricing revealed that 17 of 20 produced value for money in our benchmark scenario, and 18 did so in a sensitivity analysis employing larger but plausible price declines after loss of market exclusivity. In 13 of 20 cases in the benchmark scenario (or 14 of 20 in the sensitivity analysis), the majority of value flowed not to innovators but to the rest of society.

Traditional CEA methods omit sources of social value that appear quantitatively significant. Applying GCEA in health technology assessment can lead to more complete and accurate estimates of societal value, facilitating more efficient resource-allocation better aligned with the welfare of patients present and future.

CONTENTS:

THE GCEA VALUE FLOWER

Courtesy of NPLB, based on ISPOR Value Flower [9]

I. INTRODUCTION

Determining the value of new medicines sheds light on how much to invest in the utilization of current treatments and, ultimately, into research and development of new treatments. Since health improvements play an outsized role in human well-being [1], much rides on getting the math right around value assessment.

Throughout the world, analysts and policymakers assess the value of new medical therapies, particularly biopharmaceutical products, almost universally using traditional cost-effectiveness analysis (CEA) methods. The U.K.'s National Institute for Care and Effectiveness (NICE) pioneered use of CEA, beginning after World War II. In 2007, Australia formally introduced cost-effectiveness measures for drugs for inclusion in its Pharmaceutical Benefits Scheme. Use of CEA or its variants has spread worldwide, including in France, Germany, Japan, the Netherlands, Norway, Sweden, and elsewhere. In the U.S., the private Institute for Clinical and Economic Review has conducted many such analyses in recent years with increasing use by health payors. We will describe this as $ICER_{ORG}$ to distinguish it from the Incremental Cost-Effectiveness Ratio (ICER), a common summary measure of value that we discuss later.

Unfortunately, standard CEA methods often fail to capture important components of social value for biopharmaceutical and other innovations. To take just two examples, CEA fails to recognize the heightened value of treating patients with permanent disabilities or severe acute illnesses, and it fails to recognize that drugs' prices can fall markedly after patent exclusivity ends. Solutions exist for both these deficiencies. Generalized Risk-Adjusted Cost Effectiveness (GRACE) properly accounts for value of health gains in different circumstances [2-6]. "Dynamic pricing" approaches incorporate the effect of price reductions at patent expiration [7, 8]. These generalized cost-effectiveness analysis (GCEA) approaches add some complication to value assessment, leading to the obvious and important question: *When and to what extent do these new methods materially alter conclusions about the societal value of new medicines?* To answer this question, we compared a set of 20 recent $ICER_{ORG}$ evaluations of prescription drugs with alternative ICER values that incorporate these new methods. We used EntityRisk's Pricing, Outcomes, and Value Estimation (PROVEN) software, which allows the computation of GRACE and GCEA results at scale. PROVEN can take traditional CEA results as inputs and produce GCEA results efficiently. We focused on a set of drugs treating severe and rare illness, along with several other medicines for more common conditions. After establishing a uniform basis for comparison, we used GRACE for valuing health gains.

Second, we incorporated dynamic pricing effects. These comparisons illuminate the importance of using these new methodologies when evaluating biopharmaceutical and related therapeutic, diagnostic and preventive innovations.

As a brief summary of our results, according to traditional CEA, only 8 of the 20 medicines in our sample produced value for money to society. However, after accounting for disease severity and employing relatively conservative assumptions about dynamic pricing, this figure inverts, and at least 17 of the 20 medicines produce value for money. Stronger dynamic pricing assumptions imply that 18 of the 20 medicines produce value for money. Notably, neither of the two as-yet cost-ineffective products have received full FDA approval, implying that all the fully approved FDA indications in our sample turn out to be cost-effective in our analyses. Moreover, our framework incorporates only a few of the elements of value that have been identified in the economic literature [9].

The question of how to measure the societal value of new medicines is especially timely. The Centers for Medicare and Medicaid Services (CMS) is preparing to set "maximum fair prices" for certain medicines in the US, but they have not yet set forth the analytic methods they will use [10-12]. Meanwhile, some state governments have begun establishing prescription drug affordability boards and empowering them to assess the value of drugs and take steps to alter prices in response [13].

Our work takes a societal value perspective. Such a perspective is necessary to inform decisions about how much governments should invest in the creation, uptake and use of medical technologies. Basic science investments such as the U.S. National Institutes of Health, the European Union's Horizon programs, and others provide the backbone for many new health-improving technologies. Properly designed and broadly supported prescription drug insurance can help assure that uptake and use of new innovations are properly supported [14, 15].

To assist in understanding the importance of these issues, we first present standard CEA methods in detail in Section II. Section III explains introduces the GRACE methodology in more detail. Section IV discusses the issue of "dynamic pricing," the change in prices upon patent expiration. Section V presents our primary results, followed in Section VI with discussion and concluding comments.

II. STANDARD COST-EFFECTIVENESS ANALYSIS (CEA) AND ITS LIMITATIONS

Standard CEA methodology estimates incremental costs, $\Delta Cost$, and health gains, $\Delta Health$. It then compares their ratio, called the Incremental Cost-Effectiveness Ratio (ICER) against a threshold that defines what is deemed to be "cost-effective," K, the value of one year at full heath. The decision rule is that a treatment is deemed cost-effective if $K \geq \Delta Cost \div \Delta Health$. In the U.S., a loose consensus suggests that \$100,000 ≤ K ≤ \$200,000 with a "central" value of about K = \$150,000 per Quality-Adjusted Life Year (QALY) [16].

With ICERs, less is better—lower ICERs indicate better value. ICER values can improve either by reductions in cost (in the numerator) or increases in the value of health outcomes (in the denominator). We assess both issues in the analysis that follows.

Standard CEA methods were first reconciled with the economic theory of efficiency by Garber and Phelps in 1997 [17]. That work, following then-conventional use of CEA, assumed that value (utility) was always produced by health in constant proportions, so that a 10 percent gain in health creates a 10 percent gain in utility, a structure known as "constant returns to health," a concept to which we will return subsequently.

Estimating health gains, $\Delta Health$, requires a method to combine gains in life expectancy (LE) and health-related quality of life (HRQoL) into a single measure. Understanding how CEA combines such gains is fundamental to understanding where it can go wrong, so we proceed here with a clear statement of how CEA works.

In standard CEA, HRQoL is rated on a scale from zero to one, where "0" is the worst and "1"is the best imaginable health ("perfect" health), so 0 ≤ H ≤ 1. HRQoL "scales" the value of a life-year to create a measure known as "quality-adjusted life-years" or QALYs. In standard CEA, a gain of one Quality-Adjusted-Life-Year (QALY) can arise from various combinations of health or life expectancy gains. For example, two years of additional life expectancy for a

disease where HRQoL = 0.5 results in 1.0 QALYs, or two years of life multiplied by 0.5. So also, adding one year of life in a disease state where HRQoL is considered "perfect" (1.0) yields 1.0 QALYs of gain, and a gain of five years of LE in a disease state with HRQoL = 0.2 yields a 1.0 QALY gain. As one leader in developing and using CEA states, "…a QALY is a QALY is a QALY…" [18]. Neither the untreated health state nor who receives the health gains matter.

The logic of standard CEA leads to a controversial conclusion. If health-related quality of life is measured as lower for persons with disability or severe illness, then life expectancy gains produce fewer QALYs and, by extension less value, for these groups. Because of this implication, the U.S. Affordable Care Act (ACA) forbids Medicare and certain other federal agencies from using any method that reduces the value of improving people's health because of disabilities. The Inflation Reduction Act (IRA) extends this language, and the newly proposed HR 485 would expand this prohibition further.

Several proposals have been made to resolve this problem by assuming that, when estimating ICERs, people with permanent disabilities should be considered non-disabled [19, 20]. These methods do not address the fundamental flaw in CEA—the undervaluation of treatments for those with heightened permanent disability or acute diseases.

Closely related to the issue concerning disability, standard CEA does not account for differential values of health gains for sicker people. It says that a 0.1 gain in HRQoL has the same value, no matter whether received by a person with very poor health, or by in a person in quite-good health.

In so doing, standard CEA fails to incorporate one of the most fundamental concepts of economics: When something is scarcer, getting more of it creates heightened value. For sick or disabled people, HRQoL is scarce. Adding to their HRQoL creates more value than adding the same increment of health to persons in relatively good health. Scarcity matters.

To see this, consider Example 1, comparing two otherwise-similar people, one living in a 1000 square foot apartment, the other in a 3,500 square-foot home. To which would adding 200 square feet of space be more valuable?

In Example 2, consider two otherwise-similar people with identical incomes and fringe benefits, except that one has five weeks of paid vacation and the other has two weeks. For which would an additional week of paid vacation have the greatest value?

These types of comparisons shed light on a somewhat different dynamic, related to health losses rather than gains. Consider a perfectly healthy person that suddenly loses the use of their right index finger. Now imagine instead a bedridden, immobile, and cognitively impaired patient that also then happens to lose use of their right index finger. One can imagine that this incremental loss of function would be felt more keenly by the person that began with perfect health. Indeed, someone in extremely severe circumstances might place little value on small gains or losses, focusing instead on the possibility – however slim – of a major change in health that would finally move the needle into better functioning. Prior research identifies this "value of hope" as a real phenomenon among people facing the most dire kinds of health circumstances [21].

These two factors taken together paint a more nuanced picture that moves beyond the simplistic "QALY is a QALY" mantra. Marginal health improvements are more valuable to those with moderately severe illnesses than to those with mild disease, a conclusion supported by survey evidence in the economic literature [22-24]. Yet, those modest improvements in turn may not move the needle for those with the most crippling and debilitating illness. Among these patients, therapies with even small chances for major improvements are much more valuable than they would be to healthier groups, as documented by studies of patients with grave or terminal conditions [21, 25], and therapies producing modest gains might be correspondingly less valuable.

We can now see the fundamental flaw in standard CEA. It does not recognize the importance of context when measuring the value of any given health gain. It treats all gains the same, no matter who receives them, their untreated health level, or the extent to which the health gain changes the circumstances of their life. GRACE, which we present next, corrects these important errors of omission..

III. GENERALIZED COST-EFFECTIVENESS ANALYSIS (GCEA) METHODS

Generalized Cost-Effectiveness Analysis incorporates multiple elements of value neglected in traditional cost-effectiveness analysis. Two such elements include: generalized risk-adjusted cost-effectiveness (GRACE) to adjust for disease severity and risk; and dynamic pricing to account for changes in price over the life-cycle of new medicines. While not an exhaustive list of GCEA elements, these two components of GCEA nonetheless significantly alter the conclusions of traditional cost-effectiveness analysis. Here, we discuss the GRACE and dynamic pricing methodologies in more detail.

A. GENERALIZED COST-EFFECTIVENESS ANALYSIS (GCEA) METHODS

A new method to value health gains has emerged in recent years. Known as the Generalized Risk-Adjusted Cost Effectiveness (GRACE) model [2-6, 26]. GRACE makes one simple change from standard CEA—it recognizes the effects of scarcity. It says that the willingness to pay (WTP) for health gains depends on the circumstances in which these gains accrue. Compared with standard CEA, GRACE leads to at least four important conclusions:

- The value of any given health gain initially rises as the level of untreated health falls. Severity matters.
- The willingness to pay for gains in HRQoL initially rises as the severity of permanent disability increases. Reversing standard CEA conclusion, GRACE says that it is worth more—not less—to improve the health of disabled people.
- The willingness to pay for modest gains in HRQoL eventually falls, for patients in highly debilitated conditions, where even small chances of major improvements create reasons for hope.
- The traditional quality-adjusted life-year (QALY) is too restrictive and fails to reflect the full range of patient preferences over quality of life and life expectancy. GRACE demonstrates how to consider HRQoL and longevity separately, without focusing exclusively on the QALY as a single index of both quality and quantity.

Returning to the issue of permanent disability, GRACE reverses the disturbing conclusion from standard CEA. Since disabled people have lower health levels (more "scarcity"), the value of improving their lives is not just worth "the same" as for a non-disabled person, but in many circumstances, it is worth more. This result applies not only to medical therapies but to such things as architectural accommodations (ramps, mechanized doors, elevators) and restructuring medical facilities to better-accommodate disabilities, a major remaining issue [27]. Implementing GRACE requires measuring real people's attitudes towards uncertainty in health outcomes and the associated rates at which their well-being increases with improvements in health. Incorporating these real-world preferences into the analysis is the fundamental difference between GRACE and standard CEA, which assumes that people have constant returns to health in producing utility. All difference between GRACE and CEA rest on how preferences change when people do not have constant returns to health.

In brief, to measure these newly-required values, a University of Southern California (USC) research team used responses from a nationally representative American panel of N = 1,114 respondents [28]. They combined this with a highly-flexible mathematical representation of how health affects utility, known as Expo-Power (EP) utility, to describe people's attitudes toward health risk and gains from increasing health at various degrees of illness [29]. These data provided the basis for measuring the preferences of real people about health gains in various situation. This study provides the first such estimates in the economics literature [28].

B. DYNAMIC PRICING

GRACE addresses errors of omission in estimating the *value of health gains*. Consideration of dynamic pricing addresses an error of commission in measuring the *cost of treatment*. A key feature in assessing the societal costs of prescription drugs is the path of prices over time, particularly at the time when patent protection expires. With generic entry, societal drug costs often decline substantially. Analyses that fail to account for this dynamic effect therefore introduce an error into the second part of the ICER ratio by overstating societal costs once patent expiry has occurred.

No two patented drugs will have the same generic competition, since each has unique attributes. Sometimes this arises because of technical difficulties in reproducing the drug. Sometimes it involves steps taken by patent holders to extend the period of market exclusivity. In general, US patent law gives protection for 20 years, extended to 25 years in most cases by the 1983 "Orphan Drug Act" for biopharmaceutical products. Offsetting this, however, is the extensive time needed for studies of treatments' effectiveness and safety. Combining these, the average time for patent exclusivity in the U.S. is about 14 years, a number we use in our analyses.

We also needed to choose broad estimates of the extent of price reduction that occurs upon patent expiration. In so doing, we were guided by two studies. A recent study estimated price reductions of 76 percent using data from the period of 1998 to 2008 [30]. Prior research estimated price reductions of 83 percent [31] and recognized the presence of variability in this effect across different drugs, We use a 76 percent price reduction as our benchmark. To test the sensitivity of our results to variation across drugs, we also explore the implications of 90 percent price reductions. Even a 90% drop may be conservative in some cases, since generic price erosion for widely sold drugs can often approach 99% [32].

Introducing dynamic pricing comes together with another change in our calculations compared with standard CEA methods. We introduce new cohorts of patients into the world each year, based in the incidence of the diseases in question. For any chronic condition, the means that once new drugs enter the market, they treat those who had the disease at the time, and then in each successive year, new cohorts of patients who can be treated. These "stacked cohorts" reflect the true nature of benefit that any drug can provide. Their use is particularly important in diseases with many years of chronic treatment involved, including, for example, multiple sclerosis, sickle cell disease, non-alcoholic steatohepatitis, diabetes, cystic fibrosis, psoriasis, and ulcerative colitis.

The first step in our analysis harmonized the ICER estimates so they shared a common basis for pricing and time-horizon. For studies that used list prices to measure drug costs, we converted these to net prices, inclusive of real-world cost after discounts and rebates. Net prices are estimated using published research on the ratio of list to net prices [33]. This adjustment is made to both treatment and standard of care drugs, whenever list prices are used. Non-drug costs are not affected by this adjustment.

The second step in our analysis estimated ICERs using GRACE and also accounted for the pricing effects of patent expiration. To reflect the effect of patent expiration, we assume that the annual net price for the drug remains constant for an average of 14 years [33], at which point it falls by 76% [30][1]. In addition and as noted earlier, to reflect societal benefits and costs, we account for new cohorts of patients starting treatment. Sixty annual cohorts of patients initiate treatment. The clinical benefits of treatment remain the same across cohorts; prices change according to the dynamic pricing rules described earlier. Next, we conduct a sensitivity analysis in which the drug net prices are assumed to fall 90% after 14 years, to reflect a larger drop due to the loss of market exclusivity. As context, research by FDA economists demonstrates that prices fall by 90% after 6 generic firms enter the market [32], and several of the drugs in our sample experienced price declines above the 90% threshold, adding to its salience.[2] Finally, we measure how social value is distributed between the innovators that created it and all other stakeholders in society. We measure this in two ways: 1) incremental drug costs -- i.e., the additional social costs that flow to innovators – as a share of incremental social value created by the drug; and 2) the ratio of incremental social value to incremental drug price (the "value-price" ratio), which measures the divergence between the price of the drug and its value to all social stakeholders other than the innovator. In both cases, incremental social value is the value of incremental health benefits from the drug, less any incremental non-drug costs associated with its use.

One technical detail deserves explanation. ICERs report costs per QALY gained. Earlier, we explained that GRACE does not use QALYs, but instead separately values

1 Helland and Seabury [30] estimate that generic entry reduces log prices by 1.433. This roughly corresponds to a 76% reduction in price in the sense that exp (-1.433)≈0.24. Moreover, both Medicaid inflation rebates and now Medicare inflation rebates (under the Inflation Reduction Act) tend towards prices that remain flat in real terms over the life-cycle [34].

2 Generic prices for atorvastatin, dimethyl fumarate, and erlotinib were reported to be: $4, $37.50, and $62.40 on costplusdrugs.com (accessed on May 5, 2023). Generic prices for apremilast and tofacitinib were reported to be $78 and $220 on pharmacychecker.com (accessed on May 5, 2023). The net prices for these medicines used in our analysis were: $348; $21,083; $8218; $16,174; and $457, respectively.

improvements in life expectancy and HRQoL. Fortunately, however, GRACE implies a "rate of exchange" that allows us to convert the ICER into costs per unit of HRQoL; this is comparable to the traditional ICER and facilitates a fair comparison between value under GRACE and value under traditional CEA.

We selected a convenience sample of 20 drug/indications for study. Since disease severity was of particular interest as a modifier of value, half of these were treatments for cancer or rare disease. The other half consist of treatments for prevalent, visible, and/or high-expenditure disease areas: anaphylaxis, asthma, cardiovascular disease, gastroesophageal reflux disease, Hepatitis-C, HIV, non-alcoholic steatohepatitis (NASH), psoriasis, stroke, and Type-2 diabetes. **Table 1** lists the drugs we studied, their indications, and the following key parameters from the original traditional cost-effectiveness studies cited therein: quality of life gains, longevity gains, baseline quality of life on standard care of treatment without the novel drug, incremental drug cost, and incremental non-drug cost.

IV. RESULTS OF GENERALIZED COST-EFFECTIVENESS ANALYSIS (GCEA)

The primary results of our GCEA analyses are summarized in Figures 1. **Figure 1** shows the ICER value created using standard CEA methods, closely replicating the values published by $ICER_{ORG}$. As discussed previously, the results in **Figure 1** are harmonized so that all studies use net prices for drug costs, rather than list prices. The original ICER calculations appear in black, and the harmonized calculations in red.

Employing the conventional decision threshold of $150,000 per one year at full health, eight of these drugs (treating cardiovascular disease, prostate cancer stroke and diabetes) would qualify for coverage using the properly adjusted ICER values. The remaining twelve drugs would not be viewed as providing value for money.

Applying the tools of GCEA, **Figure 1** also corrects the omission of disease severity and the failure to measure long-term price declines. The orange bars show the consequences of shifting from standard CEA, ΔHealth_CEA to GRACE methods of value, $\Delta Health_{GRACE}$. thereby incorporating the value-adjusted health gains implied by GCEA. As the GRACE model predicts, the greatest ICER reductions appear in the diseases with moderate severity (e.g., cystic fibrosis, stroke, prostate cancer, type 2 diabetes mellitus-related cardiovascular disease, biologic-experienced ulcerative colitis, and NASH). In the most critically severe diseases, treatments with modest annual health improvements are worth less, because they may not materially change the patient's health circumstances.

The dark green bars broaden the GCEA calculation by including the effects of dynamic pricing, where the price of the medicine falls by 76% 14 years after launch. With the inclusion of dynamic pricing to GCEA, 9 of the 20 drugs fall under the $150,000 per QALY decision. The light green bars in **Figure 1** show the combined consequences of further introducing the annual cohorts of new patients, in addition to dynamic pricing. These reductions are more dramatic, because they illustrate the long-run consequences of all other corrections once future cohorts of patients are considered. With these two GCEA changes, now 17 of the 20 drugs fall under the $150,000 per QALY decision threshold and 18 of the 20 would qualify with a more generous $200,000 per QALY threshold.

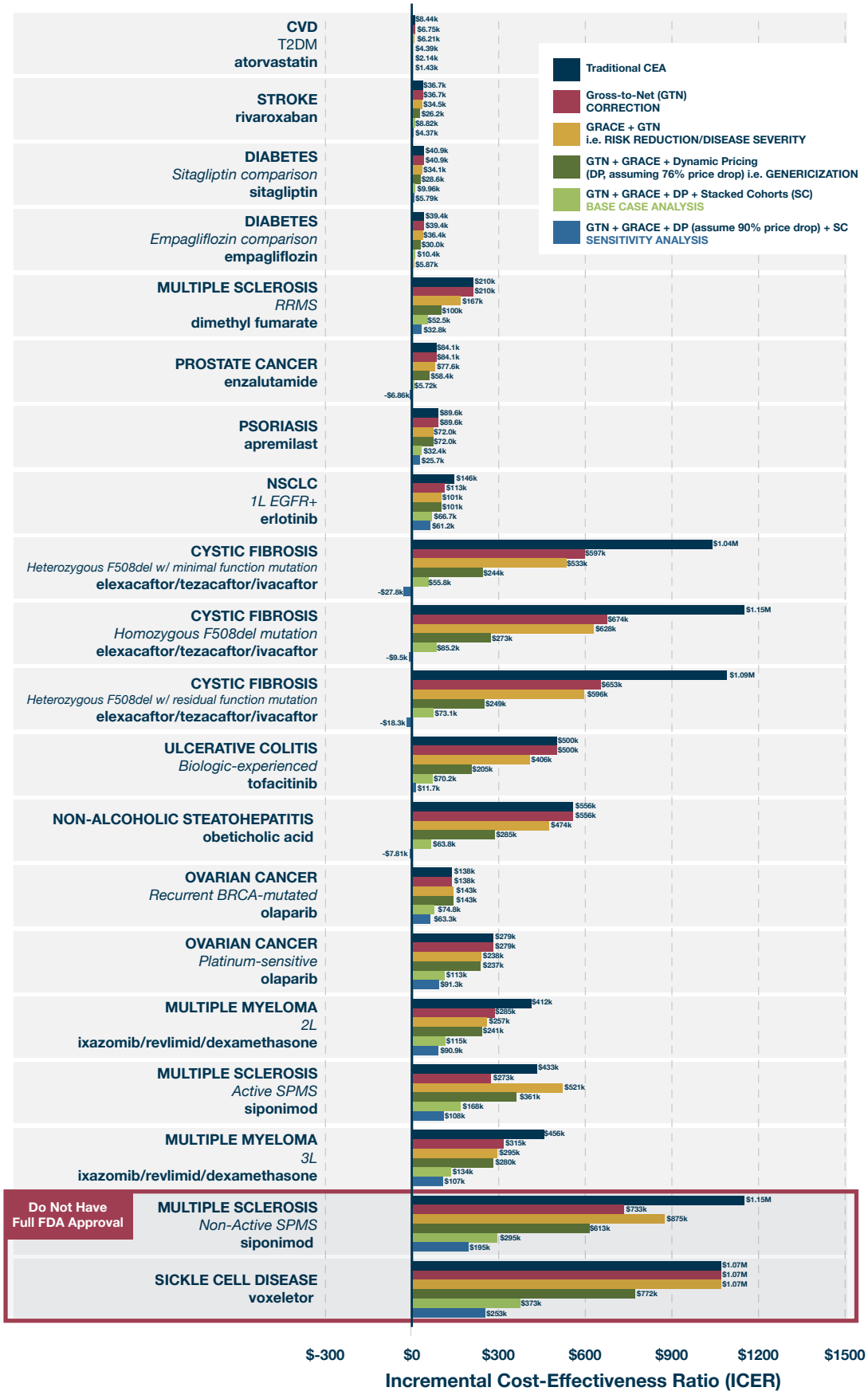
If the proper dynamic pricing adjustment is 90 percent, then 18 of the 20 drugs we evaluated would represent value for money at $150,000 per QALY. **Figure 1** shows these results, where the light blue bar illustrates the 90 percent dynamic pricing adjustment, compared to the light green bar that reports the baseline 76 percent reduction. The two as-yet cost-ineffective indications in **Figure 1** are voxeletor for sickle cell disease and siponimod for non-active Secondary Progressive Multiple Sclerosis (SPMS); neither of these indications has received final approval from FDA. Voxeletor has received accelerated approval, based on surrogate endpoint findings that it increased hemoglobin, under the condition that it collect further data to demonstrate hard evidence of improvement in patient functioning or patient reported outcomes.[3] Meanwhile, siponimod has not received FDA approval for non-active SPMS, an indication in which

3 https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-drug-treat-sickle-cell-disease-patients-aged-4-11-years#:~:text=FDA%20has%20granted%20accelerated%20approval,older%20with%20sickle%20cell%20disease.

FIGURE 1:

ICER Results With Net Dynamic Pricing & Grace, Base Case & Sensitivity

NOTES: The abbreviations in the figure legend are as follows. "GTN" corresponds to "gross-to-net," implying that net prices are used in all studies. "DP" corresponds to "dynamic pricing," where the price falls by 76% or 90% 14 years after launch, where the magnitude of the price decline is specified in the legend. "SC" corresponds to "stacked cohorts," indicating that new cohorts are introduced annually for 60 years. Assessments by $ICER_{ORG}$ report costs per quality-adjusted life year (QALY) gained. While GRACE does not use QALYs, it implies a "rate of exchange" that allows us to convert the ICER into costs per unit of health-related quality of life (HRQoL); this is comparable to the traditional ICER and facilitates a fair comparison between value under GRACE and value under traditional CEA.



its pivotal clinical trial failed to show statistically significant benefit [35].[4]

Table 2 uses our results to report the distribution of social value across innovators and the rest of society. The table reports incremental drug costs as a fraction of this incremental social value (third column and fifth column), and it reports the ratio of value to drug price (fourth column and sixth column); these are each reported under both the benchmark "green bar" base case that assumes a 76% price decline at loss of exclusivity and the "blue bar" sensitivity analysis scenario in **Figure 1**, where price is assumed to decline by 90% at loss of exclusivity. In our benchmark scenario, the median share of value accruing to innovators is around 40%, with a value-price ratio of around 2.5. In our sensitivity analysis scenario, innovators' share of value falls to around 30% and the value-price ratio rises to 3.2. The three cystic fibrosis-related indications, which lie around the median, are instructive. The benchmark value-price ratios for these drugs range from around 2.3 to 2.5. In other words, the prices of these drugs could have been up to 2.5 times higher, while still providing social value on net. **Figure 2** presents the share of value accruing to society, rather than the share accruing to innovators. In 13 of the 20 cases studied (or 14 of 20, in the sensitivity analyses), society – not innovators – derives most of the benefit. In an additional 4 cases, society accrues a minority of the benefit. Nonetheless, in these cases too, the launch and uptake of the innovation produced positive net value to society, beyond what was retained by innovators. It is also worth reiterating that this analysis excludes other elements of social value that have been identified, including caregiver burden and scientific spillovers.

V. DISCUSSION

Together, these results show that systematic health technology assessment must incorporate at least two important methodological components of Generalized Cost-Effectiveness Analysis (GCEA)—GRACE and dynamic pricing—to properly ascertain the cost-effectiveness of new medical interventions. Including these two elements of GCEA alone, along with stacked cohorts for a societal perspective on value, inverts the findings of standard cost-effectiveness analysis for a number of drugs treating severe illness. Traditional CEA concludes that 8 of the 20 indications in our sample are cost-effective. In contrast, our limited application of GCEA concludes that 17 to 18 of these indications are cost-effective from a societal standpoint. Of the two indications that are never cost-effective in any of our scenarios, neither has been fully approved by FDA due to outstanding questions about clinical benefit to patients.

Including other elements of value from GCEA could further alter the conventional wisdom around the societal value of new medicines, beyond the findings in this paper. For example, our adjustments still fail to account for the effects of new drugs on the pace of subsequent innovation, value to family and caregivers, implications for equity, or other elements of value that have been identified in the literature [9]. Future research should correct the omissions in past value assessments by incorporating these additional elements of value into GCEA calculations. In all cases, analysts should rely on rigorous quantitative methods, not *ad hoc* adjustments or subjective determinations.

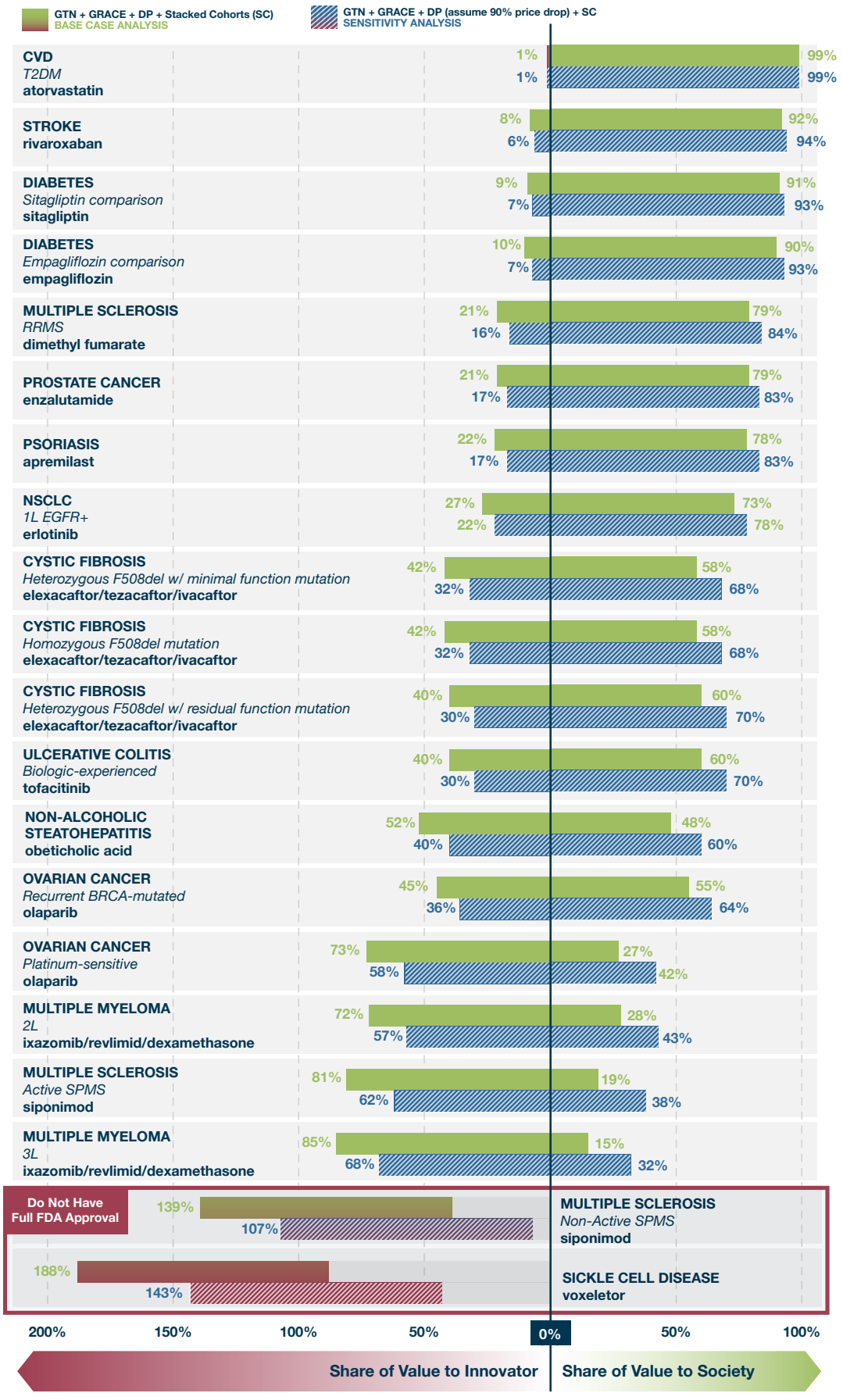
Our results indicate that CEA's standard assumptions do not align with real-world valuations of gains in health from medical interventions. From a policy perspective, our results show that healthcare decisions based on traditional CEA have significantly undervalued interventions for most of the disorders represented in our sample of drugs. GCEA allows value measures to match actual patient preferences and ensures the best possible guidance to decision-makers about healthcare resource allocation. Our results also strongly indicate that the lifetime ICER values for many prescription drugs crucially depend upon proper valuation and incorporation of dynamic pricing.

Even more salient, methods for valuing medical interventions are used to support actual reimbursement to providers and payments for biopharmaceutical products. Widespread calls now seek to align reimbursement methods more closely to value [37, 38]. As this trend expands, the methods for measuring value will translate into innovator's expectations about the rewards of finding new treatments, whether biopharmaceutical products, medical devices or other innovations. The prices that are paid "today" set expectations for what new treatments will emerge in the future. The standard CEA valuation methods in current

4 Confirmed disability progression at 3 and 6 months in the non-active SPMS population was not statistically different across the siponimod and placebo arms [35, Supplemental Table S2]. Additionally, siponimod did not statistically improve cognitive endpoints in the non-active SPMS population [35, Supplemental Table S3].

FIGURE 2:

Share Of Social Value Surplus Accruing To Innovators Versus Society Across Indications



use will result in too little innovation, particularly for highly severe and highly disabling diseases, and some valuable drugs will fail to reach patients.

Erroneous signals sent to innovators of new drugs, medical devices and other treatments about their value will unfavorably distort patterns of development of new drugs and other treatments as they continue to ignore the importance of value-based health gains and the consequences of price declines when patent exclusivity expires. Widespread adoption of GRACE and proper inclusion of dynamic pricing into technology assessments can reverse this unfortunate situation.

We asked in our introduction, *"When and to what extent do these new methods materially alter conclusions about the social value of new medicines?"* Based on these results, the clear answer is that GCEA methods for valuation of medical treatments matter often, perhaps almost always, and that the differences between more-generalized methods and standard CEA have great importance. Almost three-quarters of the drugs in our sample would be improperly withheld from patients if cost-effectiveness models using standard CEA were employed, whereas GCEA methods properly establish their value-for-cost.

Further refinement in the estimates of GRACE-related preferences and the best ways to account for dynamic pricing could further modify these results. However, we view it as highly likely that the fundamental conclusions from this study will persist: Proper technology evaluation should no longer rely on the now-outmoded standard CEA methods, but should incorporate proper valuation methods from GCEA, at least including GRACE and dynamic pricing, to assess treatments' values from a societal perspective.

VI. TABLES AND FIGURES

TABLE 1:
Incremental Outcomes for Traditional CEA

INDICATION	STRATEGY	Baseline QoL	QALYs Gained	Life-years Gained	Incremental Total Costs	Incremental Non-Drug Costs	Incremental Drug Costs
CVD, T2DM [39]	*atorvastatin*	0.74	0.38	18.10	$3,180.52	$0.00	$3,180.52
Cystic Fibrosis, Heterozygous F508del w/ minimal function mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	0.73	5.00	22.06	$5,208,860.53	-$956,511.64	$6,165,372.18
Cystic Fibrosis, Heterozygous F508del w/ residual function mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	0.81	6.02	24.49	$6,565,658.01	-$1,027,142.00	$7,592,800.02
Cystic Fibrosis, Homozygous F508del mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	0.79	5.44	24.06	$6,265,643.85	-$926,966.43	$7,192,610.28
Diabetes, Empagliflozin comparison [41]	*empagliflozin*	0.45	0.33	12.30	$13,136.91	-$2,503.65	$15,640.56
Diabetes, Sitagliptin comparison [41]	*sitagliptin*	0.44	0.10	12.10	$3,954.89	-$742.29	$4,697.19
Multiple Myeloma, 2L [42]	*ixazomib/revlimid/ dexamethasone*	0.61	0.67	11.95	$274,887.48	$6,361.09	$268,526.40
Multiple Myeloma, 3L [42]	*ixazomib/revlimid/ dexamethasone*	0.52	0.55	10.09	$249,331.80	$6,153.01	$243,178.78
Multiple Sclerosis, Active SPMS [43]	*siponimod*	0.16	0.91	4.18	$393,217.87	-$8,511.69	$401,729.57
Multiple Sclerosis, RRMS [44]	*dimethyl fumarate*	0.40	3.22	10.14	$674,319.06	$0.00	$674,319.06
Multiple Sclerosis, Non-Active SPMS [43]	*siponimod*	0.23	0.73	5.93	$835,272.16	-$6,647.35	$841,919.51
Non-alcoholic steatohepatitis [45]	*obeticholic acid*	0.67	0.41	18.31	$229,277.41	-$77,029.46	$306,306.87
NSCLC, 1L EGFR+ [46]	*erlotinib*	0.51	0.57	4.00	$83,821.51	$23,817.80	$60,003.71
Ovarian Cancer, Platinum-sensitive [47]	*olaparib*	0.61	0.79	6.98	$221,058.41	$10,314.45	$210,743.96
Ovarian Cancer, Recurrent BRCA-mutated [47]	*olaparib*	0.43	0.77	4.95	$106,237.20	$10,391.48	$95,845.71
Prostate Cancer [48]	*enzalutamide*	0.77	1.48	19.82	$124,542.56	-$68,596.80	$193,139.37
Psoriasis [49]	*apremilast*	0.73	0.74	5.79	$66,236.93	$0.00	$66,236.93
Sickle Cell Disease [50]	*voxeletor*	0.55	1.01	10.65	$1,077,351.88	$5,812.95	$1,071,538.94
Stroke [51]	*rivaroxaban*	0.79	0.36	16.02	$13,370.36	-$2,636.18	$16,006.54
Ulcerative Colitis, Biologic-experienced [52]	*tofacitinib*	0.69	0.05	20.31	$25,387.87	-$5,541.54	$30,929.41

NOTES: *The traditional CEA parameter values for each therapy are taken from the sources cited numerically in the "indication" column.*

TABLE 2:
Share of Social Value Surplus Accruing to Innovators Across Indications

		GRACE + GTN + SC + DP (76% at 14y)		GRACE + GTN + SC + DP (90% at 14y)	
INDICATION	**STRATEGY**	**Share of Value to the Innovator**	**Value-Price Ratio**	**Share of Value to the Innovator**	**Value-Price Ratio**
CVD, T2DM [39]	*atorvastatin*	1%	96.51	1%	126.22
Cystic Fibrosis, Heterozygous F508del w/ minimal function mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	42%	2.41	32%	3.17
Cystic Fibrosis, Heterozygous F508del w/ residual function mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	40%	2.53	30%	3.34
Cystic Fibrosis, Homozygous F508del mutation [40]	*elexacaftor/tezacaftor/ ivacaftor*	42%	2.35	32%	3.11
Diabetes, Empagliflozin comparison [41]	*empagliflozin*	10%	10.47	7%	13.42
Diabetes, Sitagliptin comparison [41]	*sitagliptin*	9%	10.90	7%	13.95
Multiple Myeloma, 2L [42]	*ixazomib/revlimid/ dexamethasone*	72%	1.39	57%	1.76
Multiple Myeloma, 3L [42]	*ixazomib/revlimid/ dexamethasone*	85%	1.18	68%	1.48
Multiple Sclerosis, Active SPMS [43]	*siponimod*	81%	1.24	62%	1.61
Multiple Sclerosis, RRMS [44]	*dimethyl fumarate*	21%	4.73	16%	6.24
Multiple Sclerosis, Non-Active SPMS [43]	*siponimod*	139%	0.72	107%	0.94
Non-alcoholic steatohepatitis [45]	*obeticholic acid*	52%	1.93	40%	2.50
NSCLC, 1L EGFR+ [46]	*erlotinib*	27%	3.69	22%	4.50
Ovarian Cancer, Platinum-sensitive [47]	*olaparib*	73%	1.38	58%	1.74
Ovarian Cancer, Recurrent BRCA-mutated [47]	*olaparib*	45%	2.23	36%	2.74
Prostate Cancer [48]	*enzalutamide*	21%	4.69	17%	6.02
Psoriasis [49]	*apremilast*	22%	4.62	17%	5.84
Sickle Cell Disease [50]	*voxeletor*	188%	0.53	143%	0.70
Stroke [51]	*rivaroxaban*	8%	12.32	6%	15.97
Ulcerative Colitis, Biologic-experienced [52]	*tofacitinib*	40%	2.52	30%	3.32

NOTES: *The incremental cost-effectiveness ratio in Table 1 represents* $\frac{\Delta Drug\ Cost - \Delta NonDrug\ Cost}{\Delta HRQoL}$.

The "share of value accruing to the innovator" is equal to: $\frac{\Delta Drug\ Cost}{\Delta HRQoL - \Delta NonDrug\ Cost}$.

The "value-price ratio" is equal to: $\frac{\Delta HRQoL - \Delta NonDrugCost}{\Delta Drug\ Cost}$.

The latter represents the ratio between the incremental social value of the drug (measured as the value of its incremental health benefits less any incremental non-drug costs) and the incremental cost of the drug.

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