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ISSUE BRIEF

Inherently Flawed: Why ICER's cost-effectiveness models hinder our understanding of value

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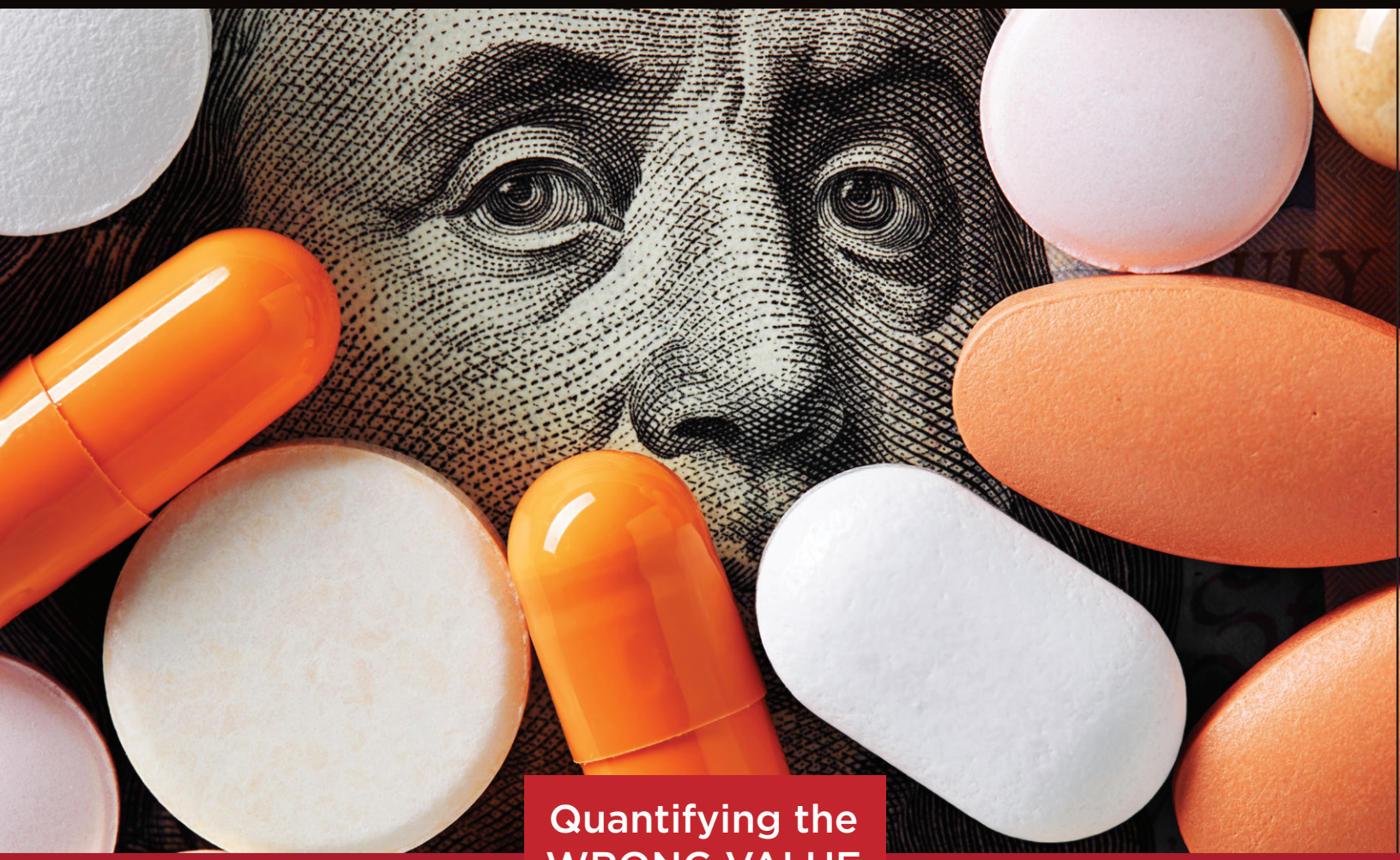

Quantifying the WRONG VALUE *series*

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Inherently Flawed: Why ICER's cost-effectiveness models hinder our understanding of value
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Executive Summary

The Institute for Clinical and Economic Review (ICER) is a private organization that claims it can determine the value of new medicines and treatments. ICER's value estimates are precisely wrong, however.

In order to calculate an actual cost estimate for any medicine, ICER must make many assumptions, but there is no objective "truth" that underlie these assumptions. The assumptions reflect ICER's subjective beliefs, which are often inappropriate or simply wrong. Running complex models on top of subjective assumptions does not create an objectively quantified estimate that miraculously discovers the value of a treatment. Instead, the models are simply complex quantifications of the logic behind ICER's initial and inappropriate assumptions.

In addition to this fundamental flaw, ICER commits specific methodological and implementation errors that include:

- Basing the cost-effectiveness models on a population perspective, which is inappropriate for determining value;
- Using a budget constraint methodology that imposes an artificial cap on value;
- Using a questionable Evidence Ratings Matrix that introduces unknown subjectivity into the value assessment;
- Relying on the fundamentally flawed Quality Adjusted Life Year (QALY) concept;
- Evaluating a drug's cost-effectiveness before the necessary data have been produced; and,
- Undervaluing non-healthcare benefits.

While not a comprehensive listing of ICER's implementation flaws, they demonstrate that ICER's models create inaccurate results that are biased toward undervaluing medicines. These biases raise serious concerns that ICER's value assessments do not enhance our understanding regarding the value created by medicines and other medical devices, and in many situations, ICER's reports detract from our understanding.

The objective of Part I of this research series is to demonstrate that, due to the methodological errors committed by ICER, the cost-effectiveness models do not accurately measure a drug's value. Instead, the models are a means for implementing price controls by stealth that will disincentivize innovation. Less innovation means fewer efficacious treatments for patients in the future. Price controls also lead to unwarranted access restrictions, which means less access to currently available medicines. The consequences from these impacts are a lower quality of life, and for some patients, a higher risk of death.

"Price controls also lead to unwarranted access restrictions, which means less access to currently available medicines.

Despite its fundamental flaws, ICER raises an important question that needs to be satisfactorily answered: How can the healthcare system establish prices for medicines and devices that reflect their value? The next paper in this research series will outline an alternative methodology for achieving this goal.

While the details are complex, the premise of this alternative methodology is that a centralized organization cannot accurately establish prices that reflect medicines' value. Therefore, reforms should not empower another third party to become the official arbiter of value.

Instead, value-based pricing is being thwarted because the current environment is plagued by misaligned incentives, opaque prices, and a health insurance system that does not efficiently manage the financial risks associated with injuries and becoming ill. In combination, these flaws create an artificial separation between prices and value. Ultimately, prices of medicines will only reflect their value when these inefficiencies are eliminated, and a healthy market process is established that effectively connects prices to value.

Introduction

The mission of the Institute for Clinical and Economic Review (ICER) is to provide "an independent source of evidence reviews" to determine how much better a new treatment is, what the fair price of that treatment should be, and how insurers should cover the drug to create the best patient outcomes.[1]

ICER fails to achieve these lofty ambitions.

By definition, ICER cannot achieve the first part of the above mission. An organization that neither runs any clinical trials, nor treats any patients, is incapable of "determining how much better a new treatment is" for patients. The clinical efficacy of a new treatment can only be determined by the scientists performing rigorous clinical trials and the providers who are treating patients. A similar argument holds for the third part of ICER's self-appointed mission – "how insurers should cover the drug to create the best patient outcomes". Fixing healthcare in the U.S. requires fundamentally reforming the health insurance system. Empowering an additional bureaucracy to decide which medicines are appropriate for patients makes the current health insurance system worse, not better. The fact that the ICER bureaucracy has absolutely no connection to patients makes the organization's recommendations even less appropriate. Once again, by definition, ICER cannot achieve the third part of its mission.

This leaves the second part of ICER's mission – determining a treatment's "fair price". ICER's detailed cost effectiveness reports are the main vehicle the institute uses to communicate its value/cost-effectiveness assessments. As ICER has noted, by executing this mission it "has become known as the nation's drug pricing watchdog".[2] [3] From an implementation perspective, ICER's analyses commit key errors that undermine the accuracy of its reports. These errors include relying on inappropriate methodologies and hiding subjective judgments as objectively quantified calculations. In addition to these errors, ICER reports often require questionable assumptions that introduce unknown errors into its estimates. Consequently, ICER's cost-effectiveness reports do not improve our understanding of the value created by drugs.

Documenting these problems is essential because ICER's influence over patient access to efficacious medicines is growing. As Cohen (2019) documents, "explicit rationing is no longer something that's merely done in single-payer systems or international markets. ICER is partly responsible for reintroducing the discussion of explicit rationing in the U.S. Last summer, CVS Caremark established a formulary based on cost-per-QALY (cost per quality-adjusted life year) estimates. Specifically, CVS Caremark ***provided clients the option of excluding drugs from coverage if they don't meet a benchmark of $100,000 per QALY in analyses carried out by ICER***."[4]

The combination of ICER's growing influence and its fundamental flaws threatens patient access to efficacious medicines. The objective of Part I of this research series is to demonstrate that, due to the methodological errors committed by ICER, the cost-effectiveness models do not accurately measure a drug's value. Several of the methodological flaws evaluated universally afflict ICER's analyses and include:

- Basing the cost-effectiveness models on a population perspective, which is inappropriate for determining value;
- Using a budget constraint methodology that imposes an artificial cap on value;
- Using a questionable Evidence Ratings Matrix that introduces unknown subjectivity into the value assessment; and,
- Relying on the fundamentally flawed QALY concept.

Other flaws, while not universal, are still distressingly prevalent, and include:

- Evaluating a drug's cost-effectiveness before the necessary data have been produced; and,
- Undervaluing non-healthcare benefits.

Beyond these implementation flaws, the entire cost-effectiveness approach is problematic because the methodology impedes a process that would actually discover how much patients value a drug or medical device.

According to ICER's updated cost-effectiveness methodology document, the chosen "value framework reflects our strong underlying belief that rigorous thinking about evidence can prevent the kind of waste that strains our ability to provide patient-centered care."[5] The misconceptions behind this "strong underlying belief" are a clear demonstration that ICER has fundamentally misdiagnosed the value problem.

Undoubtedly, the U.S. healthcare system is rife with waste that needs to be minimized, but this excessive amount of healthcare waste is not straining our ability to provide patient-centered care. The *New England Journal of Medicine* described patient-centered care as a healthcare system that ensures an "individual's specific health needs and desired health outcomes are the driving force behind all health care decisions and quality measurements."[6] Decisions in the U.S. healthcare system are driven by third parties such as insurers and PBMs, and it is this excessive influence of third parties over patient healthcare decisions that is a fundamental driver of waste in the health care system.

Not only does ICER fail to recognize this reality, but it also adds to the problem because it is attempting to become another centralized organization that dictates which treatments and medicines doctors can prescribe to their patients. Dictating to doctors and patients the value of a medicine from an organization that does not treat any patients is incompatible with the goal of creating a patient-centered healthcare system that empowers the doctor-patient relationship and incentivizes a more efficient, value-driven, healthcare system. Since ICER further distorts the doctor-patient relationship, the organization is making it more difficult to discover the value of medicines.

These issues will be evaluated in Part II of this research series. This second analysis will demonstrate the fundamental deficiencies of relying on a central organization to decree a drug's value and presents an alternative approach that illustrates how improving the market process creates a more efficient means for ensuring that the prices of medicines reflect their value (i.e., value-based pricing). Part III applies these concepts to the emerging gene and cell therapies, which fundamentally differ from traditional medicines.

Value Cannot Be Determined Using a Population Perspective

ICER reports rely on a *population perspective* to evaluate the value of a medicine. As documented in the 2020-2023 Value Assessment Framework document, a population perspective,[7]

> seeks to analyze evidence in a way that supports population-level decisions and policies, such as broad guidelines on appropriate care, pricing, insurance coverage determinations, and payment mechanisms. A value framework intended to support decisions about the care of individual patients requires a structure that invites weighting of benefits, harms, and costs from the individual patient's perspective. There is an important need for better evidence-based shared decision-making tools for individual patients and clinicians, but this is not the primary intended purpose of the ICER value framework or of ICER reports.[8]

A population perspective is incapable of determining the value of drugs. Decisions about care, pricing, and coverage are not population-level decisions that can be based on averages for an entire population. Even ICER recognizes these limitations in its Value Assessment Framework document stating that,

> the diversity of patient outcomes and values in a population-level framework is difficult because there will always be an inherent tension between average findings in clinical studies and the uniqueness of every patient. There will also always be diversity in the way that patients view the balance of risks and benefits of different treatment options.[9]

However, ICER then continues claiming that "The ICER value framework does not solve these tensions, but neither does it obscure them."[10] ICER is correct that there is an inherent tension between population averages and a drug's fundamental value that they do not solve, but incorrect that their framework does not obscure these tensions. To demonstrate why ICER obscures these tensions, it is useful to imagine the consequences if an independent entity existed to determine the value of another economic good, such as a car, using a population perspective.

A population perspective on the value of cars would attempt to answer the question: what is the cost-effective price of a car? In total, there were 14.5 million cars sold in 2020,[11] and the average price for one of these new cars was $40,107.[12] Without considering ICER's budget constraint assumptions, which are evaluated in the next section, a population-level perspective argues that since the average buyer was willing to spend $40,107, this price represents the value of a new car for the entire car purchasing population.

But this average price for the entire market provides no information about the individual value assessments that enabled the average price to emerge. For instance, according to Kelley Blue Book, the average transaction price for a car during January 2020 ranged between $17,738 for a subcompact car to $114,411 for a high-performance car, see Table 1.[13]

"To demonstrate why ICER obscures these tensions, it is useful to imagine the consequences if an independent entity existed to determine the value of another economic good, such as a car, using a population perspective.

Table 1. Average Transaction Price for a New Car by Segment As of January 2020

	AVERAGE TRANSACTION PRICE		AVERAGE TRANSACTION PRICE
Subcompact Car	$17,738	Midsize SUV/Crossover	$39,611
Compact Car	$21,312	Entry-level Luxury Car	$42,981
Subcompact SUV/Crossover	$24,592	Electric Vehicle	$43,518
Midsize Car	$26,395	Luxury Compact SUV/Crossover	$46,858
Hybrid/Alternative Energy Car	$27,934	Full-size Pickup Truck	$49,980
Compact SUV/Crossover	$29,741	Luxury Midsize SUV/Crossover	$60,260
Midsize Pickup Truck	$35,688	Full-size SUV/Crossover	$62,743
Minivan	$35,691	Luxury Car	$62,933
Full-size Car	$36,437	Luxury Full-size SUV/Crossover	$88,435
Van	$37,155	High-end Luxury Car	$103,430
Sports Car	$38,868	High Performance Car	$114,411
Luxury Subcompact SUV/Crossover	$39,172		

Source: Kelley Blue Book, average transaction prices do not include applied consumer incentives

The broad range of prices demonstrate that knowing the average price for all cars ($40,107) provides insufficient information to determine the value that consumers of specific car classes realized. Additionally, there is no reliable symmetry in demand that would allow this population perspective to estimate the value received by this broad array of consumers. For example, the average high-performance car price is 185 percent higher than average, but the average subcompact car price is 56 percent lower. Given that this dispersion would be expected to vary over time, there is no way to extrapolate the value received by subcompact cars consumers based on the knowledge of the average price.

This problem is not resolved by narrowing down the definition of the relevant population either. As Table 2 demonstrates, even within the same class of automobiles there is a wide variation in prices and, consequently, value received. In the case of Table 2, the population evaluated is the class of lowest price cars, which ranged between $14,395 for the Chevrolet Spark and $20,645 for the Hyundai Elantra.

Table 2. Base Price for the 10 Cheapest Cars in 2021

CAR	BASE PRICE
Hyundai Elantra	$20,645
Nissan Sentra	$20,335
Volkswagen Jetta	$19,990
Subaru Impreza Sedan	$19,720
Kia Forte	$18,855
Kia Rio Sedan	$17,015
Hyundai Accent	$16,390
Nissan Versa	$15,855
Mitsubishi Mirage Hatchback	$15,565
Chevrolet Spark	$14,395
Average Price	**$17,877**

Source: MotorTrend

Narrowing the population even further to a specific car still fails to resolve the problem because prices (and value) will vary depending upon the features and attributes desired. The price for a Hyundai Elantra, for instance, can vary by over $8,000 depending on the specific attributes that consumers desire according to Kelley Blue Book.[14]

The prices for automobiles vary significantly because people's budgets, transportation needs, transportation desires, and tastes vary so greatly. This reality explains why there are so many different types of automobiles, and so many different price points for them. A centralized organization attempting to set prices would be unable to accurately value any specific car class, let alone a specific car, if the only information they contained was the average price.

Worse, any organization that attempted to set the value for all car consumers based on the average price would make most car buyers worse off. Essentially, the population derived value (approximately $40,000) would accurately reflect the value of only a small subset of automobiles – the value created by a midsize SUV, for instance. Since all prices would then be anchored to this population derived price, people who require low-cost compact cars would be overcharged and, in many cases, unable to afford an automobile. People who value luxury cars

> "People who value luxury cars would be unable to find these classes of cars available because the artificial low prices would discourage the production of high-cost vehicles. The result would be that widespread inefficiencies in the automobile market would arise that would significantly reduce the societal benefits created by an efficient market for automobiles.

would be unable to find these classes of cars available because the artificial low prices would discourage the production of high-cost vehicles. The result would be that widespread inefficiencies in the automobile market would arise that would significantly reduce the societal benefits created by an efficient market for automobiles.

Medicines are different than automobiles, of course, but the same logic holds. The value of a medicine cannot by established by examining population level data, even if these calculations were done correctly. A medicine's value cannot be separated from patients' individualized needs that include the condition being treated, any relevant allergies, the other medications patients may be taking, and the individualized effectiveness/side-effects to the medicines. Population-based estimates can never answer these questions indicating that attempts to establish value based on broad averages will be, by definition, inapplicable to large numbers of individual patients whose particular circumstances vary (perhaps substantially) from these population averages. Simply put, there are inherent tensions between the average result over the entire patient population and the individual values of specific patient sub-groups.

By anchoring medicines' perceived value to a population-derived estimate, ICER's framework obscures these tensions and ensures that the estimates are inappropriate for a large number of patients – even under the assumption that the population-derived estimates were accurately estimated. However, many of the issues raised below demonstrate that often this assumption does not hold and ICER's cost-effectiveness evaluations do not even accurately estimate the population-level average.

ICER's Budget Constraint Methodology Artificially Caps Value

ICER establishes a budget impact threshold for new drugs, which is based on several arbitrary assumptions including the anticipated growth in national gross domestic product (GDP) plus 1 percentage point. ICER's imposition of an arbitrary budget constraint makes it unlikely that the calculated estimates accurately reflect the value of a medicine.

Economic value and price for any product considers both demand-side considerations, such as the efficacy of the drug and the adverse health consequences of the disease, and supply-side considerations, such as the manufacturers' cost of capital. There is no reason to assume that the volatile year-to-year movements in the economy reflect the value created by a new medicine. Instead, these budget thresholds create a spending limit on drugs based on ICER's judgements on what that spending should be. These spending limits are, consequently, nothing more than suggested price controls.

In fact, there is evidence that these arbitrary price controls are inconsistent with the revealed preferences of high-income countries. Due to modern medicine's ability to keep people healthier and treat formerly untreatable diseases, people in wealthy countries may prefer to devote more resources toward healthcare services than the resources that ICER is assuming should be devoted. In an examination of this question, Loftus, Campbell and Gaebler (2018) asked whether the "revealed preferences" of 32 high-income countries between 1995 and 2014 are consistent with the budget impact assumption ICER imposes, finding that "ICER's budget impact threshold may not accurately reflect high-income Western countries' revealed preferences."[15]

It is likely, consequently, that ICER's arbitrary budget impact threshold creates a dollar ceiling that artificially caps the estimated value of a medicine. Unfortunately, ICER's *Value Assessment Framework* does not recognize that its methodology is imposing price controls on the healthcare sector, and justifies its calculations as a

> signal to stakeholders and policy makers when a new treatment, even one priced at a level commensurate with good long-term value, may add short-term health care costs that are so substantial that they would be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in insurance costs that could threaten sustainable access to high-value care for all patients. ICER seeks to include information for estimating short-term potential budget impact but also to use clinical expert testimony to identify when intended clinical use of a new treatment may be at a scale that would trigger access and affordability concerns. In such cases, the goal is to trigger discussions of possible policy steps to alleviate potential access restrictions or sudden sharp increases in health insurance premiums. ***The role of the potential budget impact analysis is not to suggest a cap on spending, but to signal to the health care system that special arrangements, such as lower prices, enhanced efforts to eliminate waste, or prioritizing treatment for the sickest, may be needed to ensure availability of the new drug without short-term adverse effects on patients and families seeking to pay for affordable health insurance***.[16]

Focusing on the emphasized sentence, ICER is claiming that the purpose of the budget impact analysis is "not to suggest a cap on spending". However, not only does the research by Loftus, Campbell and Gaebler (2018) contradict this assumption, the claim contradicts ICER's further claim that "special arrangements" that include lower prices and/or access restrictions may be required. These special arrangements, if followed, are establishing a maximum price for the drug and a total maximum recommended expenditure level. Establishing a maximum price and expenditure level for a drug undermines the claim made in the initial clause of the sentence, and demonstrates that the purpose of the budget impact analysis is, in fact, to cap total spending on medicines (i.e., to impose price controls on medicines).

Leaving aside the important concern that a private organization is empowering itself to impose price controls on the entire healthcare system, heeding these recommendations creates large economic costs and worsens patient health outcomes. No matter where they have been tried, price controls always make bad situations worse. Take rent control policies as an example of their adverse consequences.

The purpose of rent control, which is similar to the purported goal of ICER, is to improve affordability. In the case of rent controls that affordability relates to the cost of housing. The actual consequences, as exemplified by cities like New York and San Francisco, are housing shortages and sharp declines in housing quality. Diamond (2018) reviewed the literature examining the impact from price controls on rent finding that, "rent control appears to help affordability in the short run for current tenants, but in the long-run decreases affordability, fuels gentrification, and creates negative externalities on the surrounding neighborhood. These results highlight that forcing landlords to provide insurance to tenants against rent increases can ultimately be counterproductive."[17]

Price controls create similar costs when applied to the healthcare industry – there are immediate price reductions, but adverse consequences quickly arise, which then mount over time. The experiences of countries that impose price controls foreshadow the impacts we can expect here should ICER's methodology be widely adopted in the healthcare sector.

Single payer countries like Canada,[18] and universal coverage countries like the U.K.[19] and Germany,[20] face severe shortages of doctors and other medical professionals. The U.K., even before the Covid-19 pandemic, had "10,000 medical vacancies" they could not fill.[21] Such shortages are the inevitable result of price controls. Combining these doctor shortages with the Covid-19 pandemic, during the early months of the pandemic "NHS bosses…warned that waiting lists in England alone could reach 10 million by the winter".[22] And these shortages occurred. As of July 2020, "more than 83,000 patients in England waited more than a year for NHS treatment", "the highest number since October 2008 and an 81-fold increase from 1,032 in July (2019)".[23]

Under Canada's single payer system, where there is no private coverage for anything considered "medically necessary", the average wait time from seeing a primary care doctor to getting treatment by a specialist was just over five months.[24] Doctor shortages and long waiting lists create significant health risks for patients who are unable to receive necessary medical services in a timely fashion for cancer diagnoses and treatments and heart and stroke issues.

A similar problem of shortages and access issues afflict patient access to drugs across the countries in Europe and Canada that impose price controls. Compared to patients in the U.S. who have access to nearly 90 percent of all new medicines introduced over the last decade (higher access to drugs than any other country in the world), patients in Germany, the country with the next highest drug availability rate, could access just over 60 percent.[25] Canadians have access to less than half.[26] Drug price controls create access issues for the same reason that physician price controls create doctor shortages. And, they pose a similar threat to patient health. The price controls created by ICER's budget impact thresholds will ensure that the access and shortage problems that plague other countries will arise in the U.S.

"The price controls created by ICER's budget impact thresholds will ensure that the access and shortage problems that plague other countries will arise in the U.S.

Worsening these impacts, because the arbitrary budget threshold is completely unrelated to the capital costs required, and risks incurred, to develop the innovative new drugs, the cost ceiling created by ICER's budget threshold will lead to an undervaluation bias in their cost effectiveness studies. Beyond the aforementioned access and shortage problems, this undervaluation bias diminishes the incentive for future innovation. Lost innovation denies patients efficacious treatments for diseases that are untreatable today, and could, ironically, lead to higher overall medical spending as patients will still require increased hospital and physician services.

ICER's Evidence Ratings Are Unnecessary and Introduce Unknown Subjectivity into the Value Assessments

Essential evidence regarding the safety and efficacy of a new therapy is derived from rigorous clinical trials. The National Institutes of Health notes that the purpose of a clinical trial is to,

> find out if a new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment.
>
> Other clinical trials test ways to find a disease early, sometimes before there are symptoms. Still others test ways to prevent a health problem. A clinical trial may also look at how to make life better for people living with a life-threatening disease or a chronic health problem. Clinical trials sometimes study the role of caregivers or support groups.[27]

In other words, clinical trials are rigorous tests of the safety and efficacy of new treatments, which, if relevant, includes evaluating the new treatment relative to current standard treatments. Scientists at the FDA, whose mission is to protect the public health by ensuring the safety and efficacy of new drugs and medical devices, oversee and review the entire clinical trial process. Healthcare professionals have access to all of the information generated through this process including all relevant academic studies and government reports. Further, FDA approval of a medicine does not mean that scientific studies on the efficacy and safety of the drug stop. Post marketing studies continue, which are also published and widely available to healthcare professionals.

ICER's Evidence Rating Matrix does not add any new information to the results of these trials and post marketing studies. It is simply a means for ICER "to evaluate the overall strength of evidence for a variety of outcomes."[28] ICER further notes that "the evidence rating reflects a joint judgement of two critical components: a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between benefits and risks and/or adverse effects; AND b) The level of **certainty** in the best point estimate of net health benefit."[29]

The output from the Evidence Rating Matrix is a letter grade. The highest grade is an A, which is given to therapies where ICER has high certainty that the medical therapy will be a substantial comparative net health benefit. If either the certainty or net health benefit declines, then the assigned letter grade falls to a B, C, or D, which would indicate that the therapy has a high certainty of an inferior net health benefit. A rating of I is also issued in those situations where "the level of certainty in the evidence is low".

The problem arises precisely because ICER's evidence rating is nothing more than its "judgment". The organization neither conducts clinical trials nor treats patients. Making the problem worse, the methodology is opaque, invented by ICER, and is not reproducible by other health professionals. Consequently, the evidence rating is simply a means for ICER to substitute its judgment regarding the value of a medicine for doctors and other health professionals. There is no way to independently determine whether their judgement has accurately interpreted the evidence that exists, or even if accurate, whether other interpretations are more appropriate for patients or specific patient sub-groups.

ICER Relies on the Fundamentally Flawed QALY Concept

ICER uses the cost per quality-adjusted life year (QALY) to measure cost effectiveness. QALYs are defined such that one QALY is the equivalent of a person living one year of life in perfect health. One life year in less than perfect health, in pain for instance, would receive a QALY value of less than one, a QALY equal to 0.5, for instance. ICER then establishes the prices of therapies that would be consistent with spending between $100,000 and $150,000 to gain one additional QALY. Although the QALY calculation results in a precisely quantified dollar estimate, there is no connection between this quantified estimate and the value that patients place on their own health because there are many fundamental defects with the QALY concept.

The first obvious problem is precisely defining what is "one life year in perfect health." Beyond the obvious ethical problems with granting a centralized organization the power to define who is in perfect health and who is not, there is no correct answer to the question of what one life year in perfect health is worth. ICER has declared that one life year in perfect health is worth between $100,000 and $150,000, but there are no objective analyses that can be run to confirm whether this value range is correct. Instead, these are arbitrary figures that create an arbitrary value cap on the healthcare sector. If rigorously implemented, then this methodology eliminates the incentive to produce the highest valued health technologies.

Another problem with ICER's use of the QALY methodology is how to incorporate fundamental cost considerations into the value analysis. For instance, how should the analysis incorporate the potential reduction in the cost of palliative care, the adverse impact on income or education opportunities, the economic and emotional burdens on caregivers, and the adverse impacts on people's quality of life? Most QALY analyses, including ICER's, simply ignore such considerations, creating a large undervaluation bias in the results.

> "These problems demonstrate that although the QALY calculation results in a precise value, QALY value estimates are neither objective nor accurate.

These problems demonstrate that although the QALY calculation results in a precise value, QALY value estimates are neither objective nor accurate. Instead, they are simply the subjective beliefs of the organization running the models masquerading as a scientific estimate.

The harm created by the inherently subjective QALY measure, while universal, is not equally shared. Patients requiring medicines to improve their quality of life rather than to save their lives are particularly vulnerable. This problem arises because alleviating pain and discomfort adds another layer of subjectivity to the QALY methodology. As generally applied by ICER, this subjectivity inevitably leads to the models discounting the value for patients from symptom relief. And, this is not just a problem of ICER, it is inherent to the QALY methodology. As documented by Pettitt et al. (2016) in their review of the QALY literature, "the QALY system could lead to an innate preference for life saving over life enhancing treatments because preventative or basic long-term care measures generally score lower on QALY calculations than more dramatic treatments. This places certain interventions at a disadvantage – ***for example those in mental healthcare***, where treatment modalities largely fall into the remit of life enhancing measures."[30]

As other examples take medicines that treat arthritis or migraines. In both cases, the major benefit from improved treatments is the increased number of pain-free days. Since these medicines improve the quality of life, rather than extend life, ICER's QALY methodology undervalues their benefits. After all, how does one quantify the discomfort of poorly tolerated treatments for psoriasis or the pain and daily inconveniences of rheumatoid arthritis? How does one quantify the benefits from more days without the crippling pain from a migraine? Treatments for some disease states simply do not lend themselves to economic number crunching. And, the questions raised by better pain management are easier to answer than for other diseases. For example, how does one assign a value to the embarrassment and stigma felt by patients living with Tardive Dyskinesia, a condition that causes repetitive involuntary movements, caused by long-term use of neuroleptic drugs, because their face may contort uncontrollably in public?

The inability to accurately answer questions like these increases the probability that the QALY methodology is incapable of accurately assessing the value created by these life enhancing treatments; nor is the QALY methodology capable of declaring that the current prices for these drugs are "not cost effective". The fact that a QALY metric cannot accurately measure the benefits for these types of conditions does not dissuade ICER from applying this measure to life enhancing medicines. Consequently, there is a large probability that ICER's evaluations of life enhancing medicines are unjustifiably denying patients efficacious medicines because its QALY methodology is biased toward undervaluing these medicines.

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There are more patient groups who are discriminated against by the QALY methodology. Hyry et al. (2014) noted that cost-effectiveness assessments are biased toward undervaluing the benefits of medicines that treat rare diseases.[31] Rare diseases are conditions that afflict fewer than 200,000 people. Since rare diseases afflict fewer people, a treatment's costs per patient will be higher. This means that even with adjustments to the QALY thresholds, due to the small populations living with rare diseases coupled with the high cost of capital required to develop drugs,[32] the methodology is structurally biased toward undervaluing orphan drugs – or the treatments for rare diseases. Consequently, ICER's cost-effectiveness methodology will undervalue the benefits of treatments designed to help patients living with rare diseases.

Another problem with cost-effectiveness and QALYs, which will be fully addressed in Part II, is they take a drug-by-drug approach. Oversimplifying, the evaluator (in this case ICER) estimates the perceived increase in a patient's quality of life and efficacy of the drug, put a dollar value on how much 1-year of an additional quality of life is worth (either $100,000 or $150,000), and the multiplication of these values leads to the cost-effective price of the medicine. This is not a relevant calculation. You can only solve the cost-effectiveness problem over a portfolio of drugs, not on an individual basis. This is how both the supply (manufacturers) and demand (payers on behalf of patients) side of the markets actually work.

In short, QALYs create estimates that are exact, but wrong. They create the appearance that an objective analysis is being performed when, in reality, the analysis is creating an inherently subjective estimate that contains undervaluation biases.

ICER Often Evaluates the Cost-effectiveness of Therapies Before the Necessary Data are Available

The concerns discussed above are innate to ICER's cost-effectiveness methodology. Other concerns arise because ICER implements this flawed methodology in troubling ways that increases the unreliability of its estimates. One particularly troubling practice is that ICER produces its Evidence Reports well before the data that are necessary to perform the analyses are available. Specifically, determining the efficacy of new medicines requires both clinical trials data and real-world evidence that is gained once the drug has been approved by the FDA. Clinical trial data is generally viewed as insufficient for evaluating the magnitude and certainty of net health benefits. As the FDA explains regarding the drug development process:

> Even though clinical trials provide important information on a drug's efficacy and safety, it is impossible to have complete information about the safety of a drug at the time of approval. Despite the rigorous steps in the process of drug development, limitations exist. Therefore, the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace.[33]

Despite the need for "months and even years" of data to understand "the true picture" of a drug, ICER typically evaluates the cost-effectiveness of drugs that are still in clinical trials or just approved by the FDA. Examples of the Draft Evidence Reports that commit this error include,

- At the time of its 2018 evaluation of Calcitonin Gene-Related Peptide (CGRP) Inhibitors for treating migraines,[34] the CGRPs studied were still in phase II or phase III clinical trials. None had secured FDA approval. Therefore, the clinical and safety data that was available for these medicines was limited and the information from post-marketing studies was not yet available. In particular, due to the novelty of these medicines, there was no available data on the long-term benefits of CGRP inhibitors, nor was there information on patients' long-term adherence rates to these medicines.
- When evaluating the benefits of monoclonal antibodies for the treatment of patients with moderate to severe asthma, many of the studies that ICER reviewed did not analyze the impact from the medicines on key efficacy measures that include the number of emergency room visits, the number of hospitalizations, and several quality-of-life indicators typically applied to asthma patients.[35]
- In its report examining dupilumab and crisaborole, which are treatments for atopic dermatitis, ICER noted that there were significant "data availability challenges" in conducting the study.[36] These data challenges existed precisely because dupilumab was not available for purchase by patients when the draft analysis was being conducted.

These data deficiencies raise particularly troubling issues with respect to the long-term conclusions that ICER draws. When ICER evaluates drugs that are still in clinical trials, or have only been approved for a short period of time, there can be no available data on the long-term benefits, long-term safety, and long-term adherence rates. This means that ICER must extrapolate the long-term effects of a medicine based on the short-term data. Extrapolating the long-term effects from short-term data introduces unknown errors into the analysis. In fact, ICER often notes these constraints in its Limitation's Sections. With respect to the CGRP inhibitors, for instance, ICER noted that "the models were based on *clinical trial results that may not hold true for longer time*

horizons or in particular patient populations different than those seen in the trials." Noting this limitation does not eliminate the concerns.

ICER Undervalues Non-Healthcare Benefits

Patients do not differentiate between the types of benefits they receive from efficacious medicines. These benefits obviously include improved health outcomes, but they also include non-healthcare benefits such as the reduced costs associated with comorbidities, the subjective benefits associated with symptom relief and feeling better, the reduced burdens on caregivers, the increased ability to earn a living (or attend school), and the reduced social costs that can be associated with some diseases. These non-healthcare benefits are often large and can materially alter the conclusions from a cost-effectiveness analysis.

The material impact that lost productivity can have on the value of a medicine demonstrates the importance of accounting for non-healthcare benefits. Karmarkar, Graff, and Westrich (2020) examined the impact of lost productivity on the value of a medicine finding that "the exclusion of productivity costs can alter, often underestimating, the assessment of value. This may affect coverage decisions—inclusion or exclusion from the insurance benefit—based on these assessments. Value assessment reports intended to be used for health care decision making should include productivity and elevate its visibility by using base-case analyses rather than scenario analyses."[37] Despite the real possibility that productivity losses will materially change the results, ICER often fails to incorporate productivity considerations into the analysis, or relegates the potential impacts to secondary scenario analyses.

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The impact on lost productivity is not the only non-health care benefit that ICER typically overlooks. Often, ICER reports fail to adequately consider essential social benefits enabled by the treatment under evaluation. For example, ICER's 2017 report evaluating the effectiveness and value of abuse deterrent formulations (ADF) of opioids failed to consider the potential ability of ADFs to reduce opioid abuse and diversion, which is the entire purpose of using an ADF opioid.[38] It was excluded despite the persuasive evidence that ADFs materially reduce opioid abuse and diversion. As one example, Severtson et al. (2013) found that OxyContin diversion fell 53 percent in the period immediately following the introduction of the ADF version,[39] and even five years after the introduction, Severtson et al. (2016) found that the reduced diversion rates continued.[40] By reducing diversion, ADFs reduce the social costs that opioid diversion generates including increased rates of abuse, increased criminal justice costs, and decreased worker productivity.

ICER's report on ADFs contained an in-depth discussion about the costs of opioid diversion, but many of the social ills associated with abuse, particularly the impacts on crime, families, and productivity, were not incorporated into the savings estimate of the base case analysis. Therefore, the reader is given the impression that the impacts on the costs of opioid abuse are being evaluated, when in reality, many of these benefits from ADFs are ignored and result in a significant understatement of the value of abuse-deterrent opioids.

It is important to note that ICER's difficulties properly accounting for the non-healthcare benefits is not unique. It is a widespread problem associated with cost-effectiveness studies. Kim et. al. (2020) examined whether cost effectiveness studies, as performed, accounted for non-health consequences.[41] Not only did most studies only take a healthcare or payer perspective on costs, but they also found that "authors often mis-specified or did not clearly state the perspective used."[42]

These problems exist because it is difficult to accurately quantify many of the non-healthcare benefits, but these difficulties do not make the benefits less important. The existence of this problem, and the difficulties ICER faces incorporating them, is a persuasive reason why cost effectiveness studies are simply the wrong approach for accurately determining the value of medicines or other treatments.

Conclusion

Cost effectiveness studies provide precise estimates, but there is no reason to believe that these estimates accurately reflect the value of medicines. As this analysis detailed, there are many methodological and implementation errors that ICER commits that include using a population perspective to determine value, imposing an arbitrary budget constraint that artificially caps the estimated value of medicines, employing a questionable and inherently subjective Evidence Ratings Matrix, relying on the fundamentally flawed QALY concept, performing evaluations before the necessary data have been produced, and undervaluing non-healthcare benefits.

While these problems are not a comprehensive listing of ICER's flaws, they are sufficient to demonstrate that ICER's results are inaccurate and biased toward undervaluing medicines. These biases raise serious concerns that ICER's value assessments do not enhance our understanding regarding the value created by medicines and other medical devices. In many situations, ICER's reports detract from our understanding. Ultimately, cost-effectiveness studies are a fancy methodology to justify uneconomical price controls on medicines. These stealth price controls will result in less innovation, which means fewer efficacious treatments for patients in the future. It also will impose unwarranted access restrictions on patients preventing people from accessing currently available medicines. The consequences from these impacts are a lower quality of life, and for some patients, a higher risk of death.

"These stealth price controls will result in less innovation, which means fewer efficacious treatments for patients in the future.

Despite the fundamental flaws to ICER's methodology, ICER raises an important issue that needs to be satisfactorily answered: How can the healthcare system establish prices for medicines and devices that reflect their value? The next paper in this research series will outline an alternative methodology for achieving this goal. While the details are complex, the premise of this alternative methodology is that a centralized organization cannot accurately establish prices that reflect medicines' value. Therefore, reforms should not empower another third party to become the official arbiter of value.

Instead, value-based pricing is being thwarted because the current environment is plagued by misaligned incentives, opaque prices, and a health insurance system that does not efficiently manage the financial risks associated with injuries and becoming ill. In combination, these flaws create an artificial separation between prices and value. Ultimately, prices of medicines will only reflect their value when these inefficiencies are eliminated, and a healthy market process is established that effectively connects prices to value.

Endnotes

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