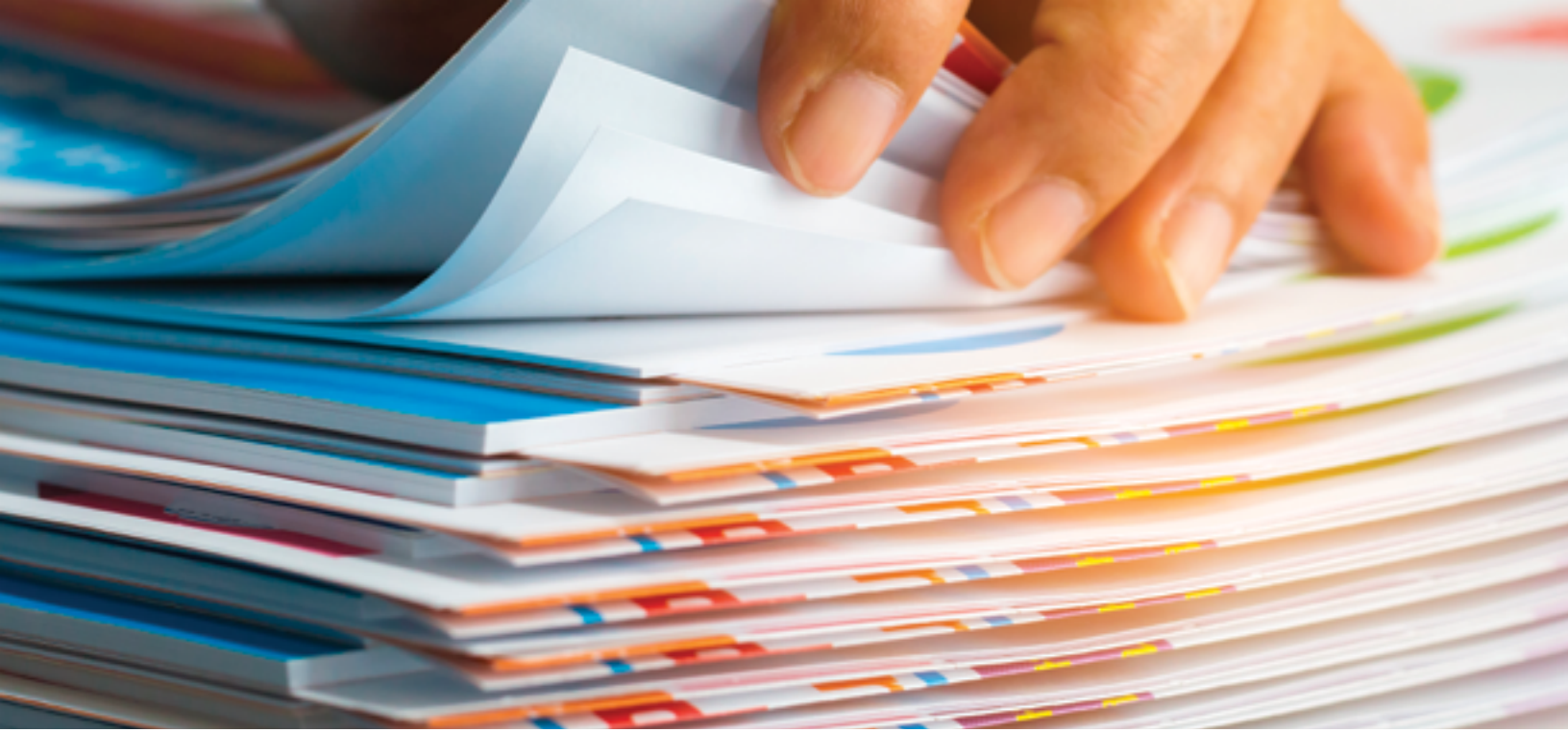

The Growing Influence of the Institute of Clinical and Economic Review on Payer Decisions in the US

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Introduction

Health technology assessment (HTA) bodies, like the National Institute for Health and Care Excellence (NICE) in the UK and the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, have become increasingly important in countries across the world as arbiters who determine the reimbursement fate of healthcare interventions in national systems, in addition to ensuring fair access to target populations. For these agencies, such reimbursement decisions are dependent on evidence of clinical efficacy and safety from pivotal clinical trials in the indicated population as well as evidence of cost-effectiveness by means of health economic evaluations. Other bodies like the Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany and the French National Authority for Health (HAS) have a slightly different approach, with economic evaluations considered necessary only after new technologies have demonstrated additional clinical benefit.

Healthcare reimbursement decision-making in the US has historically been an anomaly, given that there is no designated national reimbursement body for the sectored healthcare payer system. In marked contrast to countries with single-payer or national systems for reimbursement, the US healthcare system is fragmented, with myriad payer systems at regional and national levels. US payers also function at individual, group, employer, and government levels and provide varying benefits depending on choice, socioeconomic level, and eligibility. Coverage for and access to prescription drugs or other innovative technologies can vary widely depending on what type of insurance coverage individual patients have. The previously clear difference between the US and other industrialized countries with regards to HTA bodies is becoming increasingly blurred, however, by the role of the Institute for Clinical and Economic Review (ICER), a private research organization founded in 2006 that evaluates the value of emerging healthcare interventions from clinical and health economic perspectives.

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ICER has been receiving widespread attention and is being termed an American "HTA body," serving a purpose like that of NICE and other agencies, with a goal of influencing drug pricing and access decisions.[1] Its primary mission is to enhance the understanding of the value of newly developed health interventions, thus improving health outcomes at a reasonable cost and making fair and equitable access possible. The organization focuses on interventions under evaluation for approval to market by the US Food and Drug Administration (FDA). ICER assessments incorporate information from key players like manufacturers, patient groups, payers, physicians, and clinical experts across the US healthcare system as well as the general public. Since it is an independent organization not affiliated with the government, ICER states that all work for reports are funded by not-for-profit organizations, though other aspects of these activities are funded by manufacturer grants, private insurance companies, and similar groups.[2]

ICER's process of selecting topics for assessment involves public input and market research of the upcoming drug pipeline by an independent analytics group.[3] Based on the recommendations that are made, ICER selects the final list of drugs to be assessed based on key criteria[4] including, but not limited to:

- Presents significantly improved health benefits compared to existing treatment, warranting evaluation of comparative effectiveness
- Anticipates high impact on financial burden to health system or impact on prices of existing treatments
- Expects to receive marketing approval by the FDA within a year
- Impacts policy making or addresses one or more current unmet needs

Historically, most payers in the US have negotiated directly with drug manufacturers. From this perspective, ICER's approach of providing detailed scientific review to encourage wider policy discussions among patient groups, payers, government, and manufacturers could be viewed as a welcome change in the US healthcare system. On the other hand, however, ICER has faced criticism in recent years about its review process, specifically for their approach to economic evaluation of new drugs.[5-7] Such issues have raised a key question within the industry: whether a private organization like ICER can have major influence on reimbursement policies of private and, potentially, public payers, while also ensuring transparency in its process and accountability towards the ultimate consumers – patients.

Why Do ICER Reviews Raise Controversy?

ICER's sudden gain in prominence has caused some concern, and justifiably so.[8,9] A very common criticism centers around the "*value-based price benchmark,*" which ICER considers to be an offering that distinguishes it from other HTA agencies. As part of each evaluation, ICER calculates the benchmark according to the clinical benefit shown in clinical trials and an accompanying cost-effectiveness and budget impact model. The resulting benchmark price is the one at which a drug would be considered cost effective based on a range of recommended cost-effectiveness thresholds ($100,000 to $150,000 per quality adjusted life year [QALY]), which the organization believes reflects a fair price.[10] The benchmark price is based on some assumptions regarding short- and long-term value, as well as actual costs of existing drugs. This price can be controversial because ICER has sometimes suggested large discounts compared to list prices – e.g., as high as 97% for drugs such as inotersen, a treatment indicated for hereditary transthyretin amyloidosis.[11] The drugs at suggested discounts will be cost effective at the corresponding range of cost/QALY thresholds. Some critics also cite that the arbitrary nature of cost-effectiveness thresholds suggests biases in price benchmarks that undervalue new technologies. There has been a lack of national discussion on how to measure the value of life for policy making in the US, and thus there is a reluctance to accept it for decision making despite its prevalent use in other countries. Advocates of cost-effectiveness thresholds maintain that they are meant to merely aid in decision making and have been derived from several assumptions.[12] The cost-effectiveness threshold is supposed to be used as a tool in the appropriate context, not as a single number to make a yes or no decision.

For interventions for rare or ultra-rare diseases, the cost of drug development is extremely high, and companies often aim to have drugs enter the US market at very high list prices to ensure return on investment. HTA bodies usually make special consideration for such drugs to accommodate those interventions that meet an unmet need in a niche, vulnerable population. In some early assessments for rare conditions, ICER failed to do this and received backlash for restricting access to crucial interventions. Based on ongoing feedback from manufacturers and patient groups, ICER updated its value-assessment framework with a special accommodation for ultra-rare conditions (affects <10,000 patients in the US). The adaptation proposes that ICER will test a wider range of cost-effectiveness thresholds in sensitivity analyses of the cost-effectiveness model. They plan to continue using the value-based benchmark price for the range of $100,000 to $150,000 per QALY, but with special considerations made.[13] Such efforts show ICER's amenability to feedback and flexibility to improve their process to better address concerns that are pertinent to the healthcare system.

The timing of ICER evaluations is also controversial. Some of ICER's reports have been considered premature, when FDA decisions are pending and clinical trials still ongoing. These evaluations are commonly initiated, and sometimes completed, while technologies are still under FDA consideration. For this, ICER relies on participation of, and

discussions with, manufacturers during the review process to address potential gaps in clinical evidence. Despite this, skeptics maintain that many ICER evaluations are made public before key clinical evidence is published,[14-16] and so argue that the reports may be biased due to incorrect assumptions based on incomplete data. However, it is important to recognize that, with the growing influence of ICER, manufacturers have been proactively sharing key information with the organization to receive a fair assessment. For instance, in 2017, Sanofi Regeneron shared unpublished clinical trial data on dupilumab with ICER prior to the drug's FDA approval, and the company subsequently accepted the value-based benchmark price when the drug was launched.[17] Other HTA bodies like NICE have also initiated value assessments ahead of marketing approval to help manufacturers prepare their evidence-generation strategies. A notable difference between NICE's strategy and ICER is that the latter also projects the value-based benchmark price, setting up an expected price for the new drug (or even for existing treatments post-entry of new drug) based on assumptions that are not necessarily valid in real-world scenarios post-approval. Payers can then use this as a price-negotiation tool for formulary decisions.[18]

> With the growing influence of ICER, manufacturers have been taking ICER assessments seriously

Currently, the US has no price-control legislation in place, and the influence of economic analyses is less among public payers than private payers. Public payers are mandated to cover FDA-approved treatments and may only consider the safety and efficacy of approved drugs. Private payers, however, may consider these analyses for drug coverage or reimbursement decisions. HTA bodies like NICE and CADTH require data from economic evaluations to be part of reimbursement submissions. The UK National Health Service (NHS) is required to adhere to the recommendations made by NICE. In contrast, ICER provides an independent assessment that any party can choose to use if it suits their decision-making needs. Public and private payers have both collaborated with ICER, including the Veteran's Administration, which worked with ICER on price negotiations to support drug coverage.[19] There is also some evidence of the evolving influence of ICER evaluations on private payers, causing manufacturers to take ICER assessments more seriously.

ICER's influence has been confirmed by small surveys of health plans and payers conducted by independent organizations.[18,20] A two-part survey of decision makers within the Academy of Managed Care Pharmacy (AMCP) eDossier System reported that 58 out of 99 respondents were aware of and had read ICER reports.[21] The evidence from ICER reports was reportedly reviewed by 56% of the survey respondents during the Pharmacy and Therapeutics (P&T) Committee review. Also, 35% of respondents had used the reports to determine affordability; 13% used them as part of price negotiation discussions[21]; and 69% said they used the ICER cost-effectiveness models to inform or validate their own economic models.[21] ICER itself reported high-level findings of a survey of 18 health plans by America's Health Insurance Plans with 100% response rate. Among the findings were that 73% of plans used ICER's reports for review of current and future coverage.[22] Aside from these surveys, there have been more direct examples of the increasing value of ICER reports, including companies using ICER reports as a negotiation tactic for coverage decisions. For instance, the New York Medicaid Program has negotiated discounts for multiple drugs based on recommendations from the New York State Division of Budget to the state's Drug Utilization Review Board.[23] All but one manufacturer provided the necessary rebates to continue coverage for the patients in the state.[24] Similarly, after accepting the value-based benchmark price for dupilumab that was recommended by ICER, Sanofi Regeneron entered into a deal with Express Scripts for alirocumab (indicated for high cholesterol) to gain exclusive formulary placement for the Proprotein convertase subtilisin/kexin type 9 (PCSK9) drug class. Express Scripts will also provide improved access to eligible patients removing stringent requirements for preauthorization for coverage.[25] It should be noted that ICER assessments might be more impactful on discussions with regional health plans than large payer systems who have their own evaluation methods.

Many supporters of ICER see such agreements as success stories for ICER's mission. Negotiations that end with payers adding or retaining drugs on their list of preferred drugs positively impact patient access to new and improved health technologies. Though this process is common in many countries, the considerable opposition may stem from the lack of drug price control in the US. With the growing influence of ICER, manufacturers have been taking ICER assessments seriously since there is a slow trend among some health plans to consider budget impact analyses with the value-based benchmark price while adding new drugs to their formularies. Despite the criticism that ICER has no official responsibility to act as drug price "watchdog," they have advocates who support their efforts to evaluate new health innovations and make efficacious products available to patients at a justifiable value.[26]

Do Methodologies Differ Significantly between ICER and Other HTA Bodies?

Evaluations across ICER, NICE, and CADTH have a similar structure. Each organization completes two main components: (1) a systematic review of literature on the clinical efficacy and safety of the drug, and (2) a health economic evaluation from a payers' perspective using cost-effectiveness and budget impact models. ICER assessments typically have additional components of other benefits/risks, contextual considerations, and budget impact.[27] However, each organization has its own methodology for evaluating

clinical and cost-effectiveness evidence. Well-established, government-mandated HTA bodies like NICE and CADTH review submissions from the manufacturers who are seeking reimbursement. Manufacturers are required to submit a complete assessment including all clinical and economic evidence comparing their own drug to clinically important comparators in the market. The agencies then review the submissions and make recommendations. NICE has an independent Evidence Review Group (ERG) that reviews the company submissions and helps the organization make the final recommendations for reimbursement by the NHS.[28] In contrast, ICER conducts drug value assessments based on its unique methodology, including meta-analyses and economic models.[10,29,30]

ICER develops its own economic model, whereas NICE and CADTH review a model submitted by the manufacturer that is tailored to each respective country's health system.[31-33] With the NICE and CADTH evaluations, the respective review teams critique the manufacturer's model and conduct additional analyses that are necessary for reimbursement decisions. In such circumstances, transparency is exercised through mandated sharing of the manufacturer's modeling code, which review teams can then use to conduct sensitivity analyses to test assumptions that are considered potentially inappropriate. On the other hand, ICER conducts their own sensitivity analyses to test uncertainty associated with model inputs as well as additional inputs recommended by healthcare stakeholders, including manufacturers, patients, and payers.

The conclusions of economic models are restricted by the model assumptions. Sensitivity analyses (deterministic or probabilistic) generally demonstrate the model's sensitivity to uncertainty surrounding particular model inputs. Keeping this under consideration, a model with a perspective that does not truly reflect the assumptions that match a payer's considerations will not be generalizable. Economic models for the UK and Canada are developed from the perspective of the healthcare payer (NHS or Health Canada). These perspectives will therefore truly reflect assumptions that are amenable to the final payer in these countries. ICER also develops its model from the healthcare payer perspective[34] for its base case analyses. However, in the US, there is no single payer to whose perspective the model can be developed, and the characteristics of patients served by different insurance or payer systems vary widely. Hence, individual payers in the US ideally should use the ICER report, in context, and be aware of any assumptions that do not hold true for their target population. If those assumptions have been demonstrated to cause significant uncertainty to the results of the cost-effectiveness analyses, then the incremental cost-effectiveness ratios or value-based benchmark prices should also be viewed in light of those discrepancies. During the assessment of sacubitril/valsartan [Entresto®] (Novartis), there were differences in the inputs that were assessed for the deterministic sensitivity analyses. NICE[35] and CADTH[36] tested one or more basic model parameter variables, like time horizon and discount rate, as well as clinical and cost inputs; ICER focused only on efficacy and cost inputs including, but not limited to, duration of efficacy, risk of cardiovascular mortality, and cost of hospitalization.[37] CADTH and NICE reported a significant impact of time horizon on incremental ratios. CADTH's review committee considered that the model should probably refrain from lifetime or long-term time horizon since there were no long-term clinical data available. Their final recommendations were based on the reduced time horizon. In contrast, ICER made assumptions about long-term benefits and adjusted for duration of efficacy of sacubitril/valsartan to data available from the clinical trial; these results found that the duration significantly impacted the incremental ratios as well. Considering ICER caters to a diverse health system like the US, their assessments should address uncertainty linked to a range of model parameters to satisfactorily demonstrate the uncertainty associated with the incremental cost-effectiveness ratios they present.

ICER also differs in how they present their recommendations based on their evaluations. Since NICE and CADTH are directly answerable to the federal agencies responsible for reimbursement decisions, they make strong final recommendations. They also make recommendations for reimbursement that are subject to certain conditions the manufacturers must meet. Instead, ICER conducts independent assessments that act as a guide for policy-makers and payers; they only present the incremental cost-effectiveness ratios and the value-based benchmark prices to meet thresholds of $100,00 to $150,000 per QALY. The end consumers of the report can interpret the results presented and decide the cost-effectiveness based on their willingness to pay. This approach can be seen as strategic on ICER's part, to avoid making direct recommendations like NICE or CADTH.

How Can Manufacturers Prepare Better for ICER Evaluations?

Manufacturers can leverage ICER's stakeholder engagement processes to collaborate with their researchers and health economists throughout a drug's review. By doing so, companies can provide early input and feedback during the clinical evidence review. Engaging early in the ICER review process can, for instance, provide opportunities for manufacturers to comment on health economic model structures. Some ways of early engagement are as follows.

- Manufacturers who are knowledgeable about available literature that supports key assumptions for economic models can proactively leverage their expertise to advocate for model assumptions that are valid and justifiable.
- Early cost-effectiveness models developed in-house by the manufacturers can help them in engaging with ICER. In this way, they can gauge potential outcomes of the economic evaluations. In addition, identifying potential data gaps for the economic model, putting together

studies to address such data gaps, or alternatively, refining necessary assumptions, can all help in developing a robust economic model.

- Manufacturers can use early insights to help develop approaches to better align product value stories.
- Manufacturers can prepare for pricing negotiations with payers by understanding potential objections and working with those stakeholders to develop appropriate arguments. Companies can also gather opinions and feedback on their evidence-generation strategies from clinical experts and patient focus groups.
- In situations when a negative recommendation or significant price reduction (compared to existing or assumed list price) is a foreseen conclusion, manufacturers can actively involve stakeholders to prepare innovative strategies to avoid conflicts with payers and gain alignment using consistent and sustainable approaches.

Much of the criticism of ICER can be attributed to their evaluation approach still being novel in the US, as well as concerns about transparency and accountability. With the lack of a single healthcare payer system, it is difficult to base decisions on a single assessment. Additionally, due to various priorities of US healthcare system stakeholders, the disapproval ICER receives is often contradictory and hence can be difficult to address. If ICER's role in reimbursement policy keeps expanding, there will be expectations for ICER to adapt their methods to suit the healthcare system better. With some adaptations to their value-assessment framework, ICER has partially addressed certain criticisms and shown an ability to adapt. An overarching market access strategy early in drug development has become crucial with the ever-growing influence of ICER. It serves drug manufacturers well to be amicable partners with the organization in the process of expanding access to crucial health interventions for patients in need, rather than oppose the natural progression of value-based acceptance of new technologies in the US market. ■

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