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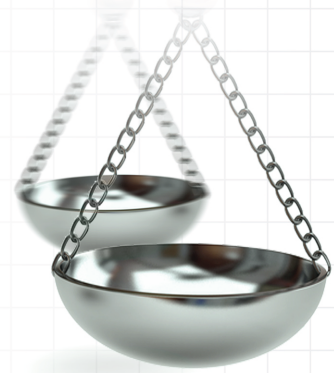

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Bridging the divide between health economics and outcomes research and biomedical investment: reflections from a health economist working in venture capital

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Despite investors' pivotal role in shaping biomedical innovation, interaction between the investment community and health economics and outcomes research professionals remains limited. Both communities seek to understand what society values and how to allocate resources accordingly, yet these conversations occur largely in parallel. This perspective article, written from the viewpoint of a health economist who joined a major biomedical investment firm, seeks to bridge that divide. Drawing on first-hand observations across three domains – profits, incentives and societal value; coverage, pricing and patient access; and public policy and innovation – it argues that health economics and outcomes research must reconnect with its economic foundations, incorporate insights from real-world investment practice, and update its methods to better inform policy, promote innovation and improve patient welfare in a market-based system.

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Introduction: the disconnect between HEOR & investment

Despite investors' pivotal role in shaping biomedical innovation, the interaction between investors and health economics and outcomes research (HEOR) professionals remains unfortunately limited [1,2]. A key focus area for HEOR professionals is to quantify the value of emergent health technologies from the perspectives of patients, payers and health systems [3–6]; whereas investors evaluate potential pipeline programs through the lens of risk-adjusted financial returns based on a wide range of market signals [7–9]. Both groups, however, aim to understand what society values, how much society is willing to pay and how to allocate our aggregate resources accordingly. Yet to date, these conversations happen largely in parallel, with little cross-fertilization.

This disconnect has consequences. The HEOR community often debates questions about value, pricing and innovation efficiency that do not always fully reflect the investment decision-making process [7,8,10,11]. Likewise, investors rarely or inconsistently draw on rigorous HEOR evidence when evaluating therapeutic areas or setting expectations for pricing and market access. As a result, policy debates, especially in an era of rapidly evolving global policy landscapes, can become polarized, and the evidence base used to inform such debates often does not fully reflect the real-world market dynamics [8,11].

Trained as a health economist, I joined a leading multistage investment firm over 2 years ago. Headquartered in the US, my company is a science-driven investment firm that allocates capital to companies across the world developing new medicines, diagnostics and other health technologies. When I joined, I was struck by how little structured dialogue existed between investors and the HEOR community. Many investors viewed HEOR as an academic box-ticking exercise – something performed for regulators or health technology assessment bodies, rather than a source

of insight into market behavior that could meaningfully improve investment decision-making. Conversely, many HEOR professionals misunderstand investors' motives, assuming that the pursuit of profit implies indifference to patient outcomes [12]; or they fail to appreciate the unique market mechanisms for healthcare inputs, and how and why these differ from competitive markets for most other goods and services.

This narrative perspective article, written primarily for an HEOR audience, seeks to bridge that divide. It presents a perspective informed by first-hand experience in both worlds, rather than based on comprehensive reviews, on a range of topics across three key domains: profits, incentives and societal value; coverage, pricing and patient access and public policy and innovation elasticity. Each section combines economic reasoning, real-world case examples and implications for advancing HEOR methods and practice.

Profits, incentives & societal value

Who are investors & how do they make decisions?

To bridge the divide, it is essential first to clarify who investors are and how they make decisions. Investors in biomedical technologies are market-based agents who study every available qualitative and quantitative signal – scientific, commercial, regulatory and behavioral – to determine what society values today and what it might value tomorrow [8,9,12]. Their role is to allocate scarce capital to development programs most likely to produce innovations that the market will recognize as valuable because they restore or prolong patients' health and wellbeing.

At an investment firm like mine, the investment team comprises individuals trained in a wide range of disciplines including medicine, biology, chemistry and finance. Their analysis of a potential project goes far beyond net present value (NPV) modeling [7]: they evaluate the scientific rationale, probability of success, existing and future treatment landscape, potential pricing and payer dynamics. The ultimate question is whether the project will yield a product that addresses important unmet needs and whether the expected risk-adjusted return justifies the investment allocation, relative to other opportunities available in health or non-health sectors in the broader capital market [9,12].

While the names of funds in the investment industry might sound foreign to HEOR professionals, it is likely that we all have a financial stake in the success of biomedical innovations. For many funds, capital comes from limited partners (LPs) – large institutional investors such as pension funds, university endowments and charitable foundations [13]. These LPs often represent the savings of ordinary citizens. Returns from venture capital and public equity investments fund scholarships, research grants and retirement income. Because of this linkage, the financial success of biomedical investments transcends the health gains from successful products, and biomedical technology investors must stay competitive to attract and retain funding.

Profit as a market signal of societal value

In academic or policy discussions about healthcare, profit is often portrayed as being in tension with patient and societal welfare. In the current market design for healthcare coverage, profit serves as an essential feedback signal for the value of medicines [14]. When a product generates profit, it reflects society's revealed willingness to pay for its clinical and economic benefits. Therefore, there is a natural alignment between market success and the societal value generated by innovative health technologies [14–16].

The profit motive is also an inevitable feature of competitive capital markets. Investors operate under a fiduciary duty to allocate capital efficiently and generate competitive returns [9,12]. Due to the competitive and dynamic nature of capital markets, a project with a positive NPV does not automatically get funded – it must meet a competitive hurdle rate relative to other available opportunities [7]. The profit motive under these market mechanisms compels investors to focus on innovations that society demonstrably values and is willing to pay for.

Consider the decision to fund an early-stage gene therapy company. The costs are immense, timelines long and outcomes uncertain [17,18]. Investors fund these projects when they believe that payers, patients and regulators will recognize the therapy's value – when the expected future cash flows justify the risk. That expectation depends critically on society's past behavior: whether previous therapies in similar areas achieved reimbursement and uptake at certain price points. Profit expectations thus embody collective social judgments about value. For some disease areas with significant unmet needs, the lack of profit incentives means we do not see a robust pipeline of investment. Next-generation antibiotics are a prominent example: despite antimicrobial resistance being linked to over one million deaths annually, private investments in next-generation antibiotics have been diminishing since the 1980s due to insufficient economic incentives driven by a series of scientific, economic and regulatory challenges [19,20].

The role of competition & 'me-too' drugs

The competitive nature of the capital market helps explain why 'me-too' drug development is not wasteful duplication but an expected feature of market incentives. These drugs are often portrayed as wasteful duplications that inflate costs without delivering incremental societal benefit [21–23]. However, such arguments sometimes fail to understand the history behind these drugs and underestimate their societal benefits.

From an investor and innovator perspective, the race typically starts when basic science research indicates the promise for a particular mechanism of action. Early in any race to treat or cure a disease, everyone hopes to be first-in-class or best-in-class. Eventually, as clinical trials reveal more information about each compound, some realize that they will not be first or best; if they think they may be close enough to the 'winning' drug, they might continue development to at least compete on price. These co-equal followers – labeled as 'me-toos' – are the byproduct of many innovators trying to be first and/or best. The classic case example is statins: despite being later entrants, atorvastatin and rosuvastatin became blockbuster drugs in the statin class, demonstrating not only superior LDL-cholesterol reduction in Phase III trials but also improved cardiovascular outcomes in landmark post-approval trials [24,25]. More recently, the race to develop HCV cures is an excellent example of how such competition played out to society's great benefit [26–28].

From a societal perspective, multiple entrants in a race are preferable [21,22,29]. First, our probability of achieving success is higher with more pipeline programs in development. Even if two pipeline programs have the same efficacy and safety profiles at the end of Phase II, they could have very different outcomes in Phase III. The recent experience with Bruton's tyrosine kinase inhibitors in multiple sclerosis illustrates this vividly: Merck KGaA's evobrutinib and Sanofi's tolebrutinib both showed substantial MRI lesion reductions in Phase II trials against the same target, yet both failed to separate from the active comparator in Phase III relapsing MS trials – possibly due to differences in CNS penetrance and patient selection rather than the mechanism itself [30,31]. Meanwhile, Novartis and other developers continue Phase III programs for the same class, informed by what these earlier candidates revealed [32]. Second, payers have the opportunity to extract lower prices from innovators in exchange for larger market share [26,28,33–36]. Moreover, patients have more choices, and are more likely to find treatments compatible with their preferences or find alternatives if one treatment fails or is poorly tolerated.

Considerable scientific knowledge is also generated from these parallel efforts. Scientific innovation is a cumulative process, where trial and error and iterations produce advances that are sometimes incremental and sometimes radical [37,38]. Each effort accumulates important scientific knowledge that can advance the fight against diseases.

Recommendations for HEOR

Taken together, the observations about incentives and competition offer important lessons for how HEOR frameworks should evolve. As a field, we should put aside our 'distaste' for profits and gain a deeper understanding of the market-based mechanisms that allocate capital for investment [9,14]. Doing so will allow us to better appreciate how profits align incentives across investors, innovators and societal wellbeing. For disease areas with significant unmet needs which lack innovations, we can also explore how HEOR methods can better incentivize those innovations – an area where the market fails to recognize and reward societal value, and where government can play a more active role.

Coverage, pricing & patient access

Can drug companies charge whatever they want?

A recurring misconception in both public and academic discourse is that pharmaceutical companies set prices arbitrarily and payers must accept them [39,40]. In reality, the net price, the unit price paid to innovators, is determined by centralized (e.g., UK) or decentralized (e.g., US) negotiation processes between payers and innovators, not to mention rent-seeking middlemen (e.g., pharmacy benefit managers (PBMs) and hospital groups) in the healthcare services delivery chain [41]. The respective shares of drug spending accruing to different entities reflect the relative bargaining power of each party and the negotiation framework.

Current debates tend to be overly fixated on prices – and very often only the launch prices – of innovative therapies [42–44]. From the investors' point of view, what matters is the discounted net profits. Price is certainly an important factor, but price without volume does not generate profit. The higher the price, the more likely payers will put up access barriers for patients (e.g., prior authorization, denials, higher co-pays), creating a price/volume trade-off that many health economists ignore when viewing prices as static [42,43].

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Over the product lifecycle, negotiation is not a one-and-done process. Negotiation and renegotiation happen continuously and better approximate the true societal value of medicines as real-world outcomes data accumulate. In contrast, cost-effectiveness analyses used to estimate the value of innovative therapies tend to rely heavily on pricing and trial data at launch, under conditions of high uncertainty, and are rarely updated [5,42,44,45].

The story of Zolgensma, the one-time gene therapy for spinal muscular atrophy, illustrates this well. Priced at $2.125 million at launch – widely labeled the world's most expensive drug at the time of launch – this was still roughly half the 10-year cumulative cost of Spinraza, the incumbent chronic therapy, which carries a list price of $750,000 in year one and $375,000 annually thereafter [46]. When payers and governments chose to cover Zolgensma, they validated not its headline list price but the therapy's value proposition. Investors could reasonably interpret that outcome as relevant signals to fund other one-time cures. Had payers balked, the chilling effect on gene therapy R&D would likely have been immediate. Similar dynamics played out for cures for hepatitis C virus (HCV) infection and novel immuno-oncology treatments.

Incentive misalignment between different players can also arise. While the net prices of innovative drugs have remained steady or even declined over time, total spending has risen due to rent-seeking behavior by middlemen such as PBMs [41,47]. Innovators are also not without fault: while most drugs go generic following loss of exclusivity [33], there are instances of patent gaming [48] aimed at extracting additional profits after exclusivity ends.

Market signals sent by coverage and reimbursement decisions sometimes reveal discrepancies between what society signals it is willing to pay versus what it actually pays for effective innovative treatments. The race to find a cure for HCV is a noteworthy example [26–28]. Before curative HCV pills were approved beginning in 2013, payers covered HCV treatment based on injected interferon – a difficult-to-tolerate treatment that worked only 40% of the time, costing around $40,000 per course, implying a willingness to pay of $100,000 per cured patient [26]. Yet when Gilead Sciences launched the first 'nearly perfect' HCV cure for $84,000 per patient, it triggered a media storm [26]. The demand for these drugs pressured short-term payer budgets, and some payers limited coverage to patients with advanced disease; courts eventually forced them to cover the drugs per their labels [49]. Meanwhile, competition from other HCV therapies drove costs-per-cure down dramatically – net DAA costs fell more than 80% from their initial levels within less than a decade [35]. Such discrepancies between short-term budgetary focus and long-term societal benefit can result in lack of access and hinder future innovations.

Rethinking value assessment through generalized cost-effectiveness analysis

To understand the alignment between market prices and the societal value of innovative therapies, we need to examine the analytic frameworks used in value assessment. Outside the US, health technology assessment agencies play a significant role in coverage and reimbursement decisions, particularly in countries with single-payer systems. In the US, the Institute for Clinical and Economic Review routinely produces assessments, though these are inconsistently referenced by payers and rarely inform negotiations directly [50,51].

Central to these assessments are traditional cost-effectiveness analyses (TCEAs) that take narrow health system perspectives and focus only on immediate health gains and cost savings to health systems. The limitations of TCEAs are well documented [3–5,45,52]. The narrow focus on the health system perspective means that TCEAs tend to understate the true societal value of innovation and fail to reflect real-world market dynamics (e.g., price drops due to genericization) [42,43]. These assessments are also disproportionately applied to innovative pharmaceuticals, while healthcare services – which take up a much larger share of total health spending – are rarely subject to the same scrutiny. Due to these flaws, applying insights from TCEAs in coverage and reimbursement decisions can result in delays or total lack of access to much-needed therapies, and subsequently hinders long-term innovation.

Australia offers a vivid illustration of the interaction between value assessment, price negotiations and access barriers. Trikafta was approved by the Australian Therapeutic Goods Administration in March 2021, yet the Pharmaceutical Benefits Advisory Committee (PBAC) deferred reimbursement for over a year, citing cost-effectiveness concerns – despite the drug's transformative clinical profile being well-established in four global Phase III trials [53,54]. For that period, Australian patients with cystic fibrosis were denied government-funded access to a therapy already covered in the US and more than 19 other countries. Cystic Fibrosis Australia described the situation as one where "*lives are lost, families destroyed, and futures put on hold while protracted negotiations play out*", noting that the PBAC framework had found Trikafta "*well above commonly accepted cost-effectiveness thresholds*" [53]. Trikafta was eventually listed on Australia's Pharmaceutical Benefits Scheme in April 2022 – more than 2 years after its US approval [55]. This delay was heavily influenced by the TCEA methodologies that failed to account for long-term genericization, caregiver burden and the full productivity value of restoring near-normal lung function to patients. Similar access

delays have been documented across other high-income countries that are members of the organization for economic co-operation and development (OECD) in drugs across a wide range of therapeutic areas [56], underscoring that flawed value assessments have real and measurable consequences for patients.

An updated alternative, generalized cost-effectiveness analysis (GCEA) methodology, builds on decades of methodological progress and offers a more comprehensive approach to estimating a treatment's full range of societal benefits [3–5,52,57]. GCEA expands TCEA methodology by considering a broader range of value elements important to patients and their loved ones (e.g., productivity gains, caregiver burden and scientific knowledge spillover [5,37]), and accounts for real-world market dynamics (e.g., steep price drops due to competition and genericization) [42,43].

Empirical analyses using GCEA methodology illustrate the discrepancy in TCEA-based value estimates and the real-world societal benefits of innovative medicines. For example, in a study conducted by Lakdawalla and colleagues for 20 high-impact therapies, original TCEAs indicated cost-effectiveness for 8 of the 20 therapies; adjusting for a subset of value elements showed that 17 out of 20 were cost-effective [58]. These empirical findings help to explain observed market outcomes in coverage – for example, why payers would cover the cystic fibrosis treatment Trikafta despite TCEA not considering it cost-effective.

While GCEAs can better approximate societal value and validate market-based outcomes, they are unlikely to play a significant role in price negotiations under the market-based mechanisms in the US. Payers compete with each other and seek to maximize profits within short-term budgetary constraints [44,50,51]. Their ultimate customers are employers that compete for talent in the labor market in part based on the quality of insurance plans they offer their employees. To attract and retain customers while maximizing profits, payers must strike a delicate balance between budgetary control and denying or limiting coverage of medicines that are recognized by patients and physicians as generating significant societal value. Denying a much-needed drug solely on the grounds of budgetary control is likely to provoke public outrage, resulting in reputational damage and customer attrition. Recent events in the US illustrate just how acute this tension can be. In December 2024, Anthem Blue Cross Blue Shield announced a policy to cap anesthesia reimbursement at arbitrary time limits during surgeries – a move that triggered immediate backlash from the American Society of Anesthesiologists, state governors and the public. Anthem reversed the policy within days [59]. Shortly before, UnitedHealthcare faced sustained public fury over high claim denial rates, culminating in a KFF analysis showing the insurer denied approximately one in three in-network ACA claims in 2023 – a level of coverage restriction that generated congressional scrutiny and threatened the company's market standing [60]. These episodes illustrate the competitive market discipline that constrains payer behavior: insurers who are perceived as systematically denying medically necessary coverage face tangible commercial consequences.

There is an inherent tension between the objectives of payers and the nature of value estimates from GCEAs: payers are short-term budgetary entities that focus on 1- or 3-year decision time horizons, whereas GCEAs look at the lifetime value for cohorts of patients, accounting for genericization and other market dynamics [42,50].

Contrary to the belief that GCEA is simply a way for innovators to raise value estimates and justify higher prices, GCEA adaptations do not always raise the estimated prices of innovative medicines [58]. A comparison between GCEA value estimates and market prices for innovative pharmaceuticals also shows that society tends to extract most of the societal benefits from marketed drugs [4,27,58]. But GCEAs can help reinforce the effectiveness of market-based mechanisms. There is a natural alignment between the factors that investors consider in the investment decision process and the value elements outlined in the GCEA value flower [5,58]. The GCEA framework can provide a more structured framework for investors to think through value drivers and estimate their potential impacts on returns of investment programs.

Cidara Therapeutics offers a successful pilot application based on the author's experience. Investors and economists worked together to construct a GCEA analysis earlier in the product development lifecycle for its lead asset CD388 – a seasonal influenza treatment – to inform the societal value narrative and discussion [61]. The analysis better supported internal and external conviction, and the company was subsequently acquired by Merck at a valuation of $9.2 billion USD [62].

Out-of-pocket costs & market distortions

Beyond value frameworks, out-of-pocket (OOP) costs introduce an entirely different set of distortions in the delivery of innovative health technologies, negatively affecting patient affordability and access. Copayments, deductibles and coinsurance are designed to prevent overutilization of care due to information asymmetry and moral hazard – a well-established rationale in health economics for preventing overconsumption of services [63–66]. But for high-value, life-saving drugs, this reasoning backfires. Premium-paying patients do not have an incentive to overconsume

treatments such as chemotherapy or gene therapy; OOP costs merely result in delays or abandonment of necessary care. It has been shown across disease areas that OOP costs pose significant barriers to patient access and adherence to physician-prescribed treatments [67]. As a result, high OOP costs lead to suboptimal use of effective medicines, subsequently resulting in greater healthcare resource utilization and suffering for patients and their loved ones.

OOP costs arise from misalignment of incentives for agents in the drug distribution system. In the US, the drug distribution system is rife with intermediaries, including PBMs, wholesalers, hospital systems and insurers. Each intermediary takes a share of rebates and discounts [41,68]. The resulting 'gross-to-net bubble' means that list prices can be multiples higher than what manufacturers actually receive, while patients' cost-sharing is based on inflated list prices. Studies show that rebates for top-selling drugs can exceed 80% of list price [47]. As a result, patient OOP spending has risen even as net prices remained flat or fell over time [69].

The opacity in prices and the share of drug spending pocketed by different parties distort public perception and policy debates. Patients often blame innovators for high drug costs (usually referring to list prices) when the real problem lies in misaligned incentives across the supply chain and high OOP costs. From an investor's standpoint, these distortions create uncertainty in the uptake of innovative therapies. From a societal standpoint, they represent inefficiency and inequity.

Recommendations for HEOR

To truly improve access while sustaining innovation, HEOR professionals should gain a deeper understanding of the market design for the development and coverage of innovative health technologies. Under market-based mechanisms, prices are dynamic and our methods and data inputs (e.g., health economic modeling) should reflect those changes over time. We should consider and incorporate how prices change due to competition and genericization [42,43]. Competition is not always a certainty, but almost certainly drives prices down after a drug goes generic [33,43]. We can conduct scenario analyses taking into account the number of drug candidates in development and do sensitivity analyses on pricing dynamics.

There is also too little discussion of how current pricing decisions will impact future innovations [70]. The prices set for innovations today signal society's willingness to pay for innovations in certain disease areas or novel mechanisms of action, and these are important tools for influencing how investors think about funding decisions for tomorrow's medicines. A deeper understanding of market-based mechanisms will also reveal that these mechanisms are by no means perfect. HEOR methods can help improve these market designs and better align stakeholder actions with societal welfare maximization. For example, GCEA methods can be applied to better appreciate the value of innovative medicines [3–5,52].

Although reducing or eliminating OOP costs will likely improve patient access to needed medicines and therefore improve outcomes, reducing or eliminating those costs might logically lead to premium increases, at least in the short term. Raising premiums could theoretically lead to stricter formulary design and lower rates of being insured. But it is worth considering how much insurance premiums would need to rise to compensate for abolishing OOP costs for physician-prescribed and insurer-approved medicines. In the US in 2024, commercially insured patients paid $54 billion in OOP costs [71] for prescription medicines. Incorporating those costs directly into the $1644.6 billion [72] total spending by privately insured Americans in the same year implies premiums would need to increase by 3.3%. But it is worth noting that improved outcomes are also likely to reduce downstream medical costs, offsetting some or all the need to raise premiums in the first place. Future HEOR studies can extend our existing literature and simulate the net welfare gain or loss in the short and long run to better inform policy reform on reducing or eliminating OOP costs.

Public policy through the investors' eyes

Price controls & pharmaceutical innovation

Pricing of innovative pharmaceuticals remains one of the most widely debated topics despite drugs representing a much smaller share of total healthcare spending than healthcare services [73]. Government price control of innovative pharmaceuticals has been proposed worldwide as a way to lower costs and improve access. In the US, Congress passed the Inflation Reduction Act (IRA) with a specific provision allowing the government to negotiate prices of high-impact drugs with innovators.

It is indisputable that reduced revenue and profits will reduce innovation incentives based on economic theory and existing empirical evidence [39,74,75]. The debates center around the likely magnitude of the impacts on

pharmaceutical innovations (i.e., the elasticity of innovation in response to reductions in reward size) and the impacts on patient wellbeing.

The approaches used in policy analyses (e.g., simulations conducted by the Congressional Budget Office) and empirical studies typically fail to capture the range of key factors considered in the investment process for pipeline programs [7,8,10,11]. These factors have been discussed and illustrated in a published real-world case example using NPV modeling [7]. Among these factors, policy uncertainty itself is one of the most overlooked. Following the IRA, investors have become acutely sensitive to longer-term policy risks. Given such policy uncertainty, investors will often assume a 'worst case scenario' (e.g., zero profit after year 9, when government-set prices take effect) to ensure that an investment program is commercially viable. Failure to consider the key drivers in the investment decision process risks underestimating the likely real-world impact of these policies on innovation, particularly for early-stage programs.

Three years after the passage of the IRA, early empirical evidence has emerged showing its negative impacts on innovation. Research has shown that the IRA reduced the number of assets under development, particularly for small-molecule drugs, and that even for drugs developed and approved, their maximal potential is not realized due to the shorter time window for additional indication expansion [74–76].

Many proponents of price controls believe that we are overpaying for innovative medicines, or that we can improve the efficiency of the R&D system with price controls. However, TCEAs used to assess value tend to underestimate the true societal value of innovative medicines due to their methodological and data limitations [3–5,45,52,58]. Moreover, the competitive nature of capital markets makes it highly costly for innovators to develop 'ineffective' therapies. Given these considerations, market-based mechanisms, despite their imperfections, arguably better approximate societal welfare maximization than a centralized price control system.

Global value distribution, free-riding & Most Favored Nation policies

The current administration has enacted a set of 'America First' policies, including tariffs and Most Favored Nation pricing, to ensure that other countries pay their 'fair share' for global pharmaceutical innovation [77]. Analyses show that approximately 67% of discounted profits from drugs accrue from the US market (based on one recent peer-reviewed estimate, with other analyses suggesting higher shares) [16,78,79]. This disproportionate contribution sustains global R&D.

These policies are, unfortunately, unlikely to achieve their intended goals. While reference pricing might improve affordability to the overall health system for drugs already launched, it might not necessarily translate to greater access for patients without insurance reform that significantly lowers or eliminates OOP spending. For drugs about to be launched, as US revenue constitutes a significant share of the return, it makes financial sense for companies to limit or forgo ex-US launches to preserve the majority of a drug's NPV. This will likely further exacerbate cross-country disparities. These skewed incentives will ultimately lower the return on pharmaceutical investment, resulting in less funding for future innovation efforts.

It is worth noting that some have argued that these policies were proposed so that pharmaceutical companies can pressure ex-US governments to raise their prices and increase their contribution to pharmaceutical innovations. However, this is less likely given that many ex-US countries usually have a single-payer system with a fixed budget set by the government in the short term, and individual innovators have relatively weaker bargaining power. Such an outcome is more likely to be achieved through trade negotiations between countries than between a pharmaceutical company and a country, as shown in the US–UK trade deal negotiated in December 2025 [80].

Currently, the full potential of innovative medicines is not realized globally. The lag can be staggering, even for patients in high-income OECD countries who experience significant delays in access [56]. The American public enjoys greater and more timely access to the most innovative therapies, partly due to a robust market-based system that incentivizes innovation and facilitates access. Outside the US, access challenges can be partially explained by disagreements between innovators and countries on the 'fair' price to pay. In some single-payer systems such as the UK and Canada, TCEAs are used to justify paying lower prices for innovative medicines. For all the reasons discussed above, this is likely to result in a lose-lose situation, hindering global innovation and making us all worse off in the long run.

Recommendations for HEOR

There are many alternative policy solutions that policymakers can consider to achieve improved patient access and sustainable innovation. HEOR can better inform such discussions through a more accurate representation of the

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investment decision-making process and the various market-based mechanisms discussed above. For example, we can better model the impacts of price-control policies on innovation by conducting project-level analyses that better align with real-world investment practices [7]. To improve affordability, we can estimate the impacts of insurance reform (e.g., eliminating copays for lifesaving medicines) on utilization of effective medicines and long-term health and economic gains. In designing a potential global differential pricing mechanism, we can look for alternative approaches that better reflect the true societal value of these therapies to patients worldwide.

Additional reflections & caveats

While the lessons and recommendations in this article are largely drawn from US experience, they are broadly relevant to HEOR professionals and health system stakeholders globally. The diseases we seek to cure do not respect national borders. Understanding how biomedical investment decisions are made, what drives capital toward some therapeutic areas and away from others, and what pricing outcomes sustain future R&D is relevant to all health systems that depend on a global innovation pipeline.

First, the specific examples and market dynamics described here are US-centric by design. The US funds a disproportionate share of global pharmaceutical R&D through its market-based pricing system [16,79], and its policy choices have consequences that extend well beyond its borders. This creates a shared interest among HEOR professionals across the globe in getting value assessments right: not just as a tool for allocating short-term domestic health budgets efficiently, but as part of a broader question about how the global costs and rewards of pharmaceutical innovation are distributed across borders. The existing system of global contribution to pharmaceutical innovation is under increasing political pressure from both directions [78,80]. HEOR can play a more active role in addressing this: developing value frameworks that support a more equitable and transparent global contribution to R&D efforts, rather than treating pricing purely as a domestic budget optimization problem.

Second, while some specific lessons may not translate directly to every health system context, the underlying analytic principles can still be referenced. Understanding how innovation happens and what signals drive pipeline development enables more productive engagement with pharmaceutical companies and investors, better-designed incentive mechanisms and more informed policy advocacy, particularly in areas where the development pipeline is thin and the unmet needs are significant. The discussion of OOP cost design applies wherever payers must balance access against moral hazard, timely and equitable access, and premium sustainability; the specific mechanisms differ across health systems, but the underlying trade-off is universal. And policies to control pharmaceutical prices are no longer purely domestic decisions, given the global interdependence of pharmaceutical markets; the lessons in Section 4 are therefore directly relevant to any health system considering such interventions.

Third, and most directly applicable to a concern many HEOR practitioners will probably recognize: in many countries, HEOR is institutionally defined as a tool for allocating a fixed budget determined externally by the government. The pressure to stay within that mandate – to optimize within constraints rather than question the constraints – is real and understandable. But methodological evolution is part of the normal development of any scientific field, and HEOR is no exception. Value assessment frameworks, patient preference methods, and real-world evidence methodologies are among the many areas where the field has evolved in response to new evidence and policy needs. That evolution was not a departure from HEOR's mandate; it was an expansion of it. The argument for incorporating broader societal value elements, dynamic pricing, and patient-centered outcomes into value assessment represents a similar trajectory.

The stakes of getting this right extend beyond any individual coverage decision. When value assessment frameworks systematically underestimate the societal benefits of innovative medicines (as the empirical evidence reviewed in this article suggests they do), the consequences are not merely methodological [58]. Resources may be misallocated away from technologies that generate substantial societal value toward those that appear cost-effective only because the framework fails to capture the full picture. Patients may be denied or delayed access to treatments whose true value is poorly represented in the models used to assess them [53,55]. And the signals sent by these assessments reach further than the immediate coverage decision: developers and investors observe which markets produce assessments that recognize the value of innovation and which do not, and this shapes where future R&D investment flows. Despite their best intentions, HEOR professionals who work within systems that consistently produce assessments concluding that innovative therapies are not cost-effective at their launch prices may, over time, contribute inadvertently to the pipeline gaps and access disparities they observe downstream. Value assessment is not only a retrospective accounting exercise; it also provides a forward-looking signal identifying what a health system values and what it expects from the innovation ecosystem.

These points apply even for those who accept the fixed-budget framework entirely. Even within fixed budget constraints, current methods can be improved. Failure to account for dynamic pricing over the product lifecycle, for patient risk aversion, or for value elements beyond direct health system costs does not merely produce a conservative estimate – it produces an inaccurate one. Inaccurate estimates, even when consistently applied, risk systematically misallocating scarce resources. Extending HEOR methods more consistently beyond pharmaceuticals and into all health technologies would also address an implicit asymmetry in how we currently assess value across different types of health expenditure. These improvements do not require abandoning the fixed-budget constraint; they are simply part of the ongoing work of making the methods more accurate.

Finally, underlying all the HEOR work we do is a single principle: value assessment should reflect what patients and society gain or lose, regardless of who is making the decision [6]. Specifically on value element selection: not every value element is relevant to every assessment, nor is every element feasible to quantify within realistic time and data constraints [3,4]. The recommendation is not to mandate a comprehensive societal perspective for every value assessment. Rather, it is to encourage modelers and value assessors to explicitly consider the relevance and feasibility of broader value elements before setting them aside – and where possible, to build a holistic model first, then customize it to the specific stakeholder perspective and decision context. In single-payer systems where the payer's mandate is to reflect population preferences, this is particularly relevant: the payer's perspective and the societal perspective are less different than institutional practice sometimes implies. We can start comprehensively and narrow deliberately; what we should avoid is starting narrowly and never asking whether we should have looked further.

It is also worth acknowledging that many of the changes discussed in this article extend beyond what HEOR professionals can achieve unilaterally. Improving how value is assessed, how OOP costs are structured, and how innovation incentives are calibrated requires coordinated engagement with payers, policymakers, patient advocates, and innovators. HEOR is well positioned to contribute to these conversations – not as an advocate for any stakeholder, but as a source of rigorous, transparent analysis that can help surface the trade-offs that political and commercial pressures tend to obscure. Better evidence does not automatically produce better policy, but it is a precondition for it. Where HEOR professionals engage across these communities – in policy forums, in advisory roles, in collaborative research – they can help shift conversations from zero-sum disputes over price toward more productive questions about how to design systems that sustain innovation while ensuring that its benefits reach the patients who need them.

Conclusion

Bridging the divide between HEOR professionals and investors is not about one side adopting the other's perspective entirely, but about fostering a shared understanding of the complex interplay between societal value, market dynamics, investment decisions and R&D processes. By embracing a more holistic view of value assessment, incorporating dynamic pricing and acknowledging the long-term impact of policy decisions on future R&D, both communities can contribute to a healthcare ecosystem that is more efficient, equitable and effective in delivering life-changing innovations to patients worldwide.

The journey toward this alignment will require ongoing dialogue, a willingness to challenge ingrained assumptions and a collective commitment to maximizing both health gains and sustainable investment in biomedical progress.

Author contributions

RZ Xie was solely responsible for study conception and design; acquisition, analysis and interpretation of data; drafting and critical revision of the manuscript; final approval of the version to be published; and agreement to be accountable for all aspects of the work.

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Not applicable. This is a perspective article presenting the personal views and observations of the author; it does not report original clinical, experimental, or patient data requiring institutional review board approval or informed consent.

Summary points
- The interaction between biomedical investors and health economics and outcomes research (HEOR) professionals remains limited, despite both communities sharing the goal of understanding what society values and how to allocate resources accordingly.
- Profit serves as an essential market signal of societal value: when a product generates profit it reflects society's revealed willingness to pay for its clinical and economic benefits, creating a natural alignment between societal value, market success and innovation incentives.
- 'Me-too' drug development is not wasteful duplication but an expected feature of competitive market incentives; it increases the probability of clinical success, drives in-class price competition and expands patient choice.
- Traditional cost-effectiveness analyses rely heavily on launch-time data under high uncertainty, rarely account for post-exclusivity price erosion, and can systematically underestimate the true societal value of innovative medicines when these relevant impacts and market dynamics are omitted.
- Generalized cost-effectiveness analysis offers a more comprehensive framework that can incorporate patient-centered value elements, real-world market dynamics including genericization and competitive pricing pressures that traditional cost-effectiveness analyses may ignore.
- Drug pricing policy debates are disproportionately focused on launch prices; the shares of drug spending accruing to different parties are determined by negotiation, shaped by bargaining power of payers, manufacturers, and intermediaries, and evolve substantially over the product lifecycle.
- Out-of-pocket costs are primarily driven by insurance benefit design rather than manufacturer pricing; addressing patient access and affordability therefore requires insurance reform, not solely drug price reduction.
- Policy simulations assessing the impact of price controls on innovation (such as Congressional Budget Office models) fail to capture key investment decision factors, including policy uncertainty, hurdle rates, and project-level NPV dynamics, risking systematic underestimation of long-term innovation impacts.
- HEOR has a significant opportunity to evolve: by incorporating investor-relevant value drivers, modeling dynamic pricing and quantifying the impact of insurance design on access and long-term innovation incentives, it can better inform both policy and investment decision-making.
- Bridging the divide between HEOR and biomedical investment requires ongoing dialogue, a willingness to challenge assumptions on both sides, and shared commitment to improving patient welfare through sustainable innovation.

References
Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Pizzi LT, Higashi MK. ISPOR 2026–2027 Top 10 HEOR Trends. ISPOR—The Professional Society for Health Economics and Outcomes Research (2026). https://www.ispor.org/heor-resources/top-10-heor-trends

2. ISPOR. HEOR meets investing—why are banks and VCs collaborating with health economists? ISPOR Webinar (2December 2025). https://www.ispor.org/conferences-education/event/2025/12/02/default-calendar/heor-meets-investing-why-are-banks-and-vcs-collaborating-with-health-economists
3. Garrison LP, Kamal-Bahl S, Towse A. Toward a broader concept of value: identifying and defining elements for an expanded cost-effectiveness analysis. *Value Health* 20(2), 213–216 (2017).
4. Li M. Generalized cost-effectiveness analysis: charting a path forward for measuring the societal value of medical technologies. *J. Comp. Eff. Res.* 14(1), e240213 (2024).
5. Shafrin J, Kim J, Cohen JT *et al.* Valuing the societal impact of medicines and other health technologies: a user guide to current best practices. *Forum Health Econ. Policy* 27(1), 29–116 (2024).
6. Xie RZ, Malik E, Linthicum MT, Bright JL. Putting stakeholder engagement at the center of health economic modeling for health technology assessment in the United States. *Pharmacoeconomics* 39(6), 631–638 (2021).
7. Xie RZ, Cameron T, Kolchinsky P. The impact of the Inflation Reduction Act on investment in innovative medicines: a project-level analysis. *Ther. Innov. Regul. Sci.* 59(3), 409–417 (2025).

•• **Xie *et al.*'s project-level NPV analysis of the IRA is the empirical anchor for Section 4, demonstrating concretely how policy simulations miss key investor decision factors and establishing the basis for the 'worst-case scenario' investor heuristic described in the text.**

8. Hofer MP, Radu P, Berdud M *et al.* Understanding biopharmaceutical investment decision-making: how does Congressional Budget Office's model compare to investor insights? *Health Aff. Sch.* 3(11), qxaf200 (2025).

•• **Hofer *et al.* provide a holistic comparison of Congressional Budget Office (CBO) policy models against actual investor decision-making frameworks, providing independent academic validation for the article's core claim that existing policy analyses fail to reflect investment reality.**

9. Lazonick W, Tulum Ö. US biopharmaceutical finance and the sustainability of the biotech business model. *Res. Policy* 40(9), 1170–1187 (2011).
10. Barbosu S, Axelsen K, Ezell S. Evidence to inform biopharmaceutical policy: call for research on the impact of public policies on investment in drug development. *Health Aff. Sch.* 2(12), qxae129 (2024).
11. Axelsen K, Barbosu S. The relationship between biopharma R&D investment and expected returns: improving evidence to inform policy. ITIF Report (2024). https://itif.org/publications/2024/05/06/relationship-between-biopharma-rd-investment-expected-returns/
12. Li X, Liu T, Taylor LA. Common ownership and innovation efficiency. *J. Financ. Econ.* 147(3), 475–497 (2023).
13. Cambridge Associates. US Venture Capital Index and Selected Benchmark Statistics. *Cambridge Associates Report* (2018). https://www.cambridgeassociates.com/wp-content/uploads/2018/10/WEB-2018-Q2-USVC-Benchmark-Book.pdf
14. Olivença F, Diaz J, Ramagopalan SV *et al.* Why is the market design for innovative pharmaceuticals not well understood? *J. Comp. Eff. Res.* 13(10), e240105 (2024).

•• **Olivença *et al.* provide a rigorous conceptual framework explaining why pharmaceutical markets differ fundamentally from other goods markets, directly motivating the article's central argument about health economics and outcomes research's limited engagement with market mechanisms.**

15. Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990–2015. *Health Aff.* 39(9), 1546–1556 (2020).
16. Goldman D, Lakdawalla D. The global burden of medical innovation. USC Schaeffer Center Whitepaper (2018). https://schaeffer.usc.edu/research/global-burden-of-medical-innovation/
17. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J. Health Econ.* 47, 20–33 (2016).
18. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009–2018. *JAMA* 323(9), 844–853 (2020).
19. Piddock LJV, Alimi Y, Anderson J *et al.* Advancing global antibiotic research, development and access. *Nat. Med.* 30, 2432–2443 (2024).
20. Rahman M, Gargate N, Laws M. Current economic and regulatory challenges in developing antibiotics for Gram-negative bacteria. *npj Antimicrob. Resist.* 3, 50 (2025).
21. DiMasi JA, Paquette C. The economics of follow-on drug research and development: trends in entry rates and the timing of development. *Pharmacoeconomics* 22(Suppl. 2), 1–14 (2004).

• **DiMasi and Paquette document that characterizing me-too drugs as 'duplicative and wasteful' reflects a persistent academic critique, while simultaneously providing empirical evidence that these drugs represent parallel development races rather than post hoc imitation.**

22. DiMasi JA, Faden LB. Competitiveness in follow-on drug R&D: a race or imitation? *Nat. Rev. Drug Discov.* 10, 23–27 (2011).
23. Krieger J, Li D, Papanikolaou D. Missing novelty in drug development. *Rev. Financ. Stud.* 35(2), 636–679 (2022).

24. Cannon CP, Braunwald E, McCabe CH *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N. Engl. J. Med.* 350(15), 1495–1504 (2004).
25. Ridker PM, Danielson E, Fonseca FA *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* 359(21), 2195–2207 (2008).
26. Manns MP, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. *Nat. Rev. Gastroenterol. Hepatol.* 19(8), 533–550 (2022).
27. Chou JW, Graf M, Díaz Espinosa O, Brewer I, Heim Z, Baumgardner J. Generalized cost-effectiveness analysis to assess treatment value in hepatitis C. *Am. J. Manag. Care* 29(12), 696–703 (2023).
28. Garrison LP, Jiao B, Elsisi Z *et al.* Estimating the allocation of the economic value generated by utilization of all-oral direct-acting antivirals for hepatitis C in the United States, 2015 to 2019. *Value Health* 27(8), 1021–1029 (2024).
29. Aghion P, Jaravel X. Knowledge spillovers, innovation and growth. *Econ. J.* 125(583), 533–573 (2015).
30. BioPharma Dive. German Merck's MS drug falls short in pair of Phase III tests. BioPharma Dive (December 2023). https://www.biopharmadive.com/news/merck-kgaa-evobrutinib-btk-multiple-sclerosis-negative-trial-results/701706/
31. Sanofi. Tolebrutinib GEMINI 1 and 2 Phase III study results in relapsing multiple sclerosis. Press release (20 September 2024). https://www.sanofi.com/en/media-room/press-releases/2024/2024-09-20-09-30-00-2949552
32. Roche. Roche's fenebrutinib shows unprecedented positive Phase III results as the potential first and only BTK inhibitor in both relapsing and primary progressive multiple sclerosis. *Press release (November)* 10 (2025). https://www.roche.com/media/releases/med-cor-2025-11-10
33. Grabowski H, Long G, Mortimer R, Bilginsoy M. Continuing trends in US brand-name and generic drug competition. *J. Med. Econ.* 24(1), 908–917 (2021).
34. Mulcahy AW, Schwam D, Lovejoy SL. Rand Health Q. International Prescription Drug Price Comparisons: Estimates Using 2022 Data. 3(11), PMID: 38855386; PMCID: PMC11147645 (2024).
35. Chhatwal J, Samur S, Kues B *et al.* Impact of direct-acting antiviral use for chronic hepatitis C on health care costs in Medicaid: economic model update. *Am. J. Manag. Care* 28(2), e44–e52 (2022).
36. Lin CH, Campbell JD, Motyka J, Cohen JT. US drug pricing patterns before loss of exclusivity. *Value Health* 28(6), 907–914 (2025).
37. Xie RZ, Towse A, Garrison LP. Should we pay for scientific knowledge spillovers? The underappreciated value of "failed" R&D efforts. *Int. J. Technol. Assess. Health Care* 38(1), e31 (2022).
38. Krieger JL. Trials and terminations: learning from competitors' R&D failures. *Manage. Sci.* 67(9), 5525–5548 (2021).
39. Goldman D, Grogan J, Lakdawalla D *et al.* Mitigating the Inflation Reduction Act's adverse impacts on the prescription drug market. USC Schaeffer Center Whitepaper (2023). https://schaeffer.usc.edu/research/mitigating-the-inflation-reduction-acts-potential-adverse-impacts-on-the-prescription-drug-market/
40. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA* 316(8), 858–871 (2016).
41. Sood N, Shih T, Van Nuys K *et al.* Flow of money through the pharmaceutical distribution system. USC Schaeffer Center Whitepaper (2017). https://schaeffer.usc.edu/research/flow-of-money-through-the-pharmaceutical-distribution-system/
42. Neumann PJ, Podolsky MI, Basu A *et al.* Do cost-effectiveness analyses account for drug genericization? A literature review and assessment of implications. *Value Health* 25(1), 59–68 (2022).

- **Neumann *et al.*'s systematic review is the primary evidence that published CEAs almost universally fail to account for post-exclusivity drug genericization, directly supporting the article's argument that TCEAs overestimate lifetime costs and therefore underestimate value.**

43. Whittington MD, Mattingly TJ. Estimating a drug's price after loss of exclusivity as a function of its cost of goods sold. *Appl. Health Econ. Health Policy* 23(1), 75–83 (2025).
44. Whittington MD, Garrison LP, O'Brien JM, Campbell JD. How time is accounted for when modeling pharmaceutical impacts: investment vs. assessment perspectives. *Health Aff. Sch.* 3(9), qxaf169 (2025).
45. Sanders GD, Neumann PJ, Basu A *et al.* Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA* 316(10), 1093–1103 (2016).
46. Feuerstein A. At $2.1 million, newly approved Novartis gene therapy will be world's most expensive drug. STAT News (24 May 2019). https://www.statnews.com/2019/05/24/hold-novartis-zolgensma-approval/
47. Dickson SR, Gabriel N, Gellad WF, Hernandez I. Assessment of commercial and mandatory discounts in the gross-to-net bubble for the top insulin products from 2012 to 2019. *JAMA Netw. Open* 6(6), e2318145 (2023).
48. Lidow N, Kesselheim AS, Rome BN. Biological patent thickets and delayed access to biosimilars, an American problem. *J. Law Biosci.* 9(2), lsac022 (2022).
49. Greenwald R, Waters P, Cayer S. Enforcement of legal remedies to secure hepatitis C virus treatment with direct-acting antiviral therapies in correctional facilities and Medicaid programs. *Public Health Rep.* 135(Suppl. 1), S44–S49 (2020).

50. Brogan AP, Hogue SL, Vekaria RM, Reynolds I, Coukell A. Understanding payer perspectives on value in the use of pharmaceuticals in the United States. *J. Manag. Care Spec. Pharm.* 25(12), 1319–1327 (2019).

51. Chambers JD, Enright DE, Panzer AD, Cohen JT, Ollendorf DA, Neumann PJ. Examining US commercial health plans' use of The Institute for Clinical and Economic Review's reports in specialty drug coverage decisions. *J. Manag. Care Spec. Pharm.* 29(3), 257–264 (2023).

52. Lakdawalla DN, Doshi JA, Garrison LP *et al.* Defining elements of value in health care—a health economics approach: an ISPOR Special Task Force Report. *Value Health* 21(2), 131–139 (2018).

•• **Lakdawalla *et al.*'s ISPOR Value Flower task force report provides the conceptual foundation for generalized cost-effectiveness analysis (GCEA) and the full range of value elements beyond traditional cost-effectiveness analysis (TCEA), underpinning the argument throughout Section 3 that traditional frameworks systematically undervalue innovation.**

53. Cystic Fibrosis South Australia. A tough pill to swallow. . . access deferred. https://www.cfsa.org.au/trikafta-access-deferred/

54. Middleton PG, Mall MA, Dřevínek P *et al.* Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. *N. Engl. J. Med.* 381(19), 1809–1819 (2019).

55. Vertex Pharmaceuticals. Vertex announces reimbursement agreement in Australia for TRIKAFTA® for patients with cystic fibrosis. Press release (27 March 2022). https://news.vrtx.com/news-releases/news-release-details/vertex-announces-reimbursement-agreement-australia-trikaftar

56. Mulcahy AW. Rand Health Q. Comparing New Prescription Drug Availability and Launch Timing in the United States and Other OECD Countries. 3(11), PMID: 38855389; PMCID: PMC11147638 (2024).

57. Lakdawalla DN, Phelps CE. Health technology assessment with diminishing returns to health: the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach. *Value Health* 24(2), 244–249 (2021).

58. Lakdawalla D, Phelps CE, Arndorfer S *et al.* Getting the math right when measuring the value of new medicines. EntityRisk White Paper (2023). https://nopatientleftbehind.docsend.com/view/889u6zs74tra9x4a

•• **Lakdawalla *et al.*'s empirical GCEA analysis of 20 high-impact therapies provides the quantitative evidence base for the claim that 17/20 therapies were cost-effective under GCEA versus only 8/20 under TCEA, the key empirical result supporting Section 3's argument.**

59. Fattah M, Miller S. Anthem Blue Cross Blue Shield halts anesthesia payment policy after backlash. NBC News (5 December 2024). https://www.nbcnews.com/health/health-care/anthem-blue-cross-blue-shield-time-limits-anesthesia-surgery-rcna183035

60. Pestaina K, Pollitz K, Rae M. Claims denials and appeals in ACA marketplace plans, 2021. KFF Issue Brief (January 2023). https://www.kff.org/private-insurance/issue-brief/claims-denials-and-appeals-in-aca-marketplace-plans/

61. Kolchinsky P, Tadvalkar L, Xie R. How GCEA stopped us from sandbagging our pricing and peak sales estimates for Cidara's flu drug. RApport (20 August 2025). https://www.racap.com/rapport/cidara-gcea-flu-drug

62. Merck. Merck to acquire Cidara Therapeutics, Inc., diversifying its portfolio to include late-phase antiviral agent. Press release (14 November 2025). https://www.merck.com/news/merck-to-acquire-cidara-therapeutics-inc-diversifying-its-portfolio-to-include-late-phase-antiviral-agent/

63. Robinson JC. The end of managed care. *JAMA* 285(20), 2622–2628 (2001).

64. Arrow KJ. Uncertainty and the welfare economics of medical care. *Am. Econ. Rev.* 53(5), 941–973 (1963).

65. Pauly MV. The economics of moral hazard: comment. *Am. Econ. Rev.* 58(3), 531–537 (1968).

66. Manning WG, Newhouse JP, Duan N, Keeler EB, Leibowitz A, Marquis MS. Health insurance and the demand for medical care: evidence from a randomized experiment. *Am. Econ. Rev.* 77(3), 251–277 (1987).

67. Fusco N, Sils B, Graff JS, Kistler K, Ruiz K. Cost-sharing and adherence, clinical outcomes, health care utilization, and costs: a systematic literature review. *J. Manag. Care Spec. Pharm.* 29(1), 4–16 (2023).

68. Van Nuys K, Ribero R, Ryan M, Sood N. Estimation of the share of net expenditures on insulin captured by US manufacturers, wholesalers, pharmacy benefit managers, pharmacies, and health plans from 2014 to 2018. *JAMA Health Forum.* 2(11), e213409 (2021).

69. Mallatt J, Dunn A, Fernando L. Consumer out-of-pocket drug prices grew faster than prices faced by insurers after accounting for rebates, 2007–20. *Health Aff.* 43(9), 1284–1289 (2024).

70. Ramagopalan SV, Diaz J, Mitchell G, Garrison LP Jr, Kolchinsky P. Is the price right? Paying for value today to get more value tomorrow. *BMC Med.* 22(1), 45 (2024).

71. IQVIA Institute. U.S. medicine use trends 2026. IQVIA (2026). https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/us-medicine-use-trends-2026

72. Centers for Medicare & Medicaid Services. National health expenditures 2024 highlights. CMS Office of the Actuary (2026). https://cms.gov/files/document/nhe-infographic.pdf

73. Kolchinsky P. A lot for a little: the best 8% slice of our healthcare dollar. RApport (2024). https://rapport.racap.com/all-stories/best-8-percent-of-our-healthcare-dollar

74. Grabowski H, DiMasi JA, Long G. Postapproval innovation for oncology drugs and the Inflation Reduction Act. *Health Aff.* 43(10), 1400–1409 (2024).

75. Zheng H, Patterson JA, Campbell JD. The Inflation Reduction Act and drug development: potential early signals of impact on post-approval clinical trials. *Ther. Innov. Regul. Sci.* 59(4), 781–789 (2025).

76. Rhuda J, Xie R, Cameron T, Kolchinsky P. Estimating the impacts of government-mandated price reductions on indication expansion for launched drugs: a real-world study. *Value Health* 27(12), S308 (2024).

77. Shafrin J, Garrison LP, Xie RZ. Import price, import threshold: how foreign reference pricing embeds valuations and risks undermining global innovation. *Health Aff.* Forefront (24 June 2026). https://www.healthaffairs.org/content/forefront/import-price-import-threshold-foreign-reference-pricing-embeds-valuations-and-risks

78. Kolchinsky P, Xie R. No more freeriding on the Great American Drug Deal. RApport (2025). https://rapport.racap.com/all-stories/no-more-freeriding-great-american-drug-deal

79. Frech HE III, Pauly MV, Comanor WS, Martinez JR. Pharmaceutical pricing and R&D as a global public good. *Health Econ.* 35(8), 1158–1174 (2026).

80. Office of the United States Trade Representative. US Government announces agreement in principle with the United Kingdom on pharmaceutical pricing. Press release (1 December 2025). https://ustr.gov/about/policy-offices/press-office/press-releases/2025/december/us-government-announces-agreement-principle-united-kingdom-pharmaceutical-pricing