Tailoring Generalized Cost-Effectiveness Analysis (GCEA) to the U.S. Setting: The Importance of Using the Right Prices

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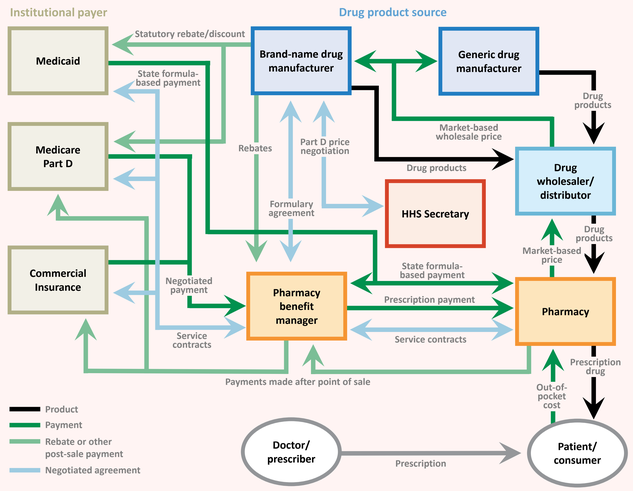
Research objectives

- **This study aimed to evaluate whether existing methodological guidance for incorporating drug prices into (GCEA) adequately reflects the complexity of the U.S. pharmaceutical market. Specifically, we examined:**
  1. **To what extent does current guidance provide advice on parameterizing dynamic drug prices?**
  2. **Does guidance sufficiently emphasize the need for metrics that reflect actual economic costs (i.e., real transaction prices) from the perspective of relevant decision-makers?**

Background

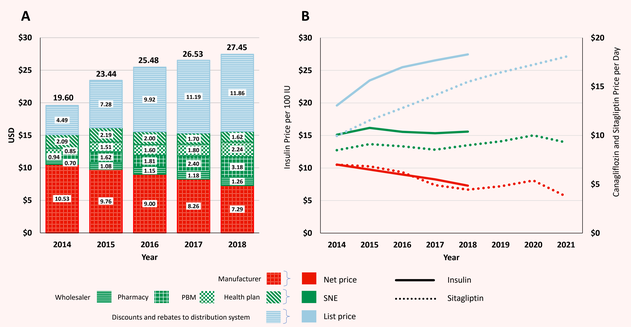
- Conventional cost-effectiveness analysis (CEA) has long relied on simplifying assumptions, many of which are increasingly being questioned—particularly in the context of the decentralized, multi-payer U.S. healthcare ecosystem. Notable examples include the assumption of constant marginal utility for additional health gains [1], and the exclusion of broader value elements such as hope, outcome certainty, the reassurance of knowing, and spillover effects on families, caregivers, and scientific progress [2].
- CEA often relies on two unrealistic simplifications in how drug prices are parameterized:
  1. Assuming prices remain constant over time, thereby ignoring market dynamics such as branded price competition and the entry of generic and biosimilar competitors
  2. Using list or net prices as proxies for true economic costs from institutional payer (i.e., commercial insurers, self-insured employers, and government payers) and societal perspectives, even though neither price metric correctly reflects those costs
     - List prices completely ignore confidential rebates, manufacturer fees, and earnings retained by drug market intermediaries
     - While accounting for price concessions, net prices overlook earnings retained by drug market intermediaries
     - Neither price metric, moreover, internalizes opportunity costs to the broader economy like transportation, productivity, and caregiver time [3]
- The fallacy of assuming that prices remain static over time is easily confirmed. Recent studies document price reductions of about 80% within 1-2 years following generic or biosimilar entry [4, 5]. Moreover, transaction prices often fluctuate significantly during the exclusivity period, reflecting evolving market dynamics.
- Multiple financial transactions occur along the complex supply chain in the U.S. prescription drug market (**Figure 1**), many of which involve transaction prices that differ significantly from both list and net prices—challenging the second assumption
  - The systemwide net expenditure (SNE) price metric [6, 7]—which accounts for confidential rebates, manufacturer fees, and earnings retained by drug market intermediaries—reflects the economic cost borne by institutional payers and captures an important and growing component of costs to society
- Criticism of the second assumption is not merely academic. In the U.S. market in 2023, estimated shares of total expenditure on brand-name medicines were distributed as follows [9]:
  - 49.9% retained by manufacturers,
  - 25.3% accrued to PBMs, insurers, and other supply chain entities like wholesalers and provider group purchasing organizations (GPOs),
  - 11.8% for government-mandated rebates and fees, including Medicaid rebates and Part D coverage gap discounts,
  - 9.6% captured through 340B provider markups and 340B pharmacy margins, and
  - 3.4% allocated to commercial cost-sharing assistance
- These magnitudes will vary across drugs given that market conditions vary. **Figure 2** provides examples for two anti-hyperglycemic medications.
  - Panel A shows a time series of estimated expenditures accruing to different drug market participants for a basket of 32 insulin products. Red bars indicate the share paid to manufacturers (i.e., the net price for 100 units of insulin); green bars indicate earnings retained by intermediaries; and blue bars indicate the share of list price passed through to consumers. The height of each bar is the average list price, and the sum of the red and green areas is the average SNE. While list prices rose and net prices fell, SNEs remained relatively stable—reflecting growing intermediary margins.
  - Panel B depicts list, net and SNE price trajectories for insulin as well as for the oral diabetes medication sitagliptin, with list (blue) and net (red) prices diverging, relatively stable SNEs (green), and rising intermediary shares
- GCEA [2, 12-17] integrates several important advances in economic evaluation, including relaxation of the assumption of constant marginal utility for additional health gains [18] and the inclusion of broader value elements such as hope, outcome certainty, the reassurance of knowing, and spillover effects on families, caregivers, and scientific progress [2]
- GCEA also highlights the importance of incorporating price dynamics—driven by branded competition, generic and biosimilar entry, and policy changes such as the Inflation Reduction Act (IRA)
- Researchers have called for additional methodological development and empirical research to refine the approach and further enhance its utility for value assessment [14, 19-22]

Figure 1: Financial, Product, and Information Flows in the U.S. Prescription Drug Market



Adapted from Figure 1.1 in the Congressional Budget Office report "Alternative Approaches to Reducing Prescription Drug Prices" [8].
Note: the relationships between commercial insurers, pharmacy benefit managers, and pharmacies are depicted here as contracted arrangements, but there is substantial integration in the industry. This diagram does not depict all possible scenarios.

Figure 2. Distribution of Expenditures per 100 Units of Insulin Across Distribution System Participants (Panel A) and Price Trajectories (Panel B)



Derived from Van Nuys et al. [7] (Panel A) and SSR Health [10] and Willis et al. [11] (Panel B)

Methods

- Targeted searches using PubMed and ISPOR Presentation Database, supplemented with backward and forward citation searches, to identify:
  - US-relevant recommendations for parameterizing drug prices
  - GCEA methodological papers and empirical applications
  - Recent CEAs (not always explicitly labeled as GCEA) incorporating price dynamics or examining price metric selection by decision-maker perspective
- Qualifying studies reviewed for:
  - Price parameterization best practice recommendations
  - Commentary on price dynamics and price metric selection
  - Empirical evidence on pricing approaches and methods

Results

Best practice recommendations for parameterizing prices in U.S. economic evaluations

2nd Panel on Cost-Effectiveness in Health and Medicine [23]:

- "Costs [including prices] should reflect the transaction prices *from the perspective of the analysis*, which requires implicitly not only the use of an appropriate price metric, but also that *prices be allowed to vary over time* in line with the economic reality

ISPOR Drug Price Task Force [24]:

- The Task Force recommended using "Drug prices *actually paid by the relevant payer* net of all rebates, copays, or other adjustments" and advised that "For drugs that are *off-patent*, or likely to be off-patent in the near future, it is appropriate to *consider multisource drug prices*"
- While this guidance emphasizes the importance of using payer-relevant prices and considers the effects of generic and biosimilar entry, it does not expound on the term "payer" or financial flows through the drug supply chain. Price changes during the patent period are not discussed explicitly.

GCEA Commentary on Parameterizing Prices

Price dynamics

- The GCEA User Guide recommends "incorporation of dynamic net health system costs into the value assessment framework" but frames this primarily in terms of pharmaceutical price changes "over their life cycles due to generic entry after brand-name drugs lose their market exclusivity" [14]

Price metrics

- The GCEA User Guide [14] defers to Second Panel on Cost Effectiveness in Health and Medicine [23], which as noted above states that prices should "reflect the transaction prices from the perspective of the analysis"
- None of the identified GCEA studies motivated the choice of price metric [14, 19-22, 25, 26]

Empirical methodology and metrics

Price dynamics

- A 2022 review found that fewer than 5% of a sample of 270 U.S. cost-utility studies with a lifetime horizon—published from 1991 to 2019—accounted for future generic or biosimilar prices [27]. The first published study to apply branded price evolution beyond uniform inflation adjustments—albeit in the Dutch setting—was published in 2023 [28].
- The GCEA User Guide offers two methods for forecasting future generic and biosimilar prices: (1) a proportional reduction from the branded price and (2) applying a multiplier to the drug's marginal cost of production. See [29] for a worked example of the latter approach.
- Nonlinear regression has also been used to extrapolate observed price trajectories [28]
- Stacked cohort modeling has been recommended to capture the value of future patient cohorts (including those who initiate treatment in the post-patent period) and to estimate the value over a drug's lifetime rather than the lifetimes of individuals [9, 30]

Price metrics

- List prices were found to be the most used price metric in U.S. CEAs [27]
- To date, only one CEA in the public domain has used the SNE price metric [11]
- Two of the seven self-identified GCEA studies used net prices [25, 26]—one of them for 20 different drug comparisons [25]

Discussion

- Value assessments can only be informative if they use the right prices, and the right metric for the question at hand. In the U.S., list and net prices are often misaligned with true economic costs due to price concessions as well as earnings retained by intermediaries. This misalignment biases the results of economic evaluations and thereby misinforms decision-makers, leading to inefficient allocation of resources and suboptimal patient outcomes.
- GCEA encourages incorporating price dynamics, but applications to date—and the examples provided in guidance—have largely focused on generic and biosimilar entry
- As Baumol [31] and Kolchinsky [12] emphasize, the existence of generics and biosimilars make the pharmaceutical market unique compared to markets for other key healthcare inputs. In the U.S., an important way in which brands compete is via price changes and concessions. Ignoring these aspects risks overstating drug costs in economic evaluations.
- Price dynamics should not be omitted in economic evaluations, especially in the U.S. context. Many other uncertain parameters in cost-effectiveness analysis, including transition probabilities and future resource utilization, are also projected (routinely). Research in the economics field on the determinants of prices should be leveraged [32-34].
- Price dynamics should not be incorporated in isolation—other model inputs, such as costs of physician visits and diagnostics, should also reflect time-based changes to avoid internal inconsistency
- List prices are public but ignore price concessions. Estimates of net prices approximate what manufacturers receive but omit a growing share of total expenditures that are retained by intermediaries.
- Systemwide net expenditures (SNEs) capture this share, and estimation requires thoughtful consideration of the specific market in question as well as assumptions to forecast, owing to the confidential nature of the financial flows among intermediaries. It is important to consider this metric in U.S. economic evaluations, however, given the structure of the pharmaceutical market [35, 36].
- Finally, the implications of this study extend beyond the U.S. Confidential contracting and discounts, supply chain markups, and generic or biosimilar competition may significantly impact many health systems.

Conclusions

- **The GCEA approach highlights several critical considerations that need to be addressed when assessing the value of medicines**
- **Further methodological development is warranted to better capture price dynamics, including those occurring during the patent period, as well as to support more explicit guidance on selecting price metrics that best reflect economic costs from the perspectives of different decision-makers**
- **The role and behavior of drug intermediaries—tailored to the specific market context—should be incorporated into economic evaluations, as this is essential to fully understand the true value of medicines**

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