The Importance of Accounting for Heterogeneity in Economic Analysis and Best Practices for the US Setting

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OBJECTIVE

To review and synthesize the literature on heterogeneity in economic evaluation, highlight aspects relevant for health care settings in the United States, and present potential solutions to ensure evaluations properly account for this key value determinant.

BACKGROUND

- Comparative economic analysis is often an important input to drug reimbursement and formulary decision-making
- Unlike clinical treatment decisions that are appropriately taken at the level of the individual patient, coverage decisions are usually taken at the population level (even though research has pointed out the potential value associated with more personalized decision-making[1])
- In reality, however, there are no "average" patients, and informing coverage decisions with analyses based on population averages can be problematic and, in fact, not patient-centric (see the National Pharmaceutical Council's "The Myth of Average"[2]) as averages can mask important sources of heterogeneity across patients and across the treatment setting[3,4]
  - Specifically, in the presence of heterogeneity:
    - A treatment judged to be *not* cost-effective based on the average can nonetheless be cost-effective for subgroups, which can lead to denial of optimal treatment for subgroups and result in wasted resources (and a missed opportunity to use more appropriate treatments)
    - Conversely, a treatment could be judged to be cost-effective on average, but not for all cases, so resources would be allocated inefficiently
  - Despite the problem being well described in the methodological literature[3,5,6] and clearly recommended in best-practice guidelines,[4,7-9] published reviews have found underwhelming empirical implementation[10,11]
    - According to a review of 200 randomly selected cost-effectiveness analysis (CEA) studies cataloged in the Tufts CEA Registry for 2014, for example, only 19% reported subgroup results based on observable or measurable patient information (though this was slightly more common in the subgroup of US studies [25%])[11]
    - In the same review, the authors reported that, of 23 sets of subgroups reported alongside average cost-effectiveness ratios, 13 reported ≥1 incremental cost-effectiveness ratio (ICER) that would lead to a different value-based decision compared to the overall group
- Reasons for this gap in the empirical evidence base may include the following:
  - Lack of awareness among practitioners
  - Inadequate clinical understanding or evidence to inform subgroup analysis[12]
  - Practical and ethical issues associated with making reimbursement decisions for subgroups[5]
  - Lack of specificity on dealing with heterogeneity in many pharmacoeconomic guidelines, which may have failed to signal its importance[8]
- For US evaluations, an additional explanation may be that the methodological heterogeneity literature has largely been developed from the perspective of a single-payer health technology assessment (HTA). As such, existing guidance is not sufficiently tailored to the decentralized US setting, and important sources of heterogeneity (e.g., variability in socioeconomic status; geographic location; patient, physician, and payer preferences; and insurance coverage) have not been given enough consideration

METHODS

- The PubMed database was searched on November 1, 2021, for methodological articles, case studies, and reviews using search terms "patient heterogeneity" AND "economic evaluation" AND "cost-effectiveness," without time exclusions but limited to articles written in English
- Methodological studies, case studies, and review studies qualified for inclusion
- 2 health economists screened the identified studies for inclusion
- Forward and backward citation searches for additional qualifying studies and internet searches for curricula vitae (CV) of key researchers were performed
- Relevant health economic evaluation guidelines that addressed heterogeneity and studies previously known were included

RESULTS

Figure 1; Box 1 and Box 2

Box 1. Types of Heterogeneity (Adapted From Sculpher et al[3])

1. Intervention-related factors (e.g., treatment-effect modifiers)

- Treatment effects can vary across patients based on observable characteristics (e.g., statins produce greater relative risk reductions for cardiovascular disease [CVD] in subgroups of patients with higher baseline low-density lipoprotein cholesterol values[13])
- Intervention-related factors can also lead to systematic cost differences (e.g., in the case of weight-based dosing)[3]

2. Factors related to the disease but not the intervention

- Even when relative treatment effects of an intervention are identical (i.e., across subgroups), absolute risk reductions may vary according to underlying disease features (e.g., disease severity)
  - The same proportional risk reduction produces greater population benefits for patients at high risk than for those at low risk. This type of risk stratification is routinely used to inform clinical decision-making (e.g., for whom to provide prophylactic CVD therapies[14,17] and cardioprotective diabetes treatments[18])
  - Translating to economic terms, the value of vaccination (e.g., against hepatitis) is larger in high-risk subpopulations (e.g., health care workers). The value of glucose lowering has also been shown to be greater for individuals with poorly controlled diabetes[19]
- Costs may also vary systematically with observable patient characteristics, leading to differences in comparative value across subgroups. For example, Ghatnekar et al found age- and sex-specific differences in the direct medical costs of stroke[20]

3. Factors unrelated to both the intervention and the health condition that affect patient outcomes

- Competing risks can limit the capacity of patients to benefit from an intervention
  - For example, the elderly generally face greater risks for debilitating and life-threatening chronic diseases, which may limit the benefits of preventive treatments (e.g., long-term survival following liver transplantation is significantly greater for younger recipients[21])

4. Patient preferences

- Preferences for different health states have been shown to vary across patients and over time (e.g., Dolan et al found that age systematically affects preferences for health[22])
- Patient preferences associated with choice of health insurance are potentially important to consider in the US setting. Customers with different characteristics and different willingness to pay for achieving health outcomes may systematically be attracted to different insurance plans[23]
- Lakdawalla et al propose a new method, the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach, which uses patient risk aversity and diminishing returns to health-related quality of life to capture a "severity premium" for health gains for individuals in more severe health states[24]

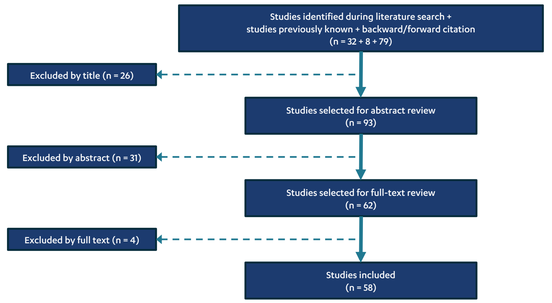
5. Factors unrelated to patients (e.g., sources of heterogeneity related to geography, societal factors, health care providers, insurers, and employers)

- Geographic heterogeneity (i.e., generalizability or transferability) can lead to variability in cost-effectiveness because costs and treatment practices are local. These factors often vary within countries/states (e.g., rural and urban areas[25]) and across treatment centers[26]
- Factors related to the care provider may also matter. For example, surgical success rates might vary according to a clinician's training and experience[27,28]
- Public preferences for health states have been found to vary according to characteristics of the underlying population of respondents[29]
- In a system with multiple institutional payers (e.g., insurers, pharmacy benefit managers [PBMs], and employers) with diverse goals and responsibilities, as in the United States, the valuation of treatments is likely to vary[23]

6. Sources of heterogeneity that are not knowable *ex ante* but become known *ex post*

- Factors that are unobservable (or not predictable) at the time of a treatment decision may still be useful for allocating resources
  - For example, if it is known that initial response is a predictor of long-term response, stopping rules can be designed
- To address such situations methodologically, the modeling should include consideration of treatment sequences[3]

Figure 1. PRISMA study attrition diagram.



Box 2. Overview of Study Design and Implementation to Address Heterogeneity

1. Comparative economic analysis study design phase

- Select relevant subgroups for analysis and determine the most appropriate methods by which the validity of this subgrouping can be established:
  - Potential subgroups should be identified using techniques such as logic models, cluster analysis, and causal inference, which aim to define subgroups based on interactions between sources of heterogeneity and outcomes
    - Clinical input into these exercises is of paramount importance
    - Ideally, the subgroups would be operationalizable for decision-making purposes, though analysts should not let data shortcomings create arbitrary hurdles for the use of meaningful subgroups
    - Consideration should also be given to equity or ethical issues
- Choose the method by which the clinical heterogeneity will be reflected in the analysis:
  - Use of subgroups in patient-level analysis or separate analysis for model-based analysis
  - Regression models can be used to address heterogeneity in economic modeling by linking patient characteristics to key model parameters, like event probabilities, survival, and costs[30]
  - In modeling, the extent of nonlinearities in key relationships between patient characteristics and outcomes should be a crucial determinant of the choice of microsimulation or cohort-level analysis, with considerations given to data availability and reasonableness of needed assumptions
- Analysis should be performed to illustrate the impact of making separate decisions for individual subgroups[31,32]

2. Study analysis phase

- Perform an empirical analysis to identify and establish the existence of patient heterogeneity
  - If possible, use individual-level patient data for costs and effects
  - Statistically significant differences alone do not support a claim that the subgroups are clinically or economically relevant for reimbursement decision-making (e.g., false-positive results if many subgroups are considered[31]). Conversely, the absence of statistically significant differences does not necessarily negate the relevance of considering subgroups. Statistical power is only 1 aspect of subgroup relevance
- If subgroups are found to be important, conduct these subgroup-specific economic analyses
- Quantify the value that can be captured by making reimbursement decisions at the subgroup level

3. Study presentation phase

- Present the underlying rationale and empirical support for the choice of subgroups or for the choice not to include subgroup analysis
- If subgroups are found to be important, the full set of comparative economic analysis results should be presented and subgroup analysis should form the basis of the main analysis
  - Provide plausible explanations for differences between subgroups
- When ethical concerns regarding the definition of subgroups arise and researchers decide not to conduct subgroup analyses, this should be noted[12]

Based on Grutters et al[5]

Search Results

- The search returned a total of 119 studies for consideration (Figure 1)
- After title, abstract, and full-text review, 58 methodological studies, case studies, review studies, and pharmacoeconomic guidelines were included. A listing of included studies is available upon request
- 20 of the included studies were identified in the citation and CV searches

Heterogeneity in the Context of Comparative Economic Analysis

- Heterogeneity is defined as "the quality or state of consisting of dissimilar or diverse elements"[13]
- In the context of the health economic setting, the word heterogeneity is often used to capture 2 different important dimensions, which sometimes causes confusion
- We refer to heterogeneity as variability in health and/or cost outcomes related systematically to characteristics that differ across observational units (e.g., patient subpopulations, countries, or health insurance plans).[5] This motivates consideration of subgroup analysis to inform decision-making
- A second common usage refers to "factors which vary between patients (e.g., age) which have a non-linear relationship with the model outcomes,"[14] referred to here as clinical heterogeneity. This motivates using patient-level evidence (e.g., with microsimulation techniques)
- As heterogeneity exists even within well-defined subgroups, choosing methods that address both aspects provides the best estimates when warranted (e.g., subgroup-specific estimates based on microsimulation modeling)

Types of Heterogeneity

- While guidelines and methodological studies focus on forms that involve patient heterogeneity, forms unrelated to patients may be relatively important in the US context. Sculpher has described 6 types of heterogeneity in the context of economic analysis[3] (Box 1). These categories are not mutually exclusive, and multiple (or even all) forms may be relevant for any given decision-making problem

Empirical Methods to Address Heterogeneity

- The cornerstone of empirically addressing *heterogeneity* in comparative economic analysis is performing the analyses separately for relevant subgroups and, when necessary, using patient-level approaches like microsimulation
- See Box 2 for an overview of recommended approaches to study design and implementation[6]

DISCUSSION

- The methodological literature was found to provide a useful description of heterogeneity in the context of economic evaluation, including a classification of the types and methods for addressing this empirically. However, 2 important gaps were identified:
  - Relatively little attention was paid to forms emanating from factors unrelated to the patients (i.e., nonpatient heterogeneity). Key factors to consider for the United States include those related to the decentralized nature of the health care ecosystem (e.g., many different payer stakeholders)
  - Heterogeneity in patient preferences is also an area that has received disproportionally less attention to date, especially preferences related to aspects not commonly considered in single-payer systems (e.g., choice of insurance)
- Another area for improvement is stakeholder guidance on incorporating heterogeneity in cost-effectiveness analysis, as this was found to be vague,[8] with the exception of the National Institute for Health and Care Excellence (NICE) in the United Kingdom[7]
- Failing to consider heterogeneity can have important consequences, including patients being "denied for being different" (e.g., when a payer covers only 1 treatment for a condition and that treatment works poorly for a specific individual)[2]
- Subgroup analyses and microsimulation appear to be underutilized in comparative economic analysis and hence reimbursement decisions. A potential reason may be lack of awareness of the importance; researchers can help fill this gap by ensuring that heterogeneity is explicitly considered in their economic evaluations

CONCLUSIONS

- A comparative economic analysis performed at population averages is the most common method currently used, even though decisions based on this type of analysis can lead to worse patient outcomes and wasted resources
- Economic evaluation can only be patient-centric and relevant to decision-making if it properly considers all relevant forms of heterogeneity tailored to features of the local health care ecosystem
- In the decentralized US setting, this should include consideration of heterogeneity arising from factors such as socioeconomic differences, geographic variability in treatment patterns and access to care, insurance coverage, as well as variability in payer and patient preferences

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