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Decision Analysis and Cost-Effectiveness Analysis for Comparative Effectiveness Research—A Primer

David J. Sher, MD, MPH,* and Rinaa S. Punglia, MD, MPH†

Although the analysis of real-world data is the foundation of comparative effectiveness analysis, not all clinical questions are easily approached with patient-derived information. Decision analysis is a set of modeling and analytic tools that simulate treatment and disease processes, including the incorporation of patient preferences, thus generating optimal treatment strategies for varying patient, disease, and treatment conditions. Although decision analysis is informed by evidence-derived outcomes, its ability to test treatment strategies under different conditions that are realistic but not necessarily reported in the literature makes it a useful and complementary technique to more standard data analysis. Similarly, cost-effectiveness analysis is a discipline in which the relative costs and benefits of treatment alternatives are rigorously compared. With the well-recognized increase in highly technical, costly radiation therapy technologies, the cost-effectiveness of these different treatments would come under progressively more scrutiny. In this review, we discuss the theoretical and practical aspects of decision analysis and cost-effectiveness analysis, providing examples that highlight their methodology and utility.
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Introduction

The Institute of Medicine (IOM) published 6 defining characteristics of methodology for comparative effectiveness research in 2009 (IOM Initial National Priorities for Comparative Effectiveness Research, 2009):

(1) Has the objective of directly informing a specific clinical decision from the patient perspective or a health policy decision from the population perspective.
(2) Compares at least 2 alternative interventions, each with the potential to be "best practice."
(3) Describes results and the population of subgroup levels.
(4) Measures outcomes—both benefits and harms—that are important to patients.
(5) Employs methods and data sources appropriate for the decision of interest.
(6) Is conducted in settings that are similar to those in which the intervention would be used in practice.

There are many well-known clinical trial, registry, and large database techniques and tools that classically conform to this definition. Randomized clinical trials—explanatory or pragmatic—serve as the backbone for obtaining level I evidence, and the importance of discerning real-world outcomes has raised the stature of both retrospective data mining and prospective registry studies. Yet, there are inherent limitations to these methodologies, as detailed in the article by Meyer et al.[1]

Randomized trials help guide decisions but require a long period for follow-up, especially when studying diseases that may have a long clinical history, before treatment differences can be discerned. Therefore, data from such studies may not have matured until the treatment itself is obsolete. Retrospective or even prospective large database analyses often do not account for key patient characteristics, either personal or disease related, that may play a key role in determining the optimal therapy for a given patient. Indeed, 1 defining characteristic of all of these methodologies is their reliance on actual patient outcomes and the ultimate reporting of a single preferred treatment or strategy for the "average person." These studies consequently have no mechanism of incorporating

*Department of Radiation Oncology, Rush University Medical Center, Chicago, IL.
†Department of Radiation Oncology, Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA.
The authors declare no conflict of interest.
Address reprint requests to David J. Sher, MD, MPH, Rush University Medical Center, Department of Radiation Oncology, Chicago, IL. E-mail: david_sher@rush.edu

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toxicity and patient preferences into the determination of the best treatment strategy.

For a given patient, the best *decision* for him or her may hinge on his or her own personal, disease, or treatment characteristics, including treatment efficacy or toxicity probabilities that cannot be specified within a clinical trial or retrospective study. The decision to add radiation therapy for patients is a personal one and dependent on an individual's specific set of clinical factors and personal preferences. Optimal decision making requires careful consideration of the potential risks and expected outcomes of radiation therapy.

As implied by the name, *decision analysis* is a set of mathematical tools whose goal is to determine the optimal outcome (whether it is the best treatment or imaging approach, or surveillance strategy, etc) for a given decision under a widely varying set of conditions. Although randomized trials and retrospective studies use real-patient data and biostatistical tools to determine the efficacy or effectiveness of a treatment, decision analysis wields finely tuned mathematical models to simulate the treatment and disease process and thus determine "winning" strategies based on computation. These models are entirely informed by the literature and thus hinge on prospective and retrospective evidence, yet the fact that they are ultimately mathematical models liberates the analyst to test different hypotheses on the importance of patient, treatment, and disease characteristics not possible in patient-based, real-world data. Thus, decision analysis provides a mechanism with which to integrate the available data to compare the outcomes of different treatment strategies. Indeed, decision analysis is perhaps the perfect means to satisfy each of the IOM's criteria for comparative effectiveness research.

The motivation for comparative effectiveness research goes beyond which treatment decision is the right one to whether a decision is right in the context of limited resources. The escalating costs of American health care are inescapable. In 2011, the United States spent $2.6 trillion on health care, which accounts for nearly one-fifth of the economy. This figure amounts to approximately $8000 per person, which is $3000 more than the next country and twice the average for developed countries. Since 1985, health spending has increased 2% per year faster than gross domestic product (GDP), such that in 2010, medical spending amounted to nearly 18% of GDP.[2]

Cancer care comprises a significant amount of the absolute health care expenditure as well as its growth. In 2010, $124.6 billion were spent in oncology; antineoplastics were the leading class of hospital drug expenditures, and biological agents accounted for 15% of all prescription drug costs.[3] Moreover, without *any* change in costs, population changes alone will increase oncology spending by 27% in the year 2020, and if costs increase by 5% per year, the costs from cancer care alone will top $200 billion.[4]

It is actually very difficult to know the extent to which radiotherapy (RT) services contribute to accelerating costs. Unfortunately, the most recent data analyzing oncology expenditures lump all treatments together by phase of care (initial, maintenance, and end-of-life), without specifying the treatments rendered. In a interesting study presented at the American Society for Radiation Oncology National Meeting in 2011, Shen et al[5] showed that the total Medicare payments for external beam RT increased 322% between 2000 and 2009, from $256 million to $1.08 billion, with most that increase attributable to intensity-modulated radiation therapy (IMRT) reimbursement. Despite the absence of published data on this topic, however, with the advent of multimillion dollar proton facilities and progressively more common implementation of IMRT and stereotactic RT, our community recognition of rising RT-related costs echoes the famous quote by Supreme Court Justice Potter Stewart: "I know it when I see it."

Decision Analysis

Motivation for Decision Analysis

Decision analytic techniques have been used to inform decision making in situations of uncertainty. Decision analyses can delineate more clearly the trade-offs for individual clinical scenarios where there are gaps in existing data regarding treatment choice in a number of ways. First, they provide a framework to combine available data from randomized and retrospective trials to study questions for which no direct evidence is currently available. Decision analysis also provides a vehicle to extrapolate results for more recent trials to model outcomes while the decision to use a treatment is still relevant. Decision analyses are especially useful when treatment decisions need to be made for the patient of today, while data from additional studies specific to the patient's clinical characteristics may be forthcoming. Second, decision models can be used to tailor expected outcomes to an individual set of clinical circumstances. Results of decision models have been published using the available data from randomized and retrospective trials to model the life course of clinical subsets of patients diagnosed with breast cancer (for example, those patients with breast cancer with genetic mutations, node-negative disease, or disease responsive to a particular systemic agent) to study long-term outcomes and inform current treatment choice.[6-8] Finally, decision analyses can model a number of different outcomes, such as overall survival or time without recurrence, allowing estimates to reflect the outcome most relevant to an individual patient.

Methodology of Decision Analysis

Structuring the Decision

A decision model or decision tree is created to represent the clinical choice. The model needs to be simple enough to be understood and feasible to do. To do this, a model needs simplifying assumptions, but at the same time, a model needs to be complex enough to describe accurately the features of the decision. Decision nodes are represented by squares in the decision tree, chance nodes by circles, and terminal nodes by triangles.

Figure 1 represents a decision in a hypothetical situation where a patient is confronted with the following treatment dilemma regarding whether to undergo radiation therapy or not for illness X. Radiation therapy for illness X is toxic and