

Challenges in Systematic Reviews of Economic Analyses

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Economic analyses can provide valuable information for health care decision makers. Systematic reviews of economic analyses can integrate information from multiple studies and provide important insights by systematically examining how differences between models lead to different results. We use our experience in developing and implementing systematic reviews of economic analyses for the U.S. Preventive Services Task Force, particularly

our systematic review of the cost-effectiveness of colorectal cancer screening, to illustrate key methodologic challenges and suggest a framework for other researchers in this area.

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Economic analyses, including cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, and cost-minimization studies, can provide valuable information for health care decision makers (for a glossary of terms, see **Appendix** at www.annals.org). Economic analyses can be performed within the context of a clinical trial or other study, or they can be based on a model, or a combination of the two. Economic analyses that incorporate models allow investigators to explore multiple questions (**Table 1**). Most important, models integrate information about effectiveness and costs and thus can provide a measure of health care value. As more economic analyses are produced, researchers and policymakers need to have methods to synthesize and interpret the results of multiple analyses that address a single issue; systematic review offers a framework for doing this.

Systematic reviews of economic analyses pose special challenges for those who perform reviews and those who use them. Traditional techniques of meta-analysis are not appropriate for economic analyses, which are themselves syntheses, and hence should not be combined as one might combine the results of different randomized trials. Instead, systematic reviews of economic modeling studies are most useful for comparing and contrasting how different investigators have chosen to structure their models and estimate key variables. They can also clarify how results differ between studies based on these different assumptions. Identifying sources of variation across studies can help individual decision makers determine which studies best apply to their particular settings and can also guide future research by identifying important areas of uncertainty. Systematic assessment of study quality can help reviewers interpret individual study results (1, 2).

We examine key methodologic challenges in performing systematic reviews of economic analyses, based on our experiences and those of other experts in the field (1, 3). To illustrate our general principles, we also describe our experience in performing a systematic review of colorectal cancer screening for the Agency for Healthcare Research and Quality (AHRQ) and the U.S. Preventive Services Task Force (USPSTF) (4, 5).

CHALLENGE: IDENTIFYING ECONOMIC ANALYSES

Literature searches to identify economic analyses should generally begin with the British National Health Service Economic Evaluation Database (NHS EED) (available at www.york.ac.uk/inst/crd/nhsdhp.htm), which systematically identifies and catalogs health-related economic analyses. The NHS EED uses a rigorous set of search terms in 4 main databases: Current Contents-Clinical Medicine (1994 onward), MEDLINE (1995 onward), CINAHL (1995 onward), and EMBASE (2002 onward). In addition, they hand-search key journals and incorporate technology assessments and working papers from a range of research institutes to assure coverage. Their search strategies are available at www.york.ac.uk/inst/crd/nfaq2.htm. When using the NHS EED, reviewers should combine topic search terms with the “economic evaluations” tab to identify relevant articles. Assistance from a research librarian will help assure good search-term coverage.

To identify other potentially eligible studies, including older analyses, reviewers can apply the full search terms recommended by the NHS EED to studies published before 1995, or they can use an abbreviated search strategy. We have found that using the Medical Subject Headings terms *costs and cost analysis* and *cost-benefit analysis* works well for identifying relevant studies in prevention and

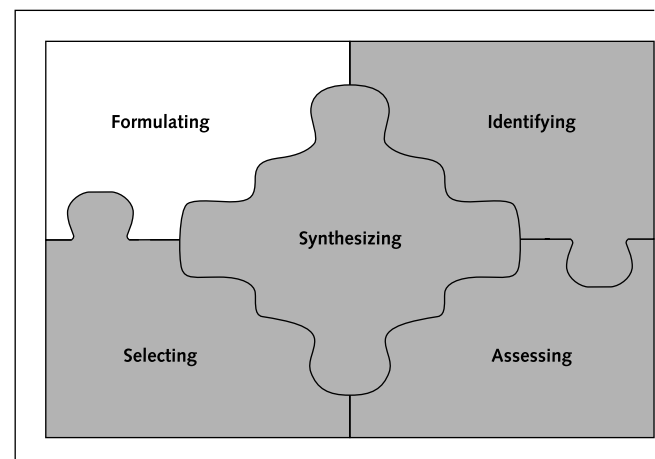


Table 1. Potential Aims of Systematic Reviews of Economic Analyses

Potential Aims	Examples
1. Quantifying differences between ≥ 2 effective services for the same condition	Which colorectal cancer screening strategy is most cost-effective?
2. Illustrating the impact of delivering a given intervention at different intervals, at different ages, or to different risk groups	At what age is it appropriate to stop screening for colorectal cancer?
3. Evaluating the potential role of new technologies	Is virtual colonoscopy more efficient than traditional approaches to screening?
4. Identifying key conditions that must be met to achieve the intended benefit of an intervention	How does lack of adherence to follow-up colonoscopy affect the cost-effectiveness of fecal occult blood testing?
5. Incorporating varying patient preferences for interventions and outcomes	How does variable tolerance of discomfort with colonoscopy affect its cost-effectiveness?
6. Ranking services in order of their costs and expected benefits	What is the relative value of colorectal cancer screening compared with other preventive services?

screening. Another useful resource is the CEA registry at the Harvard School of Public Health (available at www.hsph.harvard.edu/cearegistry). In addition, one may wish to query experts in the field and hand-search relevant article bibliographies.

CHALLENGE: SELECTING ECONOMIC ANALYSES FOR REVIEW

Effectively selecting economic analyses for review begins with carefully defining key questions; taking a methodical approach to the research topic facilitates stating them in ways that a systematic review truly can address. For the USPSTF and its partner Evidence-based Practice Centers (EPCs), the main step in this process is development of an analytic framework and related key questions (6). In this process, the USPSTF and the EPC specify the health or intermediate outcomes of interest, the types of comparisons to be made, and the populations to be included.

Systematic reviews of economic analyses can inform a variety of clinical or policy questions (Table 1). Once reviewers or decision makers specify the research questions, reviewers should develop inclusion (eligibility) criteria a priori so that they can identify studies most likely to produce unbiased, generalizable, and useful information for the issues at hand. In practical terms, determining how stringent to be in setting eligibility criteria is often difficult until the number of potential studies has been determined. Regardless of the number of studies available, analysts must apply some minimum quality criteria (1, 2). In addition, reviewers may set criteria relating to the analytic perspective taken (for example, societal, payer, health care system, or patient).

Outcomes are a significant element of eligibility criteria. Cost-effectiveness analyses and cost-utility analyses that measure generic outcomes such as cost per life-year or quality-adjusted life-year (QALY) gained, respectively, are generally more valuable than studies that measure cost per event prevented because the former 2 types yield metrics such as QALYs that can be compared across different clinical conditions. Studies examining disease-specific out-

comes may be appropriate if decision makers are interested in comparisons relevant to a single intervention or condition. This might include determining the optimal frequency for delivering a particular screening intervention (for example, mammography or cervical cancer screening) or examining the best way to address a certain variable, such as adherence to clinical advice about screening (for example, for colorectal cancer).

In economic analyses, usually only a few studies are relevant for any given topic, and the number of high-quality studies is usually lower. Thus, reviewers must set eligibility criteria to exclude low-quality analyses while still retaining enough studies, if possible, to evaluate important differences in model structure and inputs for key variables. This approach of using the best available evidence typically requires an iterative process; in this, analysts may set final selection criteria only after initially assessing of the quantity and quality of the extant literature (7).

CHALLENGE: CRITICALLY ASSESSING ECONOMIC ANALYSES

Critical appraisal begins by first systematically identifying, cataloging, and analyzing key study features of the included articles (Table 2). Several checklists for appraising

Table 2. Common Data Elements To Be Identified from Individual Studies

Research question
Model type
Analytic perspective
Interventions being compared
Type of analysis
Data sources
Effectiveness
Complications
Costs
Utilities
Study population (age, sex, race)
Costs included
Discount rate
Currency (type and year)
Time horizon
Approach to expressing uncertainty

study reporting and quality have been developed (1, 2, 8); however, a recent systematic review found that economic analyses published in the past 10 years frequently have important methodologic flaws (9). In the following paragraphs, we describe key areas for assessment and appraisal in greater depth, including model type and structure, analytic perspective, time horizon, and ways to address uncertainty.

Model Type and Structure

Those investigating the same clinical question may structure their models differently. For example, one investigator may use Markov analysis, whereas another investigator may use microsimulation or a discrete-events analysis for the same clinical question. Even within a particular model type, differences in how the model is structured and how information on natural history is used can have important effects on results. How much such differences will affect the results of the model, apart from differences in input variables, is not clear.

Analytic Perspective

Studies may differ in the perspective they use. Those using the societal perspective may produce results different from those done from the payer or the patient perspective because they include different costs and effects. Many experts prefer the societal perspective because it is the broadest and includes the greatest range of costs and effects. Even studies done from the societal perspective, however, commonly fail to address certain costs, such as those associated with patient time requirements or changes in economic productivity.

Time Horizon

Different models may use different time periods over which benefits, adverse effects, and costs of a given intervention accrue. Differences in time horizon can lead to important differences in outcomes, particularly when the benefits and adverse effects occur at different points in time. For example, carotid endarterectomy for stroke prevention leads to a short-term increase in adverse events from perioperative complications, but it reduces later events (10).

Ways To Address Uncertainty

Another important shortcoming of published economic analyses is the limited degree to which many economic analyses have examined and represented uncertainty. Uncertainty should be considered at a minimum of 2 levels: uncertainty with respect to the values used for input variables, and uncertainty with respect to the effect of combining multiple estimated variables. Many studies address the first type of uncertainty with sensitivity analysis of a limited number of variables over an often limited range of values; in some cases, the model structure might permit multiway sensitivity analyses. Few studies, however, consider the higher-level uncertainty that comes from the combined effects of the different variables, including best-

and worst-case scenarios. For example, few economic analyses report confidence or credible intervals around their main results; omitting them may engender a false sense of precision. One useful example of how to consider uncertainty effectively comes from Briggs and colleagues, who used Bayesian probabilistic sensitivity analysis to examine different treatments to heal and prevent recurrence of reflux esophagitis (11). Given the state of the literature, reviewers must be careful to point out that comparisons among the results of different analyses should be interpreted with caution, as differences in the point estimates of cost-effectiveness do not account for the uncertainty around those estimates.

CHALLENGE: PRESENTING THE RESULTS OF A SYSTEMATIC REVIEW OF ECONOMIC ANALYSES

Determining the best way to report the results of a systematic review of economic analyses can be challenging, as the amounts of data synthesized and results generated are often quite large. When reporting results, one should present, for each analysis, the incremental cost-effectiveness ratios (for example, the cost per life-years or QALY gained for each nondominated intervention that is being considered compared to the next most effective intervention) for all key strategies being tested, updated to current year dollars (5, 12, 13). When such information is not available, analysts may be able to calculate such values if the original authors have tabulated costs and outcomes for each key option. In addition to these data, reviewers should present a table of input variables from each study so that readers can see how differences in each variable affect the cost-effectiveness ratio.

CASE STUDY: SCREENING FOR COLORECTAL CANCER

Our experience in developing a systematic review of cost-effectiveness analyses on colorectal cancer (CRC) screening illustrates how a systematic review of economic analyses can help inform preventive care decisions (5). Such work can also stimulate further cooperative research among model builders to better identify and explain sources of variation between models.

Colorectal cancer screening is a good example for several reasons. It is an important issue for preventive health for U.S. adults. Several different potential screening tests are available, each with different advantages and disadvantages. These different tests have never been compared head-to-head in clinical trials, but evidence is sufficient to allow reasonable estimation of their efficacy. In addition, several different researchers have developed cost-effectiveness models for CRC screening, allowing for fruitful comparisons (14–20). We sought to determine: What is the cost-effectiveness of CRC screening compared with no screening, and is one method of screening preferred above others with respect to effectiveness or cost-effectiveness?

Table 3. Illustrative Method of Displaying Study Results: Incremental Cost-Effectiveness Ratios in 2000 U.S. Dollars*

Strategy	Cost-Effectiveness Ratio, \$				
	Wagner, 1997 (14)	Frazier et al, 2000 (15)	Khandker et al, 2000 (16)	Sonnenberg et al, 2000 (19)	Vijan et al, 2001 (20)
No screening	–	–	–	–	–
Flexible sigmoidoscopy every 5 years	WD	12 804	15 442	SD	SD
Annual FOBT	SD	16 568	34 160	10 496	5686
DCBE every 5 years	SD	SD	53 950	NR	NR
Colonoscopy every 10 years	10 997†	SD	62 000	12 271	33 016§
FOBT plus flexible sigmoidoscopy every 5 years	34 732	33 786	SD	NR	106 153

* Unless otherwise noted, each strategy is compared with the next strategy above. DCBE = double-contrast barium enema; FOBT = fecal occult blood test; NR = not reported; SD = strongly dominated (less effective and more costly); WD = weakly dominated (less effective but a higher cost-effectiveness ratio).

† Compared with flexible sigmoidoscopy every 5 years.

§ Colonoscopy at age 55 and 65 years compared with annual FOBT.

|| Compared with annual FOBT.

Our systematic review of economic analyses on CRC screening found that all commonly recommended screening tests were effective and cost-effective compared with no screening (Table 3). Five studies compared multiple methods of screening. The results were less clear for the question of whether one method of screening should be preferred because it is either more effective or more cost-effective: the different models were not consistent with respect to the most effective or most cost-effective method of screening.

Differences in results appeared to arise from differences in input variables among models and differences in model structure and assumptions. For example, the studies by Frazier and colleagues (15) and Vijan and colleagues (20) used estimates of the cost of colonoscopy (\$1012 and \$550, respectively) that differed by almost 100%. This difference was associated with a similar magnitude of difference in the cost-effectiveness ratio for colonoscopy screening (5).

In some cases, the differences in variables used reflected the uncertainty about some inputs. In others, the differences represented somewhat arbitrary or context-specific choices about inputs. Specifically, important factors included information about natural history of CRC (for example, what proportion of polyps to assume will progress to cancer and how long the period is for polyps to progress to cancer), differences in cost inputs (for example, which value to use for the cost of colonoscopy), differences in how complications were modeled, and variation in how adherence was addressed, if at all. Most of the models did not estimate the degree of uncertainty around the estimates of cost-effectiveness.

We attempted to use differences in the published input variables to understand differences in the results of these various analyses. Unfortunately, as noted for critical appraisal, the multiple differences between studies and the limited data available in the published reports on the analyses made it difficult to determine with confidence the sources of variation between studies. To overcome these problems, we called for collaborative work among modelers and researchers to standardize inputs, perform additional

research, and re-run existing models to answer questions about variation in results (5).

In response to our call for collaboration, the National Cancer Institute (NCI), in partnership with the National Academy of Sciences, convened a workshop of modelers (21). Each modeling group was asked to perform a series of standardized analyses to assess indirectly the magnitude of the effect of differences in input variables among models.

All modelers were asked to use a standard set of basic assumptions, including a 3% discount rate, 2003 U.S. dollars, and the assumption that screening begins at age 50 years and continues until age 80 years. In addition to these basic assumptions, modelers were given assumptions to be used in various combinations for the following factors: test and treatment costs, test accuracy, complication (colon perforation) rates, surveillance patterns, and adherence (set at 100% for standardized analyses).

In the interest of feasibility, the workshop organizers chose 10 scenarios for consideration. The first scenario used only the basic assumptions; the remaining variables were those of the original models. A second analysis used all the standardized inputs. Eight other scenarios then varied the variables that were or were not standardized.

The modeling exercise yielded several useful results. In summary, the models, in their nonstandardized forms, differed with respect to both costs and effectiveness of the specific screening strategies considered. Full standardization removed many, but not all, of the differences in costs. In terms of effectiveness (life-years saved), substantial differences remained after full adjustment, suggesting that variables for which we did not adjust, such as model structure or natural history assumptions, may account for much of the variation observed. Additional analyses suggested that test costs were responsible for much of the variation in total costs between models. The preferred test at different thresholds of generally accepted levels of costs per life-years saved varied widely before standardization but much less so after standardization.

We concluded from this exercise that attempts to standardize cost inputs could allow greater focus on differences

that arise from variables with true uncertainty (and hence a need for more research), such as the effectiveness of a screening test or assumptions about natural history, and from underlying differences in the model structure. In addition, we suggested that modelers develop means by which to test more sophisticated ways of representing the components of adherence to CRC screening, which are only crudely represented in several models. Overall, the workshop offered a framework for how to approach other health economic issues for which multiple models exist: perform an initial systematic review to identify potential sources of variation and follow this with collaborative work among modelers to understand these sources of variation and help set priorities for future primary research. The NCI's Cancer Intervention and Surveillance Modeling Network (CISNET)—a consortium of NCI-sponsored investigators who use modeling to improve understanding of the impact of cancer control interventions—illustrates how this can be done (available at <http://cisnet.cancer.gov>).

CONCLUSION AND RECOMMENDATIONS

Economic analyses, particularly those that are based on models, can provide important information for health care decision makers. They have particular appeal for decision making about preventive care, for which direct studies often require very large sample sizes and take many years to complete.

Economic modeling studies are complex, however, and their interpretation and evaluation can be difficult. These difficulties are greater when analysts have used several different approaches to address the same question, thus often generating different results. A systematic review of multiple well-performed analyses can improve interpretation and validation of economic questions because it offers a rigorous approach for evaluating reasons for different results among studies.

We have described our approach to identification, appraisal, and presentation of systematic reviews of economic analyses. We illustrated this approach using a case example of CRC screening. Our example illustrates the promise, difficulties, and current limitations of the use of economic analyses by health care decision makers. We, and others, have demonstrated that, at least for some well-studied topics, investigators can identify relevant articles, extract key information, report results, and consider reasons for observed differences between studies (3, 5, 9). In short, systematic reviews of economic analyses can provide decision makers with important information for policy decisions, but systematic reviews published to date have not used consistent methods for identifying or evaluating economic analyses (9).

To improve the quality of future systematic reviews of economical analyses, we offer several recommendations (see **Table 4**). First, modelers should follow consensus recommendations from the Panel on Cost-Effectiveness Re-

Table 4. Recommendations for Improving Systematic Reviews of Economic Analyses*

Reviewers	Read and use guidelines for systematic reviews of economic analyses.
Modelers	Follow consensus recommendations in developing models and reporting results (22). Include appropriate expressions of uncertainty.
Modelers and policymakers	Interact to improve existing models and facilitate greater use and better understanding of model results.
Journal editors	Develop better mechanisms for presenting modeling results. Present results of different analyses together to allow comparisons (for example, CISNET effort). Provide access to model versions that allow users to explore effects of differences in input variables without affecting the underlying model structure.

* CISNET = Cancer Intervention and Surveillance Modeling Network.

search for Performing and Reporting Economic Analyses in developing models and reporting results (22). In particular, they should include appropriate expressions of uncertainty. Second, model developers and policymakers should engage in greater ongoing dialogue (through means such as CISNET). Such discussions could facilitate greater use and better understanding of model results and improve existing models. Third, reviewers should read and use, when possible, guidelines for systematic reviews of economic analyses (5, 9, 23–26). Fourth, journal editors and research funding agencies should develop better mechanisms for presenting modeling results, including greater use of electronic publishing. Ideally, results of different analyses would be presented together to allow comparisons (as in the CISNET effort). Reviewers or users could access a version of the model that would allow them to explore differences in different variables without affecting the underlying model structure.

In conclusion, we underscore the importance of health care decision making and of taking value and economic outcomes into account when considering clinical or policy questions. Systematic reviews of economic analyses integrate information from multiple studies and offer the opportunity to provide additional insight by examining how differences in individual models influence costs, outcomes, or cost-effectiveness. Information from systematic reviews can then be used to further refine individual models, as described in the colorectal cancer screening example, thus offering another means of advancing our understanding of clinical and policy questions. To be most effective, however, systematic reviews of economic analyses must adhere to high methodologic standards for identifying, appraising, and integrating information.

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Glossary of Common Terms Used in Cost-Effectiveness and Related Analyses

Cost-benefit analysis: A technique for measuring net gain or loss to society of a new program or project. It considers allocative efficiency (see below). Values of benefits are usually given in monetary terms.

Cost-effectiveness analysis: A technique for comparing alternative approaches to care, using metrics such as cost per life-year gained. Originally derived to assess the technical efficiency (see below).

Cost-effectiveness ratio: This calculation estimates the value of additional resources (costs) required to achieve an additional unit of a health outcome.

Cost-utility analysis: A technique for comparing the costs and the utility of health gained for different alternatives, such as cost per quality-adjusted life-year gained.

Discounting: A technique for estimating the present value of costs and benefits occurring in different time periods.

Discrete-events simulation: A modeling technique in which individual patients pass from one health state to other health states and in which the time spent in each state is varied randomly on the basis of an underlying distribution defined by the modeler.

Efficiency: A term used to indicate optimal use of resources. *Technical* efficiency assesses which is the best program to meet a specific objective. *Allocative* efficiency measures the extent to which programs improve overall social welfare.

Markov model: A modeling technique commonly used to simulate health conditions that occur over time. In a Markov model, modelers assign cohorts (groups) of patients' outcome states deterministically for each time cycle of the model. Modelers determine both the distributional proportions and transition probabilities.

Microsimulation: A modeling technique in which a large number of people pass through the model one at a time. Each person's path through the model is randomly generated on the basis of the underlying probability distributions defined by the modeler. Analysts then aggregate the results for each person to give the overall results and a probability distribution of outcomes.

Perspective: The point of view from which the analysis is conducted. An economic evaluation from one perspective (for example, the patient's) may consider the impact of different sets of costs and outcomes than one conducted from another perspective (for example, the insurance company's). Most bodies recommend that analyses be conducted from the societal perspective because it considers the broadest range of costs and benefits.

Sensitivity analysis: A method of exploring uncertainty about assumptions or data included in an economic evaluation. In one-way sensitivity analysis, only one variable is changed at a time; in multiway analysis, many variables are adjusted at the same time. The method can be used to consider thresholds of patient risk, effectiveness, or cost at which a health intervention might be judged a "good buy."

Strong dominance (also known as simple dominance): An option is strongly dominated if another alternative has lower costs and is more effective; thus, the strongly dominated option can be ruled out of contention.

Utility: A term used by economists to sum up the satisfaction gained from a good or service. In health care evaluations, utility is often used in measures such as the quality-adjusted life-year or healthy-year equivalent, which take into account effect on quality of life as well as life-years gained.

Weak dominance: An option is weakly dominated when a more costly, more effective alternative exists and that alternative has a lower cost-effectiveness ratio.

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