Eur J Health Econom 2003 · 4:143–150
DOI 10.1007/s10198-003-0205-2
Published online: 10. September 2003

Uwe Siebert[1,2]
[1] Institute for Technology Assessment and Department of Radiology, Massachusetts, General Hospital, Harvard Medical School, Boston, MA, USA
[2] Bavarian Public Health Research and Coordinating Center, Institute of Medical Informatics, Biometry, and Epidemiology, Ludwig Maximilian University Munich, Germany

When should decision-analytic modeling be used in the economic evaluation of health care?

More than a quarter of a century ago Weinstein and Stason [1] introduced to the medical community the concept and methods of cost-effectiveness analysis. Although economic evaluations were not widely used at first, today they are a standard tool in the assessment of health care technologies. Health care resources continue to be limited, and new and more effective technologies often come with increased costs and bear different risks than the „standard" technology. Therefore the application of formal methods considering all dimensions relevant to the patient and society will continue to be of paramount importance in the future.

When faced with choosing between a variety of available procedures, physicians and patients may want to choose those that offer the best trade-off between potential harm and potential benefit in hopes of recommending the treatment with the maximum expected health benefit for the patient. Therefore health policy makers and health insurers must decide which procedures to promote and which to reimburse for specific groups of patients. Society may want to allocate limited health care resources in a way that maximizes the overall health of a population and avoids the implementation of ineffective or comparatively inefficient interventions. Thus decision makers at all levels are increasingly forced to consider the cost-effectiveness of alternative choices in medicine and health care.

Decision making is an essential part of health care. It involves choosing an action after weighing the risks, benefits, and costs of the options available to the individual patient or the patient population. While all decisions in health care are made under conditions of uncertainty, the degree of uncertainty depends on the availability, validity, and generalizability of clinical and economic data.

Clinical decisions and health care policy decisions must be made whether the clinical circumstances are obvious or complex. Even choosing not to perform a diagnostic test, not to intervene, or not to reimburse a health technology is a decision with consequences that will be experienced by the patient. Physicians, health policy makers, and health care payers are responsible for these decisions. Decision-analytic modeling is a systematic approach to decision making under uncertainty that is used widely in economic evaluations of pharmaceuticals and other health care technologies. In contrast to models that do not aim to inform decisions, decision-analytic models focus on situations in which a decision must be made – even under uncertainty [2, 3, 4, 5, 6].

This contribution explores and discusses situations in which decision-analytic models have been used to inform decisions in health care policy. This article is not meant to offer a step-by-step guide to performing a decision analysis. For this purpose, several excellent texts are available [2, 4, 7, 8, 9]. Nor does it give an exhaustive list of situations in which modeling can be useful. Most examples cited here are chosen from areas familiar to the author and therefore do not reflect a representative sample of decision-analytic studies. Although this text builds on numerous other excellent editorials and reviews of modeling [10, 11, 12, 13], the author alone is responsible for the views expressed.

What is a model?

Several definitions have been offered for the term „model" as it applies to the context of health care. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Good Research Practices–Modeling Studies defines a health-care evaluation model as „an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs" [13].

The United States National Research Council in its report on the uses of microsimulation modeling for social policy offered this definition of a simulation model: „a replicable, objective sequence of computations used for generating estimates of quantities of concern" [14]. Buxton and colleagues [10] defined models in scientific disciplines this way: „Models ... are a way of representing the complexity of the real world in a more simple and comprehensible form." Box and colleagues [15] distinguish between empirical and theoretical/mechanistic models. An empirical model is used to hypothesize about a situation in which „the mechanism underlying

a process is not understood sufficiently well, or is too complicated, to allow an exact model to be postulated from theory." In an empirical model the data speak for themselves, without necessarily using a mechanistic or logical connection between cause and effects. In contrast, a theoretical model is „based directly on an appreciation of physical or mechanistic theory governing the system." Weinstein and colleagues [11] used this reasoning and mentioned that a clinical trial can be thought of as an empirical model, whereas a decision-analytic model with empirically estimated parameters, including some estimated from clinical trials could be considered as a theoretical model.

Definitions and goals of decision-analytic modeling

Decision analysis is the application of explicit and quantitative methods to analyze decisions under conditions of uncertainty [2, 4]. Decision analysis is naturally suited for decisions in the prevention, diagnosis, and treatment of disease because multiple alternative options are often available with complex and uncertain outcomes. Decision analysis allows the analyst to compare the expected consequences of different strategies after considering all relevant events and complications with their probabilities and weighing all relevant clinical outcomes and costs. The results of such analyses can inform a decision both for an individual patient and a health care policy [16, 17]. Depending upon the purpose of the analysis different perspectives can be chosen, such as the patient's perspective or the perspective of society or a national health authority [18].

Whereas clinical decision analysis focuses merely on clinical outcomes such as success rates, complication rates, survival, life expectancy, and health-related quality of life associated with the compared strategies, decision analysis is more frequently used in economic evaluations of health care technologies.

Methods of decision-analytic modeling

The two basic forms of decision-analytic models are decision trees and Markov models. A decision tree is a visual representation of all the possible options and the consequences that may follow each option [9]. Each alternative action is followed by branches representing the possible events with their respective probabilities. Probabilities may depend not only on the different strategies but also on patient characteristics (e.g., subgroups with different risk factor profiles). At the end of the tree each path leads to an outcome, such as symptoms, clinical score, survival, and death. For each alternative action the expected value of the clinical outcome can be calculated as a weighted average of all possible outcomes, applying the path probabilities as weights. Decision trees work well when analyzing events with limited recursion and a limited and fixed time horizon.

In chronic diseases such as coronary heart disease and cancer, model parameters such as progression rates, quality-of-life measures (utilities), and costs may change over time, the time-to-event or time-to-progression plays an important role, and events may also recur. Under these circumstances Markov models are usually the preferred method to evaluate interventions [19, 20]. Markov models offer a methodology for considering extended (variable) time horizons, timing of events, and recurring events [9]. In a Markov model a hypothetical cohort of patients moves through defined Markov states and time is represented in cycles during which patients can (a) remain in their current health states, (b) move to another health state, or (c) die, according to certain transition probabilities. During this process cumulative life years, quality-adjusted life-years (QALYs), and costs can be accumulated in each of the interventions and then compared between the interventions [19, 20].

In addition to traditional decision trees and Markov models, other modeling techniques have been used to evaluate the consequences of health care interventions. Dynamic models based on differential equations are usually used to model transmission effects in infectious diseases [21] and sets of mathematical equations predicting costs are often used in cost simulations.

Because decision models aim to inform decisions, they must compare different alternative strategies, one of which may be the strategy of not intervening. Therefore decision models are naturally suited to be applied in full economic evaluations, defined as the comparative analysis of alternative courses of action in terms of both the costs and consequences examined [18]. One form of a full economic evaluation is cost-effectiveness analysis. The underlying premise of a cost-effectiveness analysis in health problems is that for the limited resources the decision maker wishes to maximize the aggregate health effects conferred to the population of concern [22]. In the framework of a cost-effectiveness analysis, a health technology should be adopted if the incremental cost-effectiveness ratio is below the threshold of societal willingness-to-pay (e.g., € 50,000 per QALY gained). In practice the incremental cost-effectiveness ratio of a health technology should be compared to the cost-effectiveness ratios of other well-accepted health technologies [22].

When should decision-analytic models be used?

Decision-analytic economic evaluations have been performed in different areas of medicine such as primary prevention (risk factor reduction), secondary prevention and screening, diagnostic procedures, therapy, and rehabilitation [23]. This section briefly describes several situations in which decision-analytic modeling is helpful or even required. The categories listed are neither mutually exclusive nor exhaustive. Overlaps exist between these categories, and often there are multiple reasons motivating the investigators to perform a decision analysis. In most of the situations described below decision models are used for either (a) combining or linking data from different research areas and sources or (b) transferring or extrapolating results from one time, place, population, or setting to another.

Combining evidence from short-term clinical trials and long-term epidemiological studies

For many diseases it takes years until the final health outcomes become manifest. In such cases it is common to assess intermediate clinical endpoints that serve as surrogates for the final endpoint that really

matters to the patient such as long-term morbidity (including its effects on health related quality of life) and mortality. For example, it may take patients who are chronically infected with the hepatitis C virus decades to develop advanced liver disease which is associated with reduced quality of life and high mortality [24, 25, 26, 27]. Although recent antiviral treatment strategies [28, 29] have proven effective at eliminating the virus in most patients, virus status is not the main parameter that patients are interested in. Indeed, patients ask questions such as „Does virus elimination increase my remaining life expectancy?" „Does it reduce the risk of advanced liver disease?" and „Does the expected long-term improvement in health-related quality of life outweigh the short-term quality of life decrements due to side effects during the 1 year of treatment?" Economic evaluations must include initial treatment costs as well as long-term (discounted) cost savings from advanced disease that is prevented. From a societal perspective we must answer the question, „Are the expected benefits worth the resources spent, or should the scarce health care resources be allocated to another treatment or disease?"

To answer such important questions, efficacy results from clinical trials must be linked to long-term epidemiological (observational) studies or registries that reflect the natural history of disease.

Assessment of screening programs and diagnostic procedures

The outcome parameters of diagnostic studies are sensitivity, specificity, and negative and positive predictive value. However, the accurate detection of disease is not the primary goal of medicine. Instead, it is the appropriate and early treatment of patients with disease. Thus, diagnostic procedures are clinically useful only if the information they yield can guide physicians regarding their actions in a way that improves health. The expected value of information depends strongly on prevalence of disease (prior probability of disease), risk associated with the test, diagnostic accuracy, and the relationship between the net benefit of treating truly diseased patients and the net harm of unnecessarily treating the nondiseased. Even a purely clinical decision analysis often requires a model to link the diagnostic accuracy data and the long-term effectiveness of available treatments. In an economic analysis savings from advanced disease prevented must be included in the model along with the costs for the diagnostic tests and treatments.

A specific challenge in diagnostic studies with continuous test results (i.e., the majority of tests, such as the prostate-specific antigen test for prostate cancer or glucose tolerance test for diabetes) is the definition of the optimal cutoff point which distinguishes between a positive and negative test result. For a given societal willingness to pay the optimal cutoff point can be derived from a model that uses receiver operating characteristic curve data (i.e., pairs of sensitivity and specificity for different cutoff points) instead of fixed sensitivity and specificity as model parameters. Similarly, the optimal (parallel or sequential) combination of multiple diagnostic tests can be determined.

The use of the prostate-specific antigen test as a screening tool for prostate cancer remains quite controversial. Because many prostate tumors grow slowly and are not aggressive, many men with the disease have a good prognosis even without treatment. Economic evaluations have demonstrated that screening can be associated with increased costs for small incremental benefits or, under specific conditions, even can cause net clinical harm [30, 31, 32]. The latter can arise from complications related to the diagnostic procedure such as increased morbidity and mortality from biopsy-induced infections or from treatment-related complications such as urinary incontinence and sexual dysfunction.

Extrapolating efficacy beyond the time horizon of a clinical trial

Pivotal clinical trials are often the initial source of reliable data on the efficacy of health care interventions. However, clinical trials are often constrained regarding the length of follow-up, and thus assumptions must be made to extrapolate the treatment effect beyond the time horizon of the clinical trial. As an example, Neumann et al. [33] developed a Markov model to evaluate the cost-effectiveness of donepezil in patients with mild or moderate Alzheimer disease (AD). This model used efficacy data from a 24-week randomized placebo-controlled clinical trial [34]. The authors used a Cox proportional hazards model to estimate the relative hazard rates for disease progression under treatment compared to placebo. However, as the trial ended after 24 weeks, the duration of the effect was uncertain and had to be based on open-label data and expert opinion about „how long ... the drug will delay progression of cognitive deterioration" [33]. As the expert answers varied, the authors analyzed different scenarios including optimistic and pessimistic assumptions regarding treatment duration and included a threshold analysis to show the point at which the drug would achieve economic savings. This example demonstrates how decision-analytic modeling can help in making assumptions explicit and in transparently reporting results conditional on the underlying assumptions. In the absence of long-term effectiveness data the formal and explicit way of exploring the uncertainty regarding the duration of treatment effect must be seen as a strength and not a weakness of the decision-analytic modeling approach.

Generalizing from efficacy to routine effectiveness

Clinical trials tend to be conducted in an artificial clinical setting and thus do not reflect the real-world conditions regarding effects and costs. Therefore data from a clinical trial must be adapted to routine clinical practice. Efficacy data from trials must be replaced by routine-effectiveness data, reduced compliance must be considered, and the expected resource utilization in the real-world setting must be used in the model.

One elaborated example that has been repeatedly used as a demonstration of using a decision model to transfer evidence to other settings [10, 35], is the economic evaluation of misoprostol, a medication that reduces the risk of gastric ulcer in patients taking a nonsteroidal anti-inflammatory drug who have gastric symptoms [36]. It has been argued that one would expect lower compliance, more frequent side effects,

and less detected „silent" ulcers when comparing the real-world setting with the situation in a clinical trial [37]. In the economic analysis these factors were taken into account by a decision tree model [37].

Transferring the evidence from one health care system or country to another

Clinical studies are increasingly performed as multinational, multicenter trials, and publication of their results often includes economic evaluations. To use these data in the context of a specific country or health care system the specific conditions of this setting must be considered. In most cases prices differ between countries, and different practice patterns may lead to different resource utilization patterns [38]. In some cases the demographic characteristics or other parameters such as efficacy or utilities vary from country to country [39, 40]. As mentioned above the prevalence of disease is a crucial parameter for the economic evaluation of diagnostic procedures, as is the risk factor distribution in the evaluation of prevention.

An example in which a comprehensive cost-effectiveness model was transferred to several countries is the Markov model for antiviral treatment of chronic hepatitis C developed by Wong and colleagues [41, 42]. This model was initially developed and validated in the context of the United States health care system but has since been extended by new pharmaceuticals and adapted to the context of several countries [43, 44, 45, 46, 47, 48].

Resource allocation

Different diseases and health care interventions require different endpoints in clinical studies. When cost-effectiveness studies are based on these endpoints, cost-effectiveness ratios should be reported as costs per natural unit (e.g., cost per reduced cholesterol unit, cost per restenosis avoided, costs per life saved, costs per liver transplantation avoided, costs per cancer detected). However, as health care budgets are constrained, decisions about health care resource allocation involve choices across all diseases and health care areas. Therefore a generic measure of health outcome is needed to compare cost-effectiveness of health care interventions across diseases. Current recommendations for economic evaluations [18, 22, 49, 50] suggest the use of QALYs gained as a generic measure of effectiveness. As outlined above, Markov modeling is one method to simulate simultaneously duration and quality of life and thus provides the cost-utility ratio (e.g., in euros per QALY gained) of the evaluated health care intervention vs. its comparator. This has led to the development of league tables which rank different interventions with respect to their cost-effectiveness ratio [51].

Considering patient preferences

Regardless of the economic purpose the combination of quality and duration of life explicitly accounts for patient preferences (utilities), and is thus the preferred method of assessment when a health care intervention has an effect on quality of life. It also allows investigators to combine different health outcome dimensions such as mortality, morbidity, and risk of severe adverse events or complications into a single effectiveness measure, the quality-adjusted life expectancy.

Decision-analytic models can also be applied in „bedside decision making" and „shared decision making," in which the decision is meant to be triggered by individual patient preferences for the different benefits and risks associated with the different health care interventions. Even without including monetary costs such analyses can be considered a form of economic analysis from the patient's perspective, as maximizing utilities is one of the most fundamental goals of economics in general. Of course, the societal perspective requires the inclusion of resource utilization into the evaluation, which is almost always done in monetary terms.

Pauker and Pauker [52, 53] presented a clinical decision model for counseling parents about amniocentesis for prenatal diagnosis. This model explicitly considered the possibilities of spontaneous and amniocentesis-induced miscarriage, an affected child (as a function of maternal age), and diagnostic errors. The decision model encouraged couples to confront their attitudes toward specific reproductive outcomes to clarify their preferences and to incorporate them, along with their current risks, into a logical decision about prenatal diagnosis.

Informing decisions in the absence of clinical trial data

For many research questions hard data from clinical trials are not available. In some cases clinical trials are not ethically feasible. In others, such as in cancer screening trials, the enormous sample sizes and extended follow-up periods may make conducting a trial difficult, if not impossible. In such situations decision-analytic modeling can play an important role and at times may be the only way to formally inform the decision. Decision models can explicitly describe the structure of the decision problem and the related parameters that influence the decision and thereby identify priorities for further data collection. For technologies that are evaluated in ongoing clinical trials the final trial results may either replace the decision-analytic results once the hard data become available, or they may update a more complex decision analysis based on multiple parameters.

As an example, Krahn and colleagues [54] developed a decision model that evaluated screening asymptomatic men for prostate cancer. This decision analysis did not support general screening. In fact, several screening scenarios were dominated and resulted in poorer health outcomes and increased costs dramatically. Also in the early 1990s large-scale randomized screening trials with the prostate cancer death rate as the primary endpoint were begun in Europe and the United States, namely, the European Randomized study of Screening for Prostate Cancer and the Prostate, Lung, Colorectal, Ovarian Cancer screening trial, respectively. Therefore a final answer to the question of whether screening for prostate cancer is truly beneficial at a population level can only be answered in several years when these trials have been completed and properly analyzed.

Fine-tune technologies

Strictly speaking, a health technology becomes a different technology even if just a single aspect of it changes. For example, consider the starting and stopping ages in screening programs, and their examina-

tion intervals. At which age should screening for colon cancer be started [55]? What is the optimal interval for cervical cancer screening [56, 57]? How long should men be screened for prostate cancer [31, 54]? In diagnostic studies clinicians are confronted with questions such as, „When is a coronary stenosis functionally significant (i.e., requiring coronary intervention)?" [58], and „What is the optimal combination of diagnostic tests for patients with chest pain" [59]? Optimal treatment management poses questions such as, „What is the optimal and economically efficient dose and duration for antiviral treatment in patients with chronic hepatitis C?" [47], „Does the answer depend on different genotypes of the virus or on demographic parameters of the patients?" [26, 48], and „What is the impact of compliance on sustained virological response rate" [60]?

It will rarely be the case that all such applicable questions have been addressed in primary and sufficiently powered comparisons within randomized clinical trials. At best, subgroup or post-hoc analyses may be available. To compare multiple subgroups and specific features or combinations of technologies modeling based on plausible assumptions will in most occasions be the only way to derive comprehensible health care decisions.

Value-of-information analysis

Raiffa [2], one of the founders of decision theory, describes the concept of value of information as the difference between the expected consequences (utility) of a decision guided by a particular piece of information and the respective expected consequences without the information. This concept is directly applicable to the assessment of whether the aquisition of more empirical information is justified including such information that can reduce uncertainty about decision parameters. Deferring approval of a drug until more empirical information about the magnitude or duration of its effect is available may include the potential of both gaining and losing health outcomes and resources in the interim. An example of applying the framework of value of information analysis to decision modeling has been demonstrated by Claxton and colleagues [61]. They analyzed the decision to adopt a new pharmaceutical for patients with Alzheimer disease. Using a Bayesian decision-theoretic approach to evaluate a probabilistic version of a published Alzheimer disease policy model [33] and to estimate the expected value of perfect information for each of the model parameters, they identified those parameters for which more precise estimates would be most valuable and determined the optimal sample size for an empirical study from a societal perspective based on the incremental cost and incremental benefit of the sample information. Usually there are two conceptually separate research questions that must be answered in health care decision making: (a) Given the available information, should the new technology be adopted? (2) Should more information be obtained to inform (i.e., confirm or change) this decision in the future? The second question can be framed in terms of the United States Food and Drug Administration's Modernization Act, which asks whether the economic claim for a new pharmaceutical can be substantiated and whether the evidence can be regarded as competent and reliable? [11, 61].

In the analysis by Claxton and colleagues [61] the authors broke these general questions into a number of specific ones: „Is additional research in Alzheimer disease potentially cost-effective? Are the estimates of the Alzheimer disease model inputs adequate? For which model inputs would more precise estimates be most valuable? Is experimental design required for subsequent research? If so, which endpoints should be included in any future clinical trial? What is the optimal follow-up period? What is the optimal sample size? How should trial entrants be allocated between the arms of the trial? What is the value of this proposed research?" [61] This approach can also be applied to clinical trial design and conduct. Decision modeling can help estimate expected clinical and economic effects on which sample size calculations are based and thus give an ethical justification of the sample size.

Health policy models and national projections

Many decision models are designed to calculate incremental cost-effectiveness ratios. These have three properties. First, the base-case analysis refers to a homogeneous cohort of patients, for example, a 40-year old man with moderate hypertension without comorbidity. These characteristics are then varied in sensitivity analyses. Second, the results are reported for a hypothetical cohort of patients with an arbitrarily chosen size (e.g., for 100,000 patients) or, even more often, as the expected values of the consequences for a single member of this cohort (e.g., quality-adjusted life expectancy, mean lifetime costs). Third, the calculation uses a fixed (or closed) cohort, that is, no new patients at risk of the disease or with incident disease are entered into the model. Within the framework of utilitaristic resource allocation, this can be sufficient to derive a recommendation about whether a technology should be adopted under the societal perspective. However, such analyses do not show the expected values of the absolute total health outcomes and costs for a heterogeneous population in a particular country.

Such information is more likely to emerge from so-called health policy models. Although this term is not consistently defined, most such models consider the heterogeneity of the actual population of a country (or other entity) regarding age, gender, ethnicity, severity of disease, or risk factor distribution and other features relevant to the decision problem. Furthermore, some health policy models report the expected total health outcomes (e.g., total severe events prevented, life-years gained, QALYs gained) and the expected total costs during a specified time horizon (e.g., 20 or 30 years). In order to validly predict the outcomes observed in the real world these models must use a dynamic cohort approach, i.e., patients must be allowed to enter and leave the decision pool (i.e., the dynamic population at a given time point including all patients for whom a decision must be made) during the analytic time horizon.

This approach may lead to conservative cost-effectiveness estimates, because the nominator of the incremental cost-effectiveness ratio may include some intervention-related expenditures in the last years of the analytic time horizon without „harvesting" the beneficial effect of the intervention on future health or cost-savings due to reduced morbidity and mortality.

However, the reported figures aim to reflect the real consequences as observed in the real world, which is especially important for health care planning.

An example of a detailed health policy model is the Coronary Heart Disease (CHD) Policy Model, which was developed to project the future mortality, morbidity, and cost of coronary heart disease in the United States [62]. This is a Markov model of CHD in United States residents aged 35–84 years without CHD [62]. The model, which consists of three submodels, includes variables for CHD event rates, case fatality rates, and costs. In the demographic-epidemiological submodel an individual develops CHD depending on his or her individual risk factor profile (240 risk subgroups). After developing CHD the individual moves into the bridge submodel, which represents the outcomes in the first 30 days after the initial CHD event. Finally, the disease history submodel simulates the subsequent events after a previous CHD event, including revascularization procedures and CHD-specific and non-CHD mortality. Multivariate risk functions were used to determine the incidence of CHD and the mortality of non-CHD [62].

This model has been used extensively in the evaluation of CHD-related interventions [63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78]. For example, a decision analysis based on this health policy model [65] was cited by the Second Adult Treatment Panel of the National Cholesterol Education Program to support its recommendation endorsing treatment of mildly elevated low-density lipoprotein in patients with a history of heart disease [79]. Shortly after this recommendation direct evidence from clinical trials confirmed that lipid-lowering drug therapy has the potential to reduce the risk of CHD morbidity and mortality as predicted by the model.

Another example of a dynamic health policy model is the Tobacco Policy Model, which was used to describe the public health impact and cost-effectiveness of an enhanced nationwide, school-based, antitobacco education program [80, 81]. This model simulates birth, death, aging, and changes in smoking status in the overall population of the United States. The population was divided into different covariates according to age, gender, and smoking status, and each year newborns entered the dynamic decision pool. The annual mortality and transition rates for smoking initiation, cessation, and relapse were modeled as functions of patient characteristics and time. The authors reported program costs, medical costs, total life years, QALYs, and incremental cost effectiveness ratios for the antitobacco program vs. the status quo after 25 and 50 years.

Health technology assessment

Health technology assessment (HTA) is defined as a multidisciplinary field of policy analysis. It studies the medical, social, ethical, and economic implications of development, diffusion, and use of health technology (International Network of Agencies for Health Technology Assessment: http://www.inahta.org/). HTA has different parts (e.g., clinical effectiveness and economic evaluations) and different approaches (qualitative: narrative review and evidence tables; quantitative: meta-analysis and decision analysis). In a growing number of HTA reports, especially in the economic section, HTA agencies go beyond qualitatively reviewing and summarizing the evidence of published international studies and now use decision-analytic methods to ensure that the results reflect the context of the investigated country's health care system. In a survey commissioned by the German Institute for Medical Documentation and Information (DIMDI) of 12 countries with HTA organizations (nine European countries, Australia, Canada, and the United States) 10 frequently or routinely used decision-analytic modeling to evaluate the cost-effectiveness of technologies in its own health care context.

The recently established German Agency for Health Technology Assessment (DAHTA) at DIMDI exemplifies this evolution. While only one modeling study was performed in DIMDI's HTAs between 1996 and 1999, before the establishment of DAHTA [82], their use in HTAs commissioned by DIMDI has since increased (http://www.dimdi.de/de/hta/hta_dimdi/index.htm). For many topics time and budget restrictions limit the use of decision-analytic models. The first draft of an HTA report is often requested within a year, which may be too short to develop a decision model from scratch and apply it to national data. Therefore DAHTA commissioned a methodological project which includes the development of a framework (a) to identify existing decision models of high quality, transparency, and flexibility, (b) to transfer, extend, and adapt them in cooperation with the original authors to the national context, and (c) to establish a collaboration network between HTA organizations of different countries that promotes and sponsors the exchange of these models between HTA agencies. To date DAHTA has planned and initiated such collaborations with the National Coordinating Centre for HTA (NCCHTA) in the United Kingdom and the Canadian Coordinating Office for Health Technology Assessment (CCOHTA). This approach is also supported by the results of the EUR-ASSESS project, which was undertaken by numerous members of European HTA agencies and programs with the aim of improving coordination in HTA. These members emphasized that collaboration would help avoid duplication and achieve synergy [83].

Discussion

Examples of different situations for decision modeling have been used to demonstrate its value as a tool for health care decision makers on all levels. Decision analysis may aid clinical decisions affecting individual patients as well as inform clinical policy decisions and decisions regarding national health policy. It can be applied to preventive strategies as well as to those aimed at diagnosis and treatment, and provides a valuable tool for the development of clinical practice guidelines.

Decision-analytic models play an important role in cost-effectiveness analysis, which is constructed to identify interventions that produce the greatest health care benefit with the resources available [22]. It must be emphasized that despite its utility decision-analytic modeling in economic evaluations is not a complete procedure for determining resource allocation decisions in health care because it cannot incorporate all the values and criteria relevant to such decisions. Rather, it should be used as an aid in the complex decision making pro-

cess [84]. In addition to the criterion of maximizing the overall health benefit of a population, health policy makers must consider other ethical criteria to comply with societal preferences. For example, equity issues and distributive justice, which include the distribution of health across different subpopulations, are not yet consistently integrated in the concept of decision analysis [85]. Although current decisions must inevitably be based on imperfect information, sensitivity analysis can show the robustness of some decision while suggesting areas where further research may be valuable in guiding others [1].

Finally, the consideration of the principles for good practice in decision-analytic modeling including different levels of model validation is an important prerequisite to increase the confidence in a model and its results. Equally important is the transparent description of the model and the comprehensible reporting of the results. Several methodological and reporting guidelines and textbooks address methodological standards. Guidelines for economic evaluations from six European countries, Australia, and Canada were summarized in a review which also reported European guidelines in the form of a consensus report of the European Network on Methodology and Application of Economic Evaluation Techniques (EUROMET) group [50].

Closing remarks

Waiting to make a decision until perfect information is available is, in most cases, only a hypothetical option. In most health care situations clinical and economic evidence must be either extrapolated through time or space, transferred from one study population to another, or combined and linked in a sensible way. Decision makers must balance the costs and consequences of adopting or discarding a health technology based on the available data vs. waiting for more precise information. They must do this formally or informally. Although the usefulness of decision-analytic models in economic evaluations does not change the fact that cost-effectiveness analysis cannot incorporate all values and criteria that are relevant for health policy decisions, these tools can help to inform these decisions in an explicit manner.

Corresponding author

Uwe Siebert MD, MDH, MPH

MGH-Institute for Technology Assesment
101 Merrimac Street
Boston, MA 02114 USA
e-mail: usiebert@mgh-ita.org

References

1. Weinstein MC, Stason WB (1977) Foundations of cost-effectiveness analysis for health and medical practices. N Engl J Med 296:716–721
2. Raiffa H (1968) Decision analysis: introductory lectures on choices under uncertainty, 1st edn. Addison Wesley: Reading
3. Pauker SG, Kassirer JP (1975) Therapeutic decision making: a cost-benefit analysis. N Engl J Med 293:229–234
4. Weinstein MC, Fineberg HV, Elstein AS et al. (1980) Clinical decision analysis, 1st edn. Saunders: Philadelphia
5. Keeney RL (1982) Decision analysis: an overview. Operations Res 30:803–838
6. Kassirer JP, Moskowitz AJ, Lau J, Pauker SG (1987) Decision analysis: a progress report. Ann Intern Med 106:275–291
7. Sox H, Blatt MA, Higgins MC, Marton KI (1988) Medical decision making. Butterworths: Boston
8. Chapman GB, Sonnenberg FA (2000) Decision making in health care: theory, psychology, and applications. Cambridge Series on Judgment and Decision Making. Cambridge University Press: New York
9. Hunink MG, Glasziou PP, Siegel JE et al. (2001) Decision making in health and medicine. Integrating evidence and values. Cambridge University Press: Cambridge
10. Buxton MJ, Drummond MF, Van Hout BA et al. (1997) Modelling in economic evaluation: an unavoidable fact of life. Health Econ 6:217–227
11. Weinstein MC, Toy EL, Sandberg EA et al. (2001) Modeling for health care and other policy decisions: uses, roles, and validity. Value Health 4:348–361
12. Sheldon TA (1996) Problems of using modelling in the economic evaluation of health care. Health Econ 5:1–11
13. Weinstein MC, O'Brien B, Hornberger J et al. (2003) Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices-Modeling Studies. Value Health 6:9–17
14. National Research Council (1991) Improving information for social policy decisions: the uses of microsimulation modelling, vol 1. National Academy Press: Washington
15. Box GEP, Hunter WG, Hunter JS (1978) Statistics for experimenters: an introduction to design, data analysis, and model building. Wiley: New York
16. Eddy DM (1990) Clinical decision making: from theory to practice. Designing a practice policy. Standards, guidelines and options. JAMA 263:3077
17. Richardson WS, Detsky AS (1995) Users' guides to the medical literature. VII. How to use a clinical decision analysis. A. Are the results of the study valid? Evidence Based Medicine Working Group. JAMA 273:1292–1295
18. Drummond MF, O'Brien B, Stoddart GL, Torrance GW (1997) Methods for the economic evaluation of health care programmes, 2nd edn. Oxford University Press: New York
19. Beck JR, Pauker SG (1983) The Markov process in medical prognosis. Med Decis Making 3:419–458
20. Sonnenberg FA, Beck JR (1993) Markov models in medical decision making: a practical guide. Med Decis Making 13:322–338
21. Anderson RM, May RM (1991) Infectious diseases of humans: dynamics and control. Oxford University Press: New York
22. Gold MR, Siegel JE, Russell LB, Weinstein MC (1996) Cost-effectiveness in health and medicine. Oxford University Press: New York
23. Tengs TO, Adams ME, Pliskin JS et al. (1995) Five-hundred life-saving interventions and their cost-effectiveness. Risk Anal 15:369–390
24. Deuffic S, Buffat L, Poynard T, Valleron AJ (1999) Modeling the hepatitis C virus epidemic in France. Hepatology 29:1596–1601
25. Wong JB, McQuillan GM, McHutchison JG, Poynard T (2000) Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Public Health 90:1562–1569
26. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ (2002) Empirically calibrated model of hepatitis C virus infection in the United States. Am J Epidemiol 156:761–773
27. Freeman AJ, Law MG, Kaldor JM, Dore GJ (2003) Predicting progression to cirrhosis in chronic hepatitis C virus infection. J Viral Hepat 10:285–293
28. Manns MP, McHutchison JG, Gordon SC et al. (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 358 958–965
29. Fried M, Shiffman M, Reddy R et al. (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347:975–982
30. Krahn MD, Mahoney JE, Eckman MH et al. (1994) Screening for prostate cancer. A decision analytic view. JAMA 272:773–780
31. Coley CM, Barry MJ, Fleming C et al. (1997) Early detection of prostate cancer. II. Estimating the risks, benefits, and costs. Ann Intern Med 126:468–479
32. Harris R, Lohr KN (2002) Screening for prostate cancer: an update of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 137:917–929
33. Neumann PJ, Hermann RC, Kuntz KM et al. (1999) Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. Neurology 52:1138–1145
34. Rogers SL, Farlow MR, Doody RS et al. (1998) A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 50:136–145
35. Greiner W, Schöffski O, Graf von der Schulenburg JM (2000) Transferability of international results on national research questions (in German). In: Schöffski O, Graf von der Schulenburg JM (eds) Gesundheitsökonomische Evaluationen, 2nd edn. Springer: Berlin Heidelberg New York, pp 403–420
36. Graham DY, Agrawal NM, Roth SH (1988) Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet II 1277–1280
37. Hillman AL, Bloom BS (1989) Economic effects of prophylactic use of misoprostol to prevent gastric ulcer in patients taking nonsteroidal anti-inflammatory drugs. Arch Intern Med 149:2061–2065
38. Baltussen R, Ament A, Leidl R (1996) Making cost assessments based on RCTs more useful to decision-makers. Health Policy 37:163–183
39. Baltussen R, Leidl R, Ament A (1996) The impact of age on cost-effectiveness ratios and its control in decision making. Health Econ 5:227–239
40. Leidl R, von der Schulenburg J-M, Wasem J (1999) Approaches and methods of economic evaluation-an international perspective (in German). Health Technology Assessment, vol 9. Nomos: Baden-Baden
41. Bennett WG, Inoue Y, Beck JR et al. (1997) Estimates of the cost-effectiveness of a single course of interferon-alpha 2b in patients with histologically mild chronic hepatitis C. Ann Intern Med 127:855–865

42. Wong JB, Poynard T, Ling MH et al. (2000) Cost-effectiveness of 24 or 48 weeks of interferon alpha-2b alone or with ribavirin as initial treatment of chronic hepatitis C. International Hepatitis Interventional Therapy Group. Am J Gastroenterol 95:1524–1530
43. Sennfält K, Reichard O, Hultkrantz R et al. (2001) Cost-effectiveness of interferon alfa-2b with and without ribavirin as therapy for chronic hepatitis C in Sweden. Scand J Gastroenterol 36:870–876
44. Sagmeister M, Wong JB, Mullhaupt B, Renner EL (2001) A pragmatic and cost-effective strategy of a combination therapy of interferon alpha-2b and ribavirin for the treatment of chronic hepatitis C. Eur J Gastroenterol Hepatol 13:483–488
45. Stein K, Rosenberg W, Wong J (2002) Cost effectiveness of combination therapy for hepatitis C: a decision analytic model. Gut 50:253–258
46. Wong JB, Nevens F (2002) Cost-effectiveness of peginterferon alfa-2b plus ribavirin compared to interferon alfa-2b plus ribavirin as initial treatment of chronic hepatitis C in Belgium. Acta Gastroenterol Belg 65:110–111
47. Siebert U, Sroczynski G, Rossol S et al. (2003) Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. Gut 52:425–432
48. Buti M, Medina M, Casado MA et al. (2003) A cost-effectiveness analysis of peginterferon alfa-2b plus ribavirin for the treatment of naive patients with chronic hepatitis C. Aliment Pharmacol Ther 17:687–694
49. Canadian Coordinating Office for Health Technology Assessment (1997) Guidelines for economic evaluation of pharmaceuticals, 2nd edn. CCOHTA: Ottawa
50. Schulenburg JM Graf von der, Hoffmann C (2000) Review of European guidelines for economic evaluation of medical technologies and pharmaceuticals. Eur J Health Econ 1:2–8
51. Mason J, Drummond MF, Torrance G (1993) Some guidelines on the use of cost effectiveness league tables. BMJ 306:570–572
52. Pauker SP, Pauker SG (1987) The amniocentesis decision: ten years of decision analytic experience. Birth defects. Original Article Series 23:151–169
53. Pauker SP, Pauker SG (1979) The amniocentesis decision: an explicit guide for parents. Birth defects. Original Article Series 15:289–324
54. Krahn MD, Mahoney JE, Eckman MH et al. (1994) Screening for prostate cancer. A decision analytic view. JAMA 272:773–780
55. Sonnenberg A, Delco F (2002) Cost-effectiveness of a single colonoscopy in screening for colorectal cancer. Arch Intern Med 162:163–168
56. Eddy DM (1987) The frequency of cervical cancer screening. Comparison of a mathematical model with empirical data. Cancer 60:1117–22
57. Goldie SJ, Kuhn L, Denny L et al. (2001) Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. JAMA 285:3107–3115 (erratum appears in 286:1026)
58. Bech GJ, De Bruyne B, Pijls NH et al. (2001) Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 103:2928–2934
59. Kuntz KM, Fleischmann KE, Hunink MGM, Douglas PS (1999) Cost-effectiveness of diagnostic strategies for patients with chest pain. Ann Intern Med 130:709–718
60. McHutchison JG, Manns M, Patel K et al. (2002) Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 123:1061–1089
61. Claxton K, Neumann PJ, Araki S, Weinstein MC (2001) Bayesian value-of-information analysis. An application to a policy model of Alzheimer's disease. Int J Technol Assess Health Care 17:38–55
62. Weinstein MC, Coxson PG, Williams LW et al. (1987) Forecasting coronary heart disease incidence, mortality, and cost: the Coronary Heart Disease Policy Model. Am J Public Health 77:1417–1426
63. Goldman L, Weinstein MC, Williams LW (1989) Relative impact of targeted versus populationwide cholesterol interventions on the incidence of coronary heart disease. Projections of the Coronary Heart Disease Policy Model. Circulation 80:254–260
64. Edelson JT, Weinstein MC, Tosteson AN et al. (1990) Long-term cost-effectiveness of various initial monotherapies for mild to moderate hypertension. JAMA 263:407–413
65. Goldman L, Weinstein MC, Goldman PA, Williams LW (1991) Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA 265:1145–1151
66. Tsevat J, Weinstein MC, Williams LW et al. (1991) Expected gains in life expectancy from various coronary heart disease risk factor modifications. Circulation 83:1194–1201
67. Hunink MG, Goldman L, Tosteson AN et al. (1997) The recent decline in mortality from coronary heart disease, 1980–1990. The effect of secular trends in risk factors and treatment. JAMA 277:535–542
68. Tosteson AN, Weinstein MC, Hunink MG et al. (1997) Cost-effectiveness of populationwide educational approaches to reduce serum cholesterol levels. Circulation 95:24–30
69. Goldman L, Coxson P, Hunink MG et al. (1999) The relative influence of secondary versus primary prevention using the National Cholesterol Education Program Adult Treatment Panel II guidelines. J Am Coll Cardiol 34:768–776
70. Prosser LA, Stinnett AA, Goldman PA et al. (2000) Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. Ann Intern Med 132:769–779
71. Phillips KA, Shlipak MG, Coxson P et al. (2000) Health and economic benefits of increased beta-blocker use following myocardial infarction. JAMA 284:2748–2754
72. Goldman L, Phillips KA, Coxson P et al. (2001) The effect of risk factor reductions between 1981 and 1990 on coronary heart disease incidence, prevalence, mortality and cost. J Am Coll Cardiol 38:1012–1017
73. Tice JA, Ross E, Coxson PG et al. (2001) Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the prevention of coronary heart disease: effect of grain fortification and beyond. JAMA 286:936–943
74. Tsevat J (1992) Impact and cost-effectiveness of smoking interventions. Am J Med 93:43S–47S
75. Goldman L, Gordon DJ, Rifkind BM et al. (1992) Cost and health implications of cholesterol lowering. Circulation 85:1960–1968
76. Tosteson AN, Weinstein MC, Williams LW, Goldman L (1990) Long-term impact of smoking cessation on the incidence of coronary heart disease. Am J Public Health 80:1481–1486
77. Goldman L, Goldman PA, Williams LW, Weinstein MC (1993) Cost-effectiveness considerations in the treatment of heterozygous familial hypercholesterolemia with medications. Am J Cardiol 72:75D–79D
78. Stinnett A, Mittleman A, Weinstein M et al. (1996) The cost-effectiveness of dietary and pharmacologic therapy for cholesterol reduction in adults. In: Gold MR, Siegel JE, Russell LB, Weinstein MC (eds) Cost-effectiveness in health and medicine: report on the panel of cost-effectiveness in health and medicine. Oxford University Press: New York, 349–391
79. Anonymous (1993) Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 269:3015–3023
80. Tengs TO, Osgood ND, Lin TH (2001) Public health impact of changes in smoking behavior: results from the Tobacco Policy Model. Med Care 39:1131–1141
81. Tengs TO, Osgood ND, Chen LL (2001) The cost-effectiveness of intensive national school-based anti-tobacco education: results from the tobacco policy model. Prev Med 33:558–570
82. Perleth M, Busse R (2000) Health technology assessment in Germany. Status, challenges, and development. Int J Technol Assess Health Care 16:412–428
83. Sassi F (2000) The European way to health technology assessment. Lessons from an evaluation of EUR-ASSESS. Int J Technol Assess Health Care 16:282–290
84. Russell LB, Gold MR, Siegel JE et al. (1996) The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 276:1172–1177
85. Marckmann G, Siebert U (2002) Kosteneffektivität als Allokationskriterium in der Gesundheitsversorgung. Z Med Ethik 48:171–190